CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22382Orig1s000

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
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Addendum to Clinical Review: Review of updated list of post-treatment SAEs and incidence of blisters

NDA Number (Doc #):	**22-382 (26)**
Drug Name (generic):	***SPRIX* (ketorolac tromethamine nasal spray)**
Sponsor:	**Roxro Pharma**
Indication:	**Short term management of moderately severe pain**
Type of Submission:	**NDA amendment containing post-treatment SAEs**
Date of Submission:	**24 August 2009**
Date Received:	**25 August 2009**
Date of Review:	**05 October 2009**
Reviewer:	**Robert A. Levin, M.D.**
Project Manager:	**Jessica Benjamin**

Background

NDA 22-382, ketorolac tromethamine nasal spray (Sprix) for the indication of the short term management of moderately severe pain was submitted December 5, 2008. Subsequent to completing my review of this NDA, the applicant submitted on August 24, 2009 an additional 32 post-treatment SAEs that were not previously included in the Integrated Summary of Safety. The applicant reports that they have now reported all of the SAEs associated with the clinical studies for Sprix.

This addendum includes a review of the 32 post-treatment SAEs that were reported in association with ROXRO's clinical studies for Sprix, but were not previously included in the initial NDA submission. The narrative's for all 32 post-treatment SAEs were reviewed by me. From review of these case narratives it was possible to exclude intranasal ketorolac as the likely cause for most of the SAEs with the exception of some SAEs related to bleeding. In my initial review, bleeding at the surgical site was identified as a safety concern. The applicant's narratives for all six bleeding SAEs are provided below.

This addendum also includes an analysis of the apparent increased incidence of blisters in subjects receiving Sprix compared to placebo.

Patient Narratives

STUDY 2003-01
PATIENT # 81044

Study Drug: ROX-888
Dates of Study Drug Administration: 2/24/04 - 2/28/04
SAE: Pelvic Hematoma
Onset: (b) (6)

Patient 81044 in Study 2003-01 was a 35 year-old Native Hawaiian/ Pacific Island / Polynesian female who underwent abdominal hysterectomy on (b) (6) The patient was randomized to ROX-888 and received 12 doses of study drug. While in the hospital after surgery she experienced moderate anemia and heavy oozing from the wound drain site was noted on (b) (6) She received packed red blood cells on (b) (6) She also experienced adverse events (AEs) of increased AST and ALT. She completed the study as planed on 3/1/04.

On 3/15/04 the patient developed abdominal pain and lethargy. The pain persisted and became more severe along the suture line on (b) (6) and she was admitted to the hospital. A pelvic hematoma was confirmed by ultrasound. Intravenous antibiotics were instituted. The patient was discharged on (b) (6) and was to continue oral antibiotics at home. A follow-up ultrasound was planned for 4/16/04 but the patient chose not to have the study done because she felt healthy. The event was considered resolved after the patient was contacted on 5/14/04. The SAE of pelvic hematoma was considered serious because it required hospitalization. The event was considered moderate in severity and the Investigator assessed the SAE as probably not related to study drug.

Impression

Although the pelvic hematoma was diagnosed over two weeks after her last dose of ROX-888 she had some evidence of postoperative bleeding early on while on ROX-888. Therefore ROX-888 cannot be completely excluded as a contributing factor in this patient's pelvic hematoma.

STUDY 2003-01
PATIENT # 81180
Study Drug: ROX-888
Dates of Study Drug Administration: 7/27/04 -7/28/04
SAE: Wound Hematoma
Onset: (b) (6)

Patient 81180 in Study 2003-01 was a 59 year-old white female who underwent left total hip joint replacement (LTHJR) on (b) (6). Past medical history included Type 2 diabetes mellitus. The patient was randomized to ROX-888 and received 3 doses of study drug. The patient terminated from the study early on 7/29/04 because of adverse events of nasal and throat irritation.

On (b) (6) the patient was readmitted to the hospital because of discharge from the surgical site and a hematoma at the distal end of the LTHJR wound. Oral antibiotics (flucloxacillin) were given. The infection improved, the SAE resolved on (b) (6) and the patient was discharged.

The SAE of wound hematoma was considered serious because it required hospitalization. The event was considered moderate in severity and the Investigator assessed the SAE as probably not related to study drug.

Impression
There is no evidence to suggest that ROX-888 contributed to her SAE of wound hematoma that developed (b) (6) after her last dose of ROX-888

STUDY 2003-01
PATIENT # 81181
Study Drug: ROX-888
Dates of Study Drug Administration: 7/12/04 -7/16/04
SAE: Wound Hematoma (Second Hospital Admission)
Onset: (b) (6)

Patient 81181 in Study 2003-01 was a 72 year-old white male who underwent left total hip joint replacement on (b) (6) The patient was randomized to ROX-888 and received 13 doses of study drug. He terminated from the study as planned on 7/17/04 and he was discharged on (b) (6). Wound oozing was noted from (b) (6). On (b) (6) the patient was readmitted to the hospital because of a wound hematoma and recent onset of bilateral pedal edema which extended to both thighs. No venous thromboses were noted and the edema improved somewhat and he was discharged on (b) (6)
On (b) (6) the patient was readmitted for his wound hematoma and a draining sinus was noted. He underwent surgical washout to remove pus from the hip wound and the wound was debrided. Intravenous antibiotics were administered. The SAE of wound hematoma resolved on (b) (6) at which time the wound was reported to be "dry and healthy".

The SAE of wound hematoma was considered serious because it required hospitalization. The event was considered moderate in severity and the Investigator assessed the SAE as probably not related to study drug.

Impression
Although this subject was coded for the SAE of wound hematoma, he also had a wound infection requiring intravenous antibiotics and surgical washout. It is noted that the subject had wound oozing while on ROX-888 during his initial hospitalization.

STUDY 2003-01
PATIENT # 81552
Study Drug: ROX-888
Dates of Study Drug Administration: 4/26/05 - 4/28/05
SAE: Bleeding from Surgical Site
Onset: (b) (6)

Patient 81552 in Study 2003-01 was a 45 year-old white female who underwent total abdominal hysterectomy on (b) (6) The patient was randomized to ROX-888 and received 7 doses of study drug. She also received Clexane (enoxaparin) for prophylaxis of venous embolism. She terminated from the study early on 4/28/05 when she withdrew her consent. At the time of study

termination she was experiencing adverse events of nausea, pyrexia, and had blood-tinged mucus of both nostrils which was considered mild in severity and possibly related to study drug.

On (b) (6) the patient was hospitalized with bleeding from the surgical site and a postoperative hematoma. Cultures of the wound were taken and oral antibiotics were given prophylactically. The bleeding resolved on (b) (6) and she was discharged.

The SAE was considered serious because the patient required hospitalization, The event was considered mild in severity and the Investigator assessed the SAE as probably not related to study drug.

Impression
This patient was on enoxaparin which may have contributed to her developing a wound hematoma. There is no evidence that ROX-888 contributed to her hematoma

STUDY 2003-01
PATIENT # 81754
Study Drug: Placebo
Dates of Study Drug Administration: 2/23/05 -2/24/05
SAE: Postoperative Anemia
Onset: (b) (6)

Patient 81754 in Study 2003-01 was a 72 year-old Native Hawaiian/Pacific Islander/ Polynesian female who underwent left total hip joint replacement on (b) (6). The patient was randomized to placebo and received 3 doses of study drug. The patient terminated from the study early on (b) (6) because of an adverse event of mild incoherence which began on (b) (6) and resolved on (b) (6) and which was not considered to be related to study drug. The patient also experience anemia and rectal bleeding from hemorrhoids during this hospitalization. The patient was discharged to a convalescent home on (b) (6)

On (b) (6) the patient experienced fatigue and dyspnea and her hemoglobin level was 87g/L (normal values 115 - 165) she was hospitalized and given two units of packed red blood cells. Her hemoglobin on (b) (6) was 120 g/L. The SAE was considered as resolved on (b) (6) when the patient was discharged to home.

The SAE was considered serious because the patient required hospitalization. The event was considered mild in severity and the Investigator assessed the SAE as probably not related to study drug.

Impression
This subject on placebo had bleeding hemorrhoids which may have contributed to her developing a postoperative anemia.

STUDY 2001-03

PATIENT # (81) 899
Study Drug: 10 mg IN Ketorolac
Dates of Study Drug Administration: 9/17/02 - 9/19/02
SAE: Hematemesis
Onset: (b) (6)

Patient 899 (b) (6), 47-year-old Caucasian female, underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy on (b) (6). Patient completed 6 doses of study drug during the first 48 hours of study and completed the follow-up visit on 9/20/02. Patient had an uneventful recovery and was well until she saw her local MD on 10/03/02 complaining of headache and vomiting, which the MD thought was a UTI and treated her with antibiotics. Patient returned on 10/07/02 and MD changed diagnosis to wound infection and changed antibiotic to Penicilln. On (b) (6) patient admitted to hospital for "Hematemesis" which was listed as the SAE of "mild" intensity. SAE resolved and patient discharged home on (b) (6)

Impression
It is unlikely that 10 mg of intranasal ketorolac contributed to this patient developing hematemesis approximately three weeks after her last dose of study drug.

Summary of Serious Adverse Events
The 32 SAEs (23 ROX-888, 1 10 mg ketorolac, and 8 placebo) occurred in 29 patients (21 ROX-888, 1 10 mg ketorolac, and 7 placebo). All of the SAEs occurred in multiple dose efficacy Studies 2003-01, 2005-01 and 2001-03 except for one SAE (cardiac arrest) occurred in the pediatric pharmacokinetic study (ROX 2006-02). There was no evidence that intranasal ketorolac contributed at all to this subject's cardiac arrest. This 13 year old girl had a history of repaired Tetralogy of Fallot and had the cardiac arrest approximately three weeks after receiving a single dose of 15.5 mg of intranasal ketorolac during cardiac surgery. During surgery, the right ventricle was entered resulting in significant bleeding, hypotension, ventricular fibrillation and cardiac arrest.

There were six SAEs involving bleeding: 3 hematomas (ROX-888), 1 bleeding from surgical site (ROX-888 and enoxaprin), 1 postoperative anemia (placebo) and 1 hematemesis (10 mg IN ketorolac). There was no strong evidence that any of the SAEs were related to intranasal ketorolac. However, in two cases there was evidence of bleeding or wound oozing while the subject was on ROX-888 prior to the occurrence of the post-treatment SAE. Aside from bleeding other causes of SAEs in the ROX-888 group included: wound infection (3), pulmonary embolism (2), abdominal pain (1), pitting pedal edema (1), abscess in vaginal vault (1), lymphedema (1), DVT (1), shortness of breath (1), postoperative confusion (1), UTI (1), nausea and vomiting (1), small bowel obstruction (1), peritonitis (1), possible allergy - rash started over 10 days after receiving study drug (1), myocardial infarction (1) and cardiac arrest (1). The SAEs in the placebo group included: abdominal pain (2), chest pain (1), UTI (1), postop anemia (1), recto-vaginal fistula (1), pelvic fluid collection (1), DVT (1).

Analysis of Incidence of Blisters

The applicant reports that the incidence of blisters in the Sprix group was 2% compared to 0% in the placebo group. This appears to be based on using the preferred term which resulted in no blisters reported in the placebo group. However, when the verbatim term is used three subjects in the placebo group (81-174, 81-738 and 81-758 in study 2003-01) are identified with blisters. The blisters are described as around the wound or on the suture line. Using the verbatim term for the ROX-888 group, some blisters were described on the buttock (2), sacrum (1) and back (1). These blisters were likely due to pressure and friction. There was also one blister reported to be Herpes simplex. When these subjects are removed, there are 10 subjects (2.2%) remaining with blisters compared to 1.2% for placebo. Both treatment arms describe blisters around the wound. None of the blisters resulted in a SAE.

Conclusions

Review of the additional post-treatment SAEs does not change my overall safety impression of Sprix. There is no convincing evidence that the post-treatment bleeding SAEs reported in this submission were related to ROX-888. However, assuming the worst case scenario that the bleeding SAEs were drug related does not change my safety impression since postoperative bleeding at the surgical site was previously identified as a safety concern in my initial NDA review.

The apparent discrepancy in the incidence of blisters in the ROX-888 group compared to placebo group appeared larger due to use of the preferred term which missed several blisters in the placebo group and included blisters in the ROX-888 group that were most likely due to pressure/friction and Herpes simplex. When the incidence of blisters is recalculated taking into account these factors the discrepancy is only about 1%. I do not believe that this represents a significant safety issue especially considering that there were no SAEs due to blisters and the possibility of serious dermatologic adverse reactions is already included in the label.

On 5 October 2009, the final recommendation of "Withhold" for the manufacturing site was conveyed from the Office of Compliance. Therefore, I recommend a Complete Response for this application.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22382	ORIG-1	ROXRO PHARMA INC	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/

ROBERT A LEVIN
10/06/2009

ROBERT B SHIBUYA
10/06/2009

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA # **Supplement #**	22-382/000
Applicant Name	Roxro Pharma, Inc.
Date of Submission	December 5, 2008
PDUFA Goal Date	October 5, 2009
Proprietary Name / **Established (USAN) Name**	Sprix/Ketorolac tromethamine nasal spray
Dosage Forms / Strength	Intranasal spray/15% solution/15.75 mg/0.1 mL
Proposed Indication(s)	1. For the short term (up to 5 days) management of moderate to severe pain that requires analgesia at the opioid level
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Robert Levin, M.D.
Statistical Review	Feng Li, Ph.D., Dionne Price, Ph.D.
Pharmacology Toxicology Review	Newton Woo, Ph.D., Adam Wasserman, Ph.D.
CMC Review/OBP Review	Jack Leginus, Ph.D.
Microbiology Review	Robert Mello, Ph.D.
Clinical Pharmacology Review	Sayed Al Habet, R. Ph., Ph.D., Suresh Doddapaneni, Ph.D.
DDMAC Review	Twyla Thompson, Mathilda Fienkeng
DSI Review	Susan Leibenhaut, M.D., Tejashri Purohit-Sheth, M.D.
CDTL Review	Robert Shibuya, M.D.
OSE/DMEPA Review	Deveonne Hamilton-Stokes, R.N., BS.N., Todd Bridges, R.Ph.
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication ErrorsPrevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This application is a reformulation of ketorolac tromethamine for use via a novel route, intranasal administration. Ketorolac has been marketed for nearly 20 years and due to safety concerns that arose during postmarketing experience, use has been limited to no more than five days and there are a number of warnings for gastrointestinal bleeding, perioperative bleeding and contraindications for use in pregnancy due to bleeding risk that distinguish this product from other nonsteroidal anti-inflammatory drugs (NSAIDs). This memo will focus on these areas of concern as they relate to the novel route of administration.

2. Background

The applicant has submitted a 505(b)(1) application for a ketorolac tromethamine product via a new route of administration, nasal spray. Ketorolac has already been approved as a parenteral solution for intravenous and intramuscular administration and as an oral tablet. The reference drug for this application is Toradol, NDA 19-698, approved on November 30, 1989 and the reason this is a 505(b)(1) is that the applicant has submitted a letter providing right of reference to NDA 19-698.

Ketorolac tromethamine nasal spray was developed under IND 62,829 submitted on April 10, 2002.

3. CMC/Device

All necessary information about the drug substance was available by reference to Drug Master File (b) (4) which was found to be acceptable. Two identified impurities are adequately controlled at NMT 0.1%.

The drug product is formulated as a solution of ketorolac tromethamine, 15.75 mg/0.1 mL in a clear glass vial with a metered multi-dose spray pump. The drug product is manufactured as a low bioburden buffered solution, under (b) (4) conditions. The applicant does not plan to label it as sterile and the formulation does not contain any antimicrobial agents. EDTA is included as a (b) (4) There is a (b) (4) of (b) (4) of ketorolac plus an additional (b) (4) of ketorolac for the five required priming sprays. The overfill is necessary to ensure an adequate volume for the sprays. An in-use period of one day is necessary due to a reduction in the amount of product delivered beyond the first day of use.

The drug product was found to be photosensitive [redacted] (b) (4). The label will need to state that the product must be protected from light.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Stability testing supports an expiry of 24 months, refrigerated at 2-8ºC.

However, the manufacturing site inspections were not all acceptable. The Office of Compliance has classified the drug product manufacturer, Hollister Stier Laboratories, as "withhold".

The main issues with respect to cGMP are:

> The Drug Product manufacturer for NDA 22-382, Hollister Stier Laboratories, was inspected for GMP on 1/6/09 to 1/13/09. As a result, an FDA 483 was issued for: stability failures, initiation of practices prior to change approval by the QC Unit, no formal procedure for maintaining segregated vials for non-conforming material, no formal documentation of retention sample review, increase in a product's hold time [redacted] (b) (4) without formal approval from CDER, and Annual Product Reviews were not reviewed by the Quality Unit in a timely manner. The most recent inspection was conducted on 6/19/08 to 7/2/08 and resulted in an FDA 483 for failure to thoroughly review unexplained discrepancies, and a manufacturing process was not thoroughly evaluated to identify and correct possible sources of variability in critical process parameters. Because these issues have not been resolved by Hollister Stier, on 04-Aug-2009, the Office of Compliance made a recommendation of Withhold for the facility.

I concur with Dr. Leginus recommendation that the Office of Compliance recommendation of "Withhold" result in a Not Approvable finding for this NDA.

4. Nonclinical Pharmacology/Toxicology

The applicant has relied on reference to the Agency's prior findings for NDA 19-698, Toradol. Local tolerance and repeat-dose toxicology studies of up to 28 days were conducted in rats and rabbits. Target organ toxicities, notably gastrointestinal toxicities and renal changes, consistent with ketorolac were observed, however, there were no indications of adverse local toxicity in the nasal cavity or respiratory tract or additional safety concerns that arose from the nasal route of administration.

Additional studies were performed and successfully provided safety qualification for an oxidative degradant identified as (±)-5-benzoyl-1-keto-2,3-dihydro-1H-pyrrolizine (1-keto) that exceeded the ICH Q3B(R2) recommended threshold.

Dr. Woo noted that ketorolac itself demonstrated clastogenicity in the chromosomal aberration assay as described in the approved label.

Analysis of extractables and leachables of the nasal drug product revealed no detectable quantities of any chemical impurities from the vial or pump device.

As noted in Dr. Woo's review, labeling recommendations have been obtained from the Maternal Health Team. I concur with the conclusions reached by Dr. Woo that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Eleven clinical pharmacology studies were submitted in support of this NDA. Relative bioavailability studies show that the intranasal ketorolac has a pharmacokinetic profile that is similar in shape to intramuscular ketorolac, with an AUC of 73% and 60% compared to 15 mg and 30 mg intramuscular doses, respectively. The 15 mg and 30 mg doses of intranasal ketorolac are a little less than dose proportional. The use of intranasal oxymetazoline or fluticasone did not later the pharmacokinetic profile. The pharmacokinetic profile in elderly subjects was similar to younger patients with a 10% and 23% increase in Cmax and AUC, respectively. Taken with the greater risk for typical NSAID-associated adverse events in elderly patients, the applicant has proposed a reduction in dosing to 15 mg every 6 to 8 hours rather than 30 mg every 6 to 8 hours. A study of the distribution of the solution after intranasal administration using radiolabeled drug demonstrated that the product was delivered primarily to the nasal cavity and virtually none was delivered to the lungs.

Ketorolac is metabolized by hydroxylation followed by conjugation with glucuronic acid and excreted primarily by the renal route, with 60% of the dose excreted unchanged. The half-life is approximately 5 hours and Tmax is approximately 45 minutes.

I concur with the conclusions reached by the Dr. Al Habet that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

The product is not labeled as sterile and does not contain any antimicrobial agents. Manufacturing of the drug product is under (b) (4) conditions.

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Two Phase 2 and two Phase 3 efficacy studies were conducted and were reviewed in detail by Dr. Levin and Dr. Li and were summarized by Dr. Shibuya. Study ROX-2003-05, a Phase 2 study, demonstrated efficacy of a single dose of nasal ketorolac following third molar extraction and also demonstrated onset, based on time to meaningful pain relief, of 66 minutes and time to rescue of 360 minutes. Study ROX-2001-03, also a Phase 2 study, demonstrated efficacy of nasal ketorolac, compared to placebo, administered every 8 hours for over 48 hours then three times daily for up to five days in patients undergoing major surgery based on the summed pain intensity difference at 24 and 48 hours and the amount of morphine consumed. The primary outcome analysis was the total morphine consumption at 24 hours. The summed pain intensity difference over the first six hours after the first dose also demonstrated efficacy as compared to placebo. These outcomes were confirmed by Dr. Li.

The two Phase 3 studies, Studies ROX-2003-01 and ROX-2005-01 were similarly designed, randomized, double-blind, placebo-controlled, parallel-group, multiple-dose studies in patients with postoperative pain. Study ROX-2003-01 enrolled patients undergoing laparotomy or orthopedic surgery, and Study ROX-2005-01 enrolled patients undergoing laparotomy. Following surgery and after recovery from anesthesia, patients were started on a regimen of a patient controlled analgesia (PCA) regimen using morphine. In Study ROX-2003-01, on the first day of the study, the morphine was held and patients who reported a pain intensity score of at least 40 mm on a 100 mm visual analog scale (VAS) were randomized 2:1 to study drug or placebo and assessments were made for the first 6 hours to evaluate single-dose efficacy. There was no single-dose assessment in study ROX-2005-01. The dose of Sprix was 31.5 mg dosed every 8 hours in ROX-2003-01 and every 6 hours in Study ROX-2005-01. Details of the study protocols and conduct are available in the review by Dr. Levin. As noted in the reviews by Drs. Levin and Li, there was no attempt to measure pain prior to the administration of rescue. This could have impacted the outcome, inflating the effect of the study drug. Dr. Li explored this via statistical methods as described in his review and found this did not result in any notable effect. The applicant chose a summed pain intensity over 6 hours as the primary efficacy analysis, in spite of being advised by the Division that for a drug intended for multiple-dose use, the primary efficacy analysis must reflect a reasonable multiple-dose period, such as 48 hours. For the purposes of this efficacy analysis, the Division considered the summed pain intensity difference over 48 hours as the primary efficacy analysis.

As noted in the primary reviews, the summed pain intensity difference at 48 hours was statistically significantly better for active-treated patients compared to placebo-treated patients. In addition, the patients treated with placebo used more morphine by PCA than those treated with Sprix, amounting to a difference of approximately 20 mg over 48 hours in both studies. Of note, few patients in the studies, even those on placebo, discontinued for lack of efficacy, likely reflecting the availability of PCA morphine.

Dr. Levin points out that the availability of morphine and the use of an inpatient population reflect potential problems with the studies submitted in support of efficacy. Regarding the availability of morphine, Dr. Levin notes that while this could inflate the appearance of efficacy for the active treatment, the same is true for the placebo treatment. As both treatment groups had access to the morphine and efficacy was still demonstrated, and as single-dose

efficacy in the absence of morphine was demonstrated in Study ROX-2003-01 and single-dose study, ROX-2003-05 without concurrent morphine, the evidence for efficacy is acceptable.

Regarding outpatient use, Dr. Levin notes there was no efficacy data collected for those patients who received ongoing treatment with Sprix after the inpatient period of the studies. He feels the efficacy demonstrated with concomitant opioid use cannot be extrapolated to outpatient use in the absence of opioids and that there is no convincing evidence to support efficacy for multiple-dose use of in outpatients. I do not share this concern. Ketorolac has already been demonstrated to be an analgesic. In this application there is evidence of efficacy without concurrent use of an opioid as noted. This demonstration of efficacy was following a single dose and in an inpatient setting, however, there is no basis to support a concern that the nature of pain changes once a patient is discharged from the hospital. There is also no basis to support the idea that the evidence of efficacy during repeated dosing in the inpatient setting would not also be true in the outpatient setting. There is no data or evidence of rapid development of tolerance to the analgesic effect of nonsteroidal anti-inflammatory drugs in general, or ketorolac in particular. Therefore, I consider the efficacy data adequate to support a finding of efficacy for the proposed indication, "for the short term (up to 5 days) management of moderate to severe pain that requires analgesia at the opioid level."

Dr. Shibuya notes that with one imputation method, Dr. Li did not find a p-value of less than 0.05 in Study ROX-2005-01and notes that this could be construed as a problem. There is no requirement for studies to be able to demonstrate a statistically significant result for all potentially reasonable statistical methods. The positive finding using one appropriate method is sufficient and in this case, the reason for the difference in outcomes based on methods was well explained by Dr. Li.

(b) (4)

8. Safety

The intended patient population for Sprix is comparable to that for Toradol and the pharmacokinetic profile of Sprix shows that the Cmax and AUC are both lower compared to IM Toradol. Therefore, adverse reactions due to systemic exposure to ketorolac by Sprix would not be expected to be any worse than with IM Toradol and a safety database of 300-500 was requested to explore the adverse event profile of this new route of administration. The applicant submitted a safety database consisting of a total of 495 subjects who had received Sprix including 172 patients who were dosed for five days. The mean and median number of doses was approximately eight. The full extent of exposure is described in Dr. Levin's review. There were no deaths during the clinical trials for Sprix and the common nonserious adverse

events were not notably different from those described in the labeling for Toradol. These were reviewed in detail by Dr. Levin and will not be discussed further here. Nasal exams were conducted in a large number of subjects and while there were higher rates of nasal pain, erythema, congestion, erosions, and bleeding compared to treatment with placebo, these were not serious and were self-limited. Dr. Levin wrote that he believed an insufficient number of nasal exams were performed on subjects 65 years or older, as only 20 of these subjects exposed to Sprix had nasal exams. Given the lack of any notable findings in younger subjects and the lack of any particular findings in these 20 patients, I disagree and feel there is no need for further nasal examinations.

There were a number of serious adverse events. In the four Phase 2 and Phase 3 studies, there were 28 patients who experienced 38 serious adverse events out of a total of 828 patients. Dr. Levin had reviewed the serious adverse events in detail. Eight of 250 patients treated with placebo had serious adverse events, two of 43 patients who received the 10 mg IN ketorolac had serious adverse events and 18 of the 455 patients who received Sprix received had serious adverse events. The serious adverse events of note were related to bleeding. According to Dr. Levin's analysis, serious adverse events from any bleeding complication (i.e. vaginal hemorrhage, wound hematoma, post procedural hemorrhage, intestinal hemorrhage and post procedural hematoma) in the three multiple-dose efficacy studies occurred in 6/455 (1.3%) subjects in the Sprix group, 1/43 (2.3 %) subjects in the 10-mg IN ketorolac group and 1/250 (0.4%) subjects in the placebo group. Six of the seven patients treated with SPRIX underwent a surgical procedure and the seventh patient treated with SPRIX and the placebo subject received a blood transfusion. The applicant provided the same summary of the incidence of serious adverse events related to bleeding and hematoma but a slightly different analysis of treatment for the purpose of labeling:

… (b) (4)

This finding is not currently specified in the Toradol labeling, although there are additional warnings and contraindications than is present in the labeling for other NSAIDs. The following contraindications are in the Toradol package insert and is also proposed to be included in labeling for Sprix:

- Use as a prophylactic analgesic before any major surgery
- Use during the perioperative period in the setting of coronary artery bypass graft (CABG) surgery
- Use in patients with advanced renal disease or patients at risk for renal failure due to volume depletion
- Use in labor and delivery.
- Use in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis, or those for whom hemostasis is critical

As noted by Dr. Shibuya, Dr. Levin noted that only 59 patients received Sprix outside the hospital, with an average use of 3.4 doses. I agree with Dr. Shibuya, that with appropriate labeling, it would be acceptable for patients to use in the outpatient setting.

9. Advisory Committee Meeting

There as no advisory committee meeting for this NDA.

10. Pediatrics

As a new route of administration, the applicant will need to address the requirements of the Pediatric Research Equity Act. The current approved labels for the reference listed drugs indicate that ketorolac is not indicated in the pediatric population. It is important to note that the use of ketorolac is not contraindicated; it is not recommended because data related to use in pediatrics is owned by Roche who discontinued marketing these products.

The Pediatric Research Committee has agreed that Sprix must be studied from birth to age 16 years, 11 months. If efficacy data are available in the pediatric population for other formulations, efficacy could be bridged using pharmacokinetic data. An alternate route of administration should be considered for the youngest age strata (0-6 months).

11. Other Relevant Regulatory Issues

Audits of the clinical sites did not find any problems that would preclude use of the data based on inspections by the Division of Scientific Investigation.

There are no other unresolved relevant regulatory issues.

12. Labeling

The proprietary name Sprix was found acceptable by the Division of Medication Errors and Prevention.

The labeling was discussed with the applicant. All relevant warnings and contraindications from the Toradol packaging insert will be included in the labeling for Sprix. (b) (4)

There will be a medication guide for this product, the standard NSAID medication guide and, as a result, a medication guide-only REMS. This has been reviewed by OSE and has been found to be acceptable.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

The safety and efficacy data submitted support the use of Sprix for the proposed indication. The package insert adequately defines the risk and limitations of use, primarily established from experience with use of ketorolac via intravenous, intramuscular and oral routes.

Once the outstanding problems with the Drug Product manufacturer, Hollister Stier Laboratories, are corrected, and the withhold recommendation can be changed, the product can be considered for approval.

- Recommendation for Postmarketing Risk Management Activities

A medication guide-only REMS has been established.

- Recommendation for other Postmarketing Study Commitments

None.

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/s/

SARA E STRADLEY
10/05/2009

SHARON H HERTZ
10/05/2009

Cross-Discipline Team Leader Review

Date	27 August 2009
From	Robert B. Shibuya, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22-382
Applicant	Roxro
Date of Submission	5 December 2008
PDUFA Goal Date	5 October 2009
Proprietary Name / Established (USAN) names	SPRIX (ketorolac tromethamine nasal spray)
Dosage forms / Strength	Nasal spray, 15.75 mg/100 µLspray
Proposed Indication(s)	1. Short term (up to 5 days) management of moderate to severe pain, as a single agent or in combination with opioids
Recommended:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	
Primary Medical Officer Review	Robert A. Levin, M.D.
Statistical	Feng Li, Ph.D. Dionne Price, Ph.D.
Pharmacology Toxicology Review	Newton Woo, Ph.D. Adam Wasserman, Ph.D.
CMC Review	Joseph Leginus, Ph.D. Ali Al-Hakim, Ph.D.
Clinical Pharmacology Review	Sayed (Sam) Al Habet, RPh, Ph.D. Suresh Doddapaneni, Ph.D.
DSI	Susan Leibenhaut, M.D. Constance Lewin, M.D.
OSE/DMEPA	Deveonne Hamilton-Stokes, RN, BSN Denise Toyer, PharmD Carol Holquist, RPh

1. Introduction

SPRIX (identified as ROX-888 during development) is a reformulation of ketorolac tromethamine designed to be administered as a nasal spray. Throughout development, Roxro, the Applicant, had planned to use the 505(b)(2) approval pathway. However, Roxro has obtained right of reference to the data associated with Toradol, NDAs 19-698 (injectable) and 19-645 (tablets). Therefore, this is a 505(b)(1) application.

As a 505(b)(1) application, the identification of the referenced drug is less critical. However, for the purposes of consistency of labeling, it is important to note that the relevant innovator drugs, Toradol injectable and Toradol tablets, were withdrawn from marketing in 2005. In a December 19, 2008 Federal Register notice, FDA noted that Toradol was not withdrawn from marketing for reasons of safety or efficacy. The current Referenced Listed Drugs for the injectable and oral formulations are ANDA 75-222 (Bedford) and ANDA 74,761 (Mylan), respectively.

The Applicant submitted two adequate and well-controlled studies to provide the primary support for efficacy with two additional studies that complement the pivotal trials. The pivotal studies were designed with a primary efficacy endpoint of a summed pain intensity difference over 6 hours (SPID6) which is not consistent with the Division's current requirements for this type of analgesic study. Fortunately, the studies were conducted over several days and data to assess efficacy over a longer period of time and multiple doses were available. While both the primary medical reviewer (Dr. Levin) and statistical reviewer (Dr. Li) have concerns about the ad libitum use of background morphine in the pivotal trials (discussed in Section 8 of this review), they have concluded that sufficient data were submitted to support a finding of efficacy.

The clinical development program exposed approximately 500 patients and subjects to the product for up to 5 days. From the perspective of systemic toxicity, the adverse event profile was typical for a nonsteroidal anti-inflammatory drug (NSAID). Two findings of concern were identified. First, the rate of clinically meaningful bleeding (at the operative site, not the typical NSAID-related gastropathy) was more than three times higher in patients treated with SPRIX than placebo. These adverse events usually required the patient return to the operating room to achieve hemostasis. According to the available FDA reviews for Toradol, hemorrhage has been a concern for a long time with ketorolac. However, the relative risk of bleeding for ketorolac compared to comparable therapies has not been well assessed.

SPRIX clearly irritates the nose in a substantial number of patients, evidenced by relatively high rates of nasal pain, congestion, and erythema compared to placebo. Almost 6% of patients treated with SPRIX discontinued studies prematurely due to this adverse event. The nasal symptoms and signs appear self-limited and, particularly in light of the limit of use being 5 days, do not substantially affect the risk-to-benefit ratio for this product.

There are two other key points to be included in the background for SPRIX. This product uses a (b) (4) spray device. The device requires 5 pumps to prime then no further priming. The Applicant found that, when the unit is unused after priming, the delivered dose decreases with

the duration of nonuse. Thus, the Applicant has proposed that the labeling indicate that the device be discarded and a new device used every 24 hours. While it is possible that patients will not discard the device if it contains solution, the concern is one of efficacy not safety. Thus, with adequate patient education, the 24-hour limitation is acceptable.

Last, Dr. Levin notes that there are limited safety data with SPRIX when used in the outpatient environment. He notes that, presumably, patients are likely to use SPRIX instead of ketorolac tablets because their oral intake might be poor. Low effective intravascular volume is a known risk factor for NSAID-related nephrotoxicity due to the differential effects on the afferent and efferent arterioles from the relatively low levels of prostaglandin after NSAID administration. While no renal signal was identified in the 59 patients treated as outpatients for an average of 3.4 doses (less than one day), Dr. Levin has recommended restricting use to the inpatient setting because he does not think the exposure in clinical development reflects outcomes in large populations. I believe that the product can be labeled to minimize the risks of prescribing to patients at risk for low effective intravascular volume.

2. Background

Dr. Robert Levin, the primary clinical reviewer, has summarized the regulatory history for this Applicant in detail in his excellent review. I emphasize the following issues.

1. In a March 2003 meeting, the Agency indicated that (b) (4) (b) (4) is not an indication in itself. The Agency also noted that analgesics for acute pain must be tested in both the inpatient and outpatient setting. Adequate and well-controlled studies will have to be submitted to support a NDA.
2. In June 5, 2004 meeting, the Agency noted that single-dose efficacy must be established for patients off and on patient controlled analgesia and that geriatric patients should be studied.
3. In the July 17, 2004 End-of-Phase 2 meeting, the Applicant was told to establish efficacy beyond 24 hours and that the Phase 2 data suggest that an appropriate dosing interval is 6 hours. The safety database size should be more than 400 patients.
4. In an advice letter dated May 19, 2005, the Applicant was advised to provide a sizable number of patients with ENT exams after 5 days of dosing.
5. At the Pre-NDA meeting held October 4, 2007, the Applicant was told that their proposed indication (moderate to severe pain) was inappropriate.

As will be discussed in greater detail in the clinical trials section, the ketorolac moiety has some unique qualities from the perspective of its use.

The first ketorolac-containing product was first approved in 1989 for intramuscular injection. It was the first injectable NSAID approved for pain and was the only injectable NSAID approved for the indication of pain for 20 years until the approval of Caldolor (ibuprofen injection) in 2009. Indomethacin was approved as an injectable formulation for closure of a patent ductus arteriosis in 1985 and an injectable ibuprofen was approved for the same indication in 2006.

As noted in Dr. Levin's review, ketorolac has been the subject of substantial safety concerns, particularly related to the adverse event of GI bleeding. Because of this concern, ketorolac is also the only NSAID whose label limits use to a maximum of 5 days. Ketorolac was also the subject of a large observational study that confirmed its GI and renal risks. A description of this study appears in approved labeling for ketorolac-containing products.

While the Agency has provided a number of guidance meetings for the Applicant, the Applicant has chosen not to take certain advice, most significantly the advice to use a primary efficacy endpoint that assess measures pain intensity over 24 to 48 hours to assess efficacy which was explicitly stated at the July 17, 2004 End-of-Phase 2 meeting.

It is important to note that, on 10 August 2009, less than two months prior to the PDUFA date, the Applicant submitted brief line listings for 24 serious adverse events (SAEs) that had occurred as much as five years prior to NDA submission. On 12 August 2009, Project Manager, Jessica Benjamin and I conducted a teleconference to discuss this with Roxro. Roxro said that an auditor at their New Zealand site had identified these SAEs and asked Roxro why they had not been submitted in the NDA. Roxro indicated that, since they occurred post-study (but within 30 days of the end-of-study), their protocol did not require them to submit the reports. The auditor checked the protocol and found that Roxro was wrong. Roxro then submitted the SAEs.

I asked Roxro whether they were aware of these 24 SAEs at the time of NDA submission and the Applicant responded in the affirmative. I told Roxro that they were required to submit all safety data with the NDA, regardless of what their protocol said. I also requested case report forms and narratives for these SAEs. At the time of finalization of this review, this information has not been submitted.

3. CMC/Device

The Chemistry/Manufacturing/Controls (CMC) review was conducted by Joseph Leginus, Ph.D. with a secondary review by Ali Al-Hakim, Ph.D.

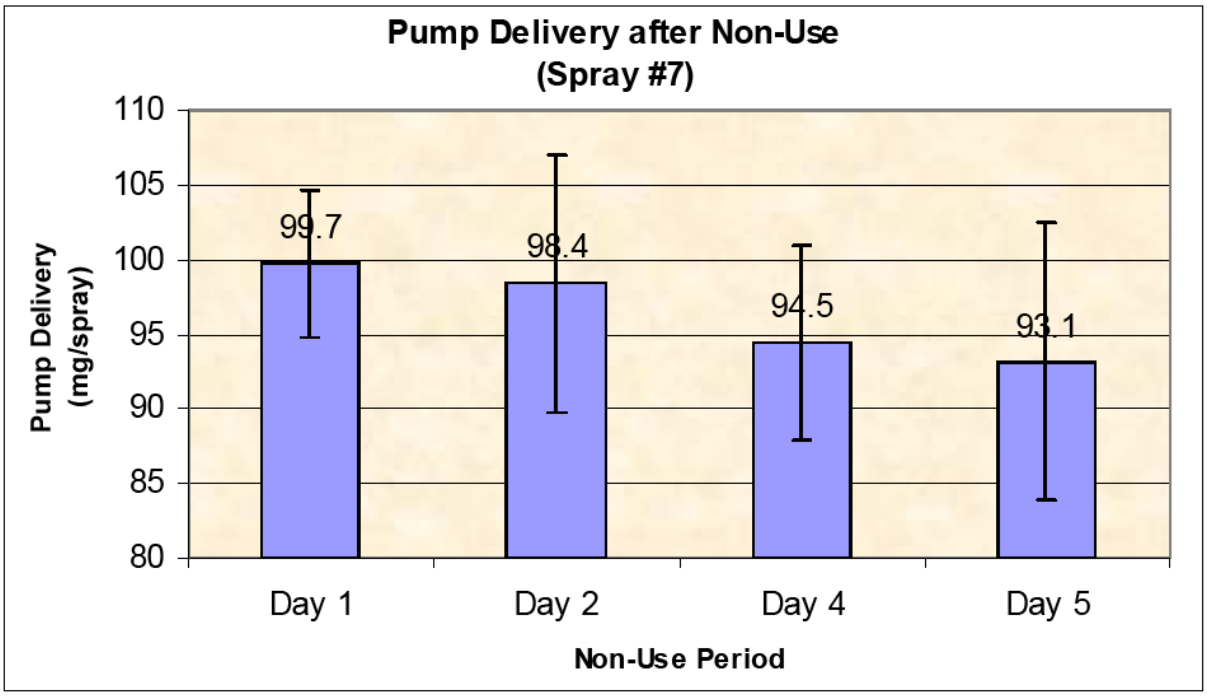
The drug substance is ketorolac tromethamine. During characterization of the drug substance impurities, a 1-hydroxy and 1-keto impurity were identified which were potential structural alerts. These impurities will be further discussed in the Pharmacology/Toxicology section of this review.

The drug substance is formulated in a simple, preservative-free aqueous solution and filled into a (b) (4) pump. Since the formulation is preservative-free, the product is filled under (b) (4) conditions. While the applicant originally intended to deliver 15 mg/100 µL spray, (b) (4) the applicant learned that 15.75 mg was actually delivered.

The pump reservoir contains (b) (4) which is sufficient for one day of dosing (8 x 100 µL sprays) + priming volume (5 pumps to prime, no reprime necessary). The labeling contains a requirement for the pump to be discarded 24 hours after initial use because the applicant found that the dispensed dose decreases with time and only the during first24-hour interval was a volume dispensed that was within specification.

Figure 1, below, shows summary data from a study where the device was opened, primed, six sprays dispensed, then left to sit for up to five days.

Figure 1: Amount dispensed (mg) for spray #7, following rest periods (sprayer opened, primed, sprayed x 6, then left unused)



Source: Dr. Leginus' review, page 27/71 of the pdf file

Figure 1 shows that the weight of spray dispensed decays with nonuse time. Dr. Leginus notes that the number of out-of-specification sprays rose from 2, 3, 6, and 6 for 1, 2, 3, and 5 days of nonuse, respectively (n=12/condition).

On 13 May 2009, the CMC review team submitted a request for information containing a total of seven issues related to documentation, drug product specifications, information regarding priming studies, and justification of the specification for the 1-keto impurity. The applicant has adequately responded to those queries.

INSPECTIONS

At this time, Drs. Leginus and Al-Hakim have recommended Not Approvable from the CMC perspective. This is based on a) an Office of Compliance recommendation of "Withhold" following the 26-Mar-2009 inspection of the drug product manufacturer, Hollister Stier Laboratories, b) a scheduled inspection of the finished dosage release tester, (b) (4)

(b) (4) (b) (4) (planned completion 20-Aug-2009), and c) an assigned, but not yet completed inspection at a finished dosage tester, (b) (4) (b) (4) Acceptable cGMP recommendations are required for all manufacturing and testing facilities before approval.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review was conducted by Newton Woo, Ph.D. with a secondary review by Adam Wasserman, Ph.D.

Given that Roxro obtained right of reference to the data generated and submitted by Syntex/Roche for Toradol (NDAs 19-698 and 19-645), the applicant limited its toxicology program to the new route of administration in this NDA.

There were two key repeat-dose local irritation and toxicology studies conducted, one in rats and one in rabbits. Briefly, while NSAID-related adverse events (predominantly gastrointestinal and renal) were observed, no formulation or administration-specific issues were identified.

As noted in the CMC review, a 1-keto impurity (an oxidative degradant) was identified in the drug substance that exceeded the qualification threshold. The degradant was negative in the Ames test but positive in the *in vitro* chromosomal aberration assay in CHO cells with metabolic activation. However, given that ketorolac itself has clastogenic properties, the 5-day limit for exposure, and a similar toxicological profile between ketorolac and ketorolac spiked with the 1-keto impurity in the 14-day rat toxicology study, the Pharm/Tox team felt that the clastogenecity finding of the 1-keto degradant would not be expected to present a risk to the intended population.

Drs. Woo and Wasserman have recommended approval from the pharmacology/toxicology perspective.

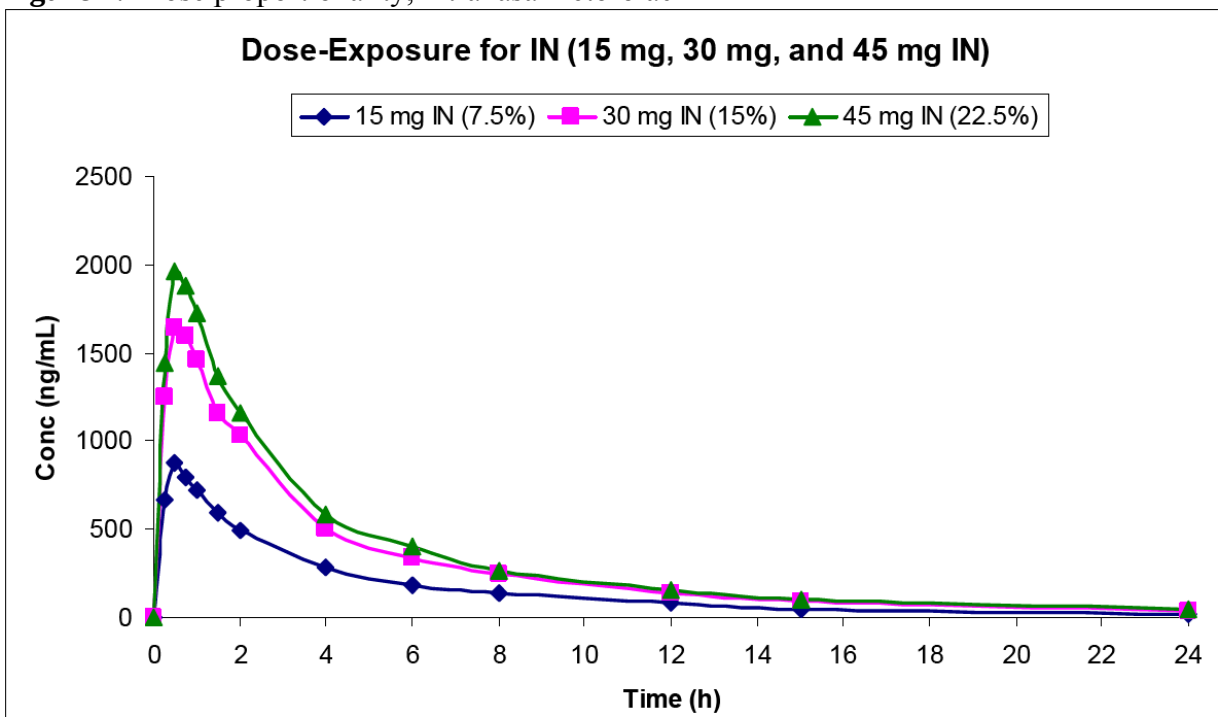
5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was conducted by Sayed Al Habet, RPh, Ph.D. with a secondary review by Suresh Doddapaneni, Ph.D.

The Applicant conducted 11 clinical pharmacology studies to support this application. Much of the clinical pharmacology work was related to developing a formulation with the goal of approximating blood levels that fell between those achieved after 15 and 30-mg intramuscular injections of ketorolac. To achieve this goal, the Applicant varied the concentration of the ketorolac between 1.5% and 22.5%, keeping the administered volume constant. (b) (4) and that 30 mg dosed at a concentration of 15% had exposures falling between the exposures of 15 and 30 mg by intramuscular injection. Multiple-dose pharmacokinetic studies of the optimized formulation showed that steady-state was reached within 24 hours.

Figure 2 shows results from a dose-proportionality study where the Applicant varied the concentration of ketorolac in the nasal spray. The figure shows that although there was an increase in exposure, dose-proportionality was not demonstrated above 30 mg.

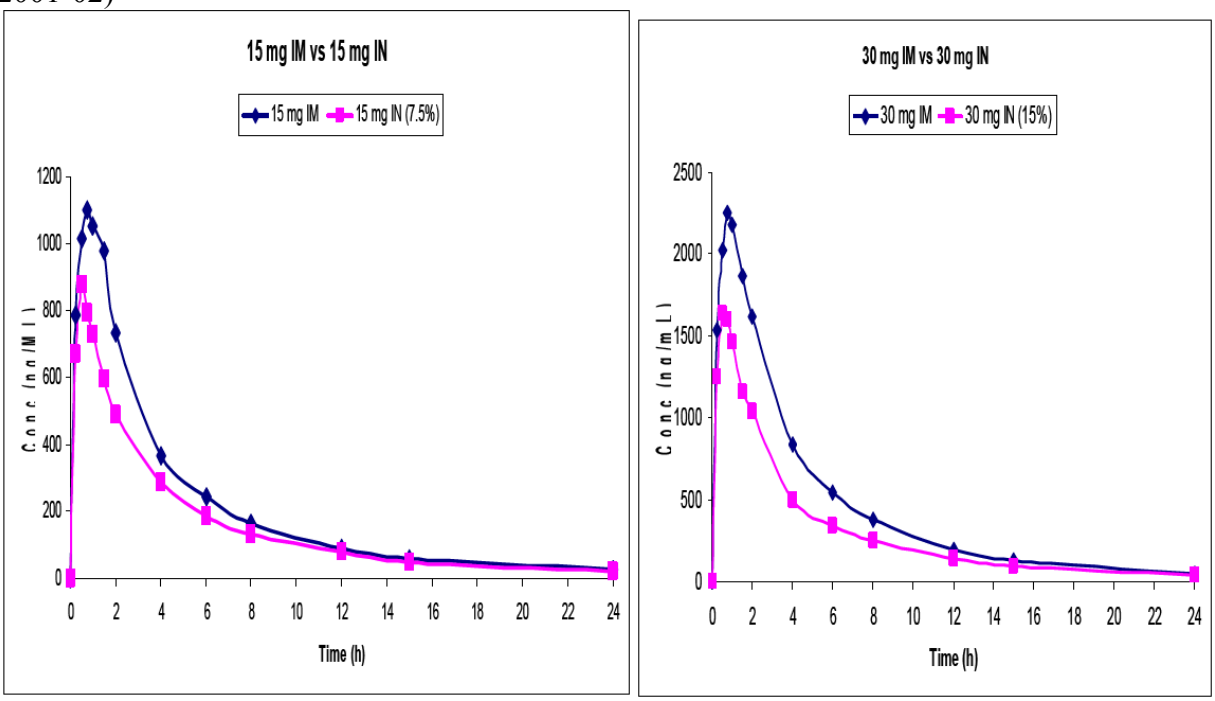
Figure 2: Dose proportionality, intranasal ketorolac



Source: Dr. Al Habet's review, page 5/139

Figure 3 shows a comparison of the concentration-time curves for both 15- and 30-mg doses of ketorolac delivered intramuscularly and intranasally. While not shown on the same figure, the 30-mg intranasal curve approximates the 15-mg intramuscular curve.

Figure 3: Relative bioavailability, intranasal versus intramuscular ketorolac (Study ROX-2001-02)



Source: Dr. Al Habet's review, page 4/139

A safety concern that had been articulated during development was whether the drug was delivered to the lung in appreciable amounts. The applicant addressed that concern in a study in healthy volunteers where radiolabeled ketorolac was administered intranasally and the volunteer underwent scintigraphy. A negligible amount (<0.5%) of the administered dose was delivered to the lungs.

Because substantial numbers of patients could be already on intranasal drugs with the potential to interact with the absorption of SPRIX, the Applicant conducted interaction studies where either fluticasone or oxymetazoline was administered prior to SPRIX and the absorption of ketorolac was assessed. There was no clinically significant difference when SPRIX was administered following either of these drugs. Fluticasone was dosed in volunteers with and without allergic rhinitis and neither condition changed the exposure to ketorolac.

The Applicant conducted a special populations study, comparing the pharmacokinetics of a single dose of SPRIX in young and elderly patients. While the pharmacokinetics were not different, because of the higher toxicity that is recognized in elderly patients with the ketorolac moiety, Drs. Al Habet and Doddapaneni have concurred with the reduction of dose (50%) proposed by the Applicant for the elderly population which is consistent with the dosing in elderly for the oral and injectable ketorolac products.

Drs. Al Habet and Doddapaneni have recommended approval from the Clinical Pharmacology perspective.

6. Clinical Microbiology

This review was pending at the time of finalization of this review. Dr. Robert Mello is the microbiology reviewer.

7. Clinical/Statistical- Efficacy

The primary clinical review was conducted by Robert Levin, M.D. and the primary statistical review was conducted by Feng Li, Ph.D. with concurrence from Dionne Price, Ph.D.

The SPRIX clinical development program consisted of four efficacy studies, two of which primarily supported a finding of efficacy.

Studies 2003-01 (Study 301) and 2005-01 (Study 501) support the efficacy of SPRIX. These were randomized, double-blind, placebo-controlled, parallel-group, multiple-dose studies in patients with pain status post laparotomy (Study 501) and pain following laparotomy or orthopedic surgery (Study 301). Study 301 included orthopedic surgery procedures to capture some elderly patients.

Briefly, patients underwent the qualifying surgery, most commonly open hysterectomy. Upon recovery from anesthesia, a patient controlled analgesia (PCA) regimen using morphine was started. Patients with a pain intensity score of at least 40mm on a 100 mm visual analog scale (VAS) were randomized 2:1 to Sprix or placebo, 31.5 mg either every 8 hours (Study 301) or every 6 hours (Study 501). Pain intensity was collected with each dose of study drug. Study 301 varied from Study 501 in that, on the morning of the first postoperative day, the PCA was stopped. When the pain reached at least 40/100mm, the dose of study drug was administered and single-dose analgesic parameters (onset of action, duration of action) were assessed.

Despite the Agency's advice to select a primary efficacy endpoint assessing pain intensity over longer periods of time, the Applicant elected to select a summed pain intensity difference (SPID) over the first 6 hours as the primary efficacy endpoint for both studies. Because the standard for approval is to assess multiple-dose efficacy over 24 to 48 hours, the Applicant was asked to reanalyze the data using a SPID24 or SPID48 as the endpoint. Dr. Feng Li, the FDA statistical reviewer, conducted analysis of SPID24 and SPID48 endpoints using several imputation schemes.

Table 1, from Dr. Li's review, shows the Applicants SPID24/48 analyses and Dr. Li's analyses using baseline observation carried forward (BOCF), last observation carried forward (LOCF), and a mixed LOCF/BOCF (worst value for adverse events and lack of efficacy and LOCF for all other dropouts) scheme for Study 301.

Table 1: SPID24 and SPID48 analyses, Study 301

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: Dr. Li's review, page 18/37

Study 301 showed evidence of efficacy, regardless of the endpoint used or method of imputation.

The applicant was interested in a claim for (b) (4) - (b) (4) Table 2 shows the total morphine consumption for various time periods during the study.

Table 2: Morphine consumption, Study 301

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: Dr. Li's review, page 19/37

Less morphine was used in patients treated with SPRIX than placebo. There were certain peculiarities regarding how morphine consumption was collected (specifically, once a patient prematurely discontinued from the study, no further morphine consumption data were collected; those data were extrapolated). Since both the active and placebo arms were subject to that procedure, potential non-random effects should have been minimized via randomization.

Dr. Li also expresses concern regarding the high proportion of patients with extrapolated pain intensity (who dropped out prior to completing 48 hours of therapy or if they used oral opioid rescue). In Study 301, the proportion of patients with extrapolated pain intensity were equal between arms (~40% at 48 hours), thus the potential impact of a large amount of imputed data to affect one treatment group more than the other should be minimal.

Table 3 shows the Applicant's reanalysis of the SPID24/48 and Dr. Li's analysis using various imputation schemes.

Table 3: SPID 24 and SPID 48 analyses, Study 501

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: Dr. Li's review, page 22/37

Study 501 was positive by both BOCF and LOCF imputation schemes but statistical significance was lost (p=0.138) when a LOCF/BOCF imputation scheme was used. Dr. Li showed that the reason for the loss of statistical significance was that the proportion of extrapolated data was higher in patients treated with placebo (85% versus 92% at 48 hours).

In the context of the Agency's previous findings of efficacy for the ketorolac moiety, the fact that Study 301 was unequivocally positive, and the fact that this study was positive by both LOCF and BOCF, I believe that Study 501 should be considered a positive study.

In Study 501, again, the applicant was interested in morphine use between the groups. Table 4 summarizes the morphine PCA consumption in the study.

Table 4: Morphine consumption, Study 501

	Amount of Morphine Used (mg)		
Time Interval	**ROX-888**	**Placebo**	***P*-value**
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: Dr. Li's review, page 24/37

Again, Study 501 shows that patients treated with SPRIX used less background morphine PCA. The applicant did not compare the incidence of opioid-related adverse events so there is no data to suggest that this difference in the amount of morphine used has any clinical significance.

The Applicant submitted two Phase 2 studies as supportive data. Study 2001-03 was a smaller dose-ranging study in patients status post abdominal surgery. It is of note that this study included a 10-mg dose of intranasal ketorolac. That dose did not show evidence of efficacy. I note that the primary efficacy outcome for Study 2001-03 was a comparison of morphine consumption and the applicant purports that the 31.5mg dose of SPRIX was superior (used less morphine) than the placebo or 10-mg groups. In Study 2001-03, pain intensity data were collected, sufficient to calculate summed pain intensity differences. Table 5 summarizes the SPIDs from Study 2001-03.

Table 5: Study 2001-03

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

Source: Dr. Li's review, page 13/37

Study 2001-03 justifies the selection of a 31.5 mg dose; the lower dose had a negligible effect.

The last study of import is Study 2003-05, a single-dose oral surgery study. This study showed that (at least as a single dose), SPRIX is effective in monotherapy. It also supported the dosing interval of 6 hours; the median time to rescue was 360 minutes for SPRIX. Table 6 shows the pain intensity difference data for this study.

Table 6: SPID8, Study 2003-05 – single-dose dental surgery

Parameter	Placebo n=40	ROX-888 n=40	*P*-value[a]
SPID4, mean (SE)	-46.7 (13.5)	90.3 (16.4)	<0.001
SPID6, mean (SE)	-76.7 (21.1)	120.5 (24.7)	<0.001
SPID8[b], mean (SE)	-105.2 (29.1)	136.7 (33.0)	<0.001
Peak PID, mean (SE)	4.6 (3.7)	38.4 (4.3)	<0.001

Source: Dr. Levin's review, page 69/122

As Drs. Levin and Li point out, the pivotal trials permitted unlimited use of morphine via patient controlled analgesia (PCA) in the population studied (post-laparotomy and post-orthopedic surgery patients). While the ad libitum use of background opioid is cause for concern regarding whether SPRIX would be effective as monotherapy, the Applicant did conduct the single-dose study in patients with pain following oral surgery that showed that ketorolac alone was superior to placebo. Furthermore, from the perspective of regulatory precedent, per the package insert, the innovator of the original ketorolac products (Syntex), conducted studies under similar circumstances to support a finding of efficacy. In light of the positive single-dose study, Roxro has demonstrated that SPRIX is effective.

8. Safety

The review of safety was also conducted by Dr. Levin. Please see his excellent review for details. For the most part, the adverse event profile for SPRIX was consistent with that of a NSAID. This review will focus on the specific safety issues identified in the clinical development program which were bleeding at the operative site and local nasal irritation.

Adequacy of exposure:

The total database size was 495 patients who received at least one dose of SPRIX which met the Division's requirement of at least 400 patients. The number of patients who received five full days of treatment with SPRIX was 172 (35%).

A total of 59 elderly patients (≥65 years of age) were exposed to SPRIX. Elderly patients had somewhat higher rates of symptomatic complaints related to the nose although those complaints appear to be self-limited. Dr. Levin notes that only 20 elderly patients had nasal exams. While Dr. Levin makes a valid point about the limited amount of safety data in elderly patients, given the short duration of treatment for SPRIX and self-limited nature of the nasal adverse events observed, I do not consider the safety evaluation in the elderly population to be inadequate.

Dr. Levin notes that the total number of patients who received SPRIX outside the hospital was 59 who received an average of 3.4 doses, less than one day of dosing. He believes that the available data do not support safe use in the outpatient setting due to small numbers and duration of therapy. While the outpatient experience with SPRIX is modest, if the product is appropriately labeled, I believe SPRIX can be safely used in the outpatient setting.

Bleeding complications:

As noted by Dr. Levin, ketorolac has been the subject of postmarketing safety reviews and was the subject of a large observational study to characterize its safety. Ketorolac was associated with high rates of serious GI bleeding and renal adverse events which resulted the limitation of use to 5 days or less. In addition, ketorolac tablets have a peculiarity in the labeling whereby administration of the oral dosage form is only permitted as follow-on therapy after being started on parenteral ketorolac. This limitation is, presumably, to minimize widespread outpatient use.

Ketorolac is also unique among the NSAIDs in that it carries additional warnings about the risk of non-GI bleeding which reads:

> **RISK OF BLEEDING**
> • Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding (see **WARNINGS** and **PRECAUTIONS**).

It is important to note that Caldolor (ibuprofen injection, approved for pain and fever) does not carry a similar warning.

Dr. Levin has covered the adverse events related to bleeding around the operative site in detail in his review and I summarize the key points below.

- Serious adverse events related to bleeding at the operative site were observed at more than three times the rate of placebo in patients treated with SPRIX or 10 mg of intranasal ketorolac [8/498 (1.5%) vs 1/250 (0.4%)] .
- Six patients required reoperation to address the bleeding.
- Evidence of increased bleeding in patients treated with SPRIX included higher incidences of decreases in hematocrit, anemia being reported as an adverse event, blood transfusions, and follow up hemoglobin levels <7 g/dL.

Dr. Levin notes that postoperative bleeding concerns were also articulated in a 1994 supplement to the Toradol NDA although, unfortunately, the bleeding risk was poorly characterized at that time.

Complaints related to the route of administration:

Toxicity associated with the intranasal route of administration was evaluated by solicitation of adverse events, a questionnaire 14-days post-study about nasal and cardiovascular safety, and ENT exams.

Adverse event data were collected in all patients. End-of-study ENT exams were conducted in Studies 301 and 501 and an exam 14-days after drug discontinuation was conducted in Study 301. Exam data exist for approximately 400 patients on-study and at end-of-study and for approximately 300 patients at the 14-day follow up. Approximately 320 patients completed the questionnaire.

Briefly, the nasal safety data show that treatment with SPRIX is associated with higher rates of nasal pain, erythema, congestion, erosions, and bleeding (or variations thereof) than treatment with placebo. These complaints resulted in patients discontinuing use at a rate of 5.9%, more than double that of placebo. The events appear to be self-limited.

Summary:

There are two substantive safety concerns. There is direct evidence of substantially higher rates of clinically significant bleeding in patients treated with ketorolac than placebo. Unfortunately, we do not know how those rates compare to the approved formulations of ketorolac.

The other safety concern is more theoretical. Dr. Levin has recommended that the use of SPRIX be limited to inpatients for several reasons but, from the perspective of patient safety, to mitigate against nephrotoxicty in patients who might be intravascularly depleted. While volume status can be more carefully managed in the inpatient setting than the outpatient setting, this product can be appropriately labeled to emphasize that patients must have good oral fluid intake to be candidates for SPRIX therapy as outpatients.

9. Advisory Committee Meeting

There was no Advisory Committee meeting held for this product.

10. Pediatrics

As a new route of administration, SPRIX triggers the Pediatric Research Equity Act (PREA). The current approved labels for the reference listed drugs [from Bedford (IV) and Mylan (tablets)] indicate that ketorolac is not indicated in the pediatric population. It is important to note that the use of ketorolac is not contraindicated; it is not recommended because data related to use in pediatrics is owned by Roche who discontinued marketing these products.

Thus, Roxro will have to fulfill the PREA requirement. The Pediatric Research Committee (PeRC) has recommended that SPRIX be studied from birth to age 16 years, 11 months. If efficacy data are available in the pediatric population for other formulations, efficacy could be bridged using pharmacokinetic data. PeRC was concerned about the delivery of the drug in the youngest age strata (0-6 months) and recommended that an alternate route of administration be considered.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigations inspected three clinical sites and found them acceptable.

12. Labeling

I concur with the labeling recommendations made by the other disciplines. Information to be emphasized in the labeling includes:

- Indicate that patients must be carefully selected to minimize the risks and consequences of post-operative hemorrhage. Warnings about the potential for hemorrhage should appear in the Boxed Warning, separate from the GI warnings.
- Labeling should emphasize the need for good hydration in patients treated with SPRIX. In addition, the label should indicate that healthcare professionals must manage the intravascular volume with care to minimize the risks of nephrotoxicity.
- Change the indication for consistency with the other ketorolac-containing drugs (moderately severe acute pain).
- Eliminate any references to (b) (4) - (b) (4)
- Maximize the probability that patients understand that the product must be discarded within 24 hours of priming, presumably in the Medication Guide.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  Complete Response. As noted by Drs. Leginus and Al-Hakim, the drug product facility is not acceptable. Also, at the present time, the review of the recently reported Serious Adverse Events has not been completed. I note that the microbiology review is pending at this time.

- Risk Benefit Assessment

  Roxro has met the requirement for efficacy. While I share Drs. Levin's and Li's concerns that the product was largely used as adjunctive analgesia in the pivotal trials, I note that the innovator product was tested under similar circumstances. Furthermore, SPRIX was effective as monotherapy in a single-dose, third-molar study. Also, even though substantial amounts of morphine were used in Studies 301 and 501, patients treated with SPRIX used less morphine and experienced greater analgesia than patients treated with placebo.

  Dr. Levin has shown that SPRIX is associated with a substantial risk of postoperative bleeding. Apparently, this finding has vexed Agency reviewers since the Toradol IV supplement in 1994 but the risk has not been well characterized. We now have data showing that the risk of substantial hemorrhage in patients treated with ketorolac is more than three times that of patients treated with placebo. The actual rate of serious bleeding at the operative site was 1.5% in controlled clinical trials. This risk should be able to be mitigated and the risk-to-benefit ratio made favorable with strong language about the risks of bleeding and appropriate patient selection being conveyed in labeling.

  As noted above, the review of the recently reported SAEs in also not complete.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  As an NSAID, this will require a Medication Guide and a Medication Guide-only REMS.

- Recommendation for other Postmarketing Requirements and Commitments

  Presuming the new SAEs do not substantially change the safety profile for SPRIX, it would be helpful to better understand the risks of postoperative hemorrhage with this product. The Agency should note this concern and reserve the option of requiring comparative postmarketing studies, particularly now that Caldolor (ibuprofen injection) is now approved.

- Recommended Comments to Applicant

  The CMC deficiency must be conveyed to the Applicant and I defer to Drs. Leginus and Al-Hakim for the wording of the comment(s).

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22382	ORIG 1	ROXRO PHARMA INC	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/

ROBERT B SHIBUYA
08/27/2009

CLINICAL REVIEW

Application Type	NDA
Application Number	22-382
Priority Designation	Standard
Submit Date	05 December 2008
Received Date	05 December 2008
PDUFA Goal Date	05 October 2009
Division	Division of Anesthesia, Analgesia and Rheumatology Products
Reviewer Name	Robert Levin, M.D.
Review Completion Date	24 July 2009
Established Name	Ketorolac tromethamine
(Proposed) Trade Name	SPRIX®
Therapeutic Class	Nonsteroidal anti-inflammatory drug (NSAID)
Applicant	ROXRO PHARMA Inc.
Formulation	15.75 mg per 100 µL intranasal spray
Proposed Dosing Regimen	For adults less than 65 years of age: 31.5 mg (2 sprays) every 6 to 8 hours For adults 65 years of age or older: 15.75 mg (1 spray) every 6 to 8 hours
Proposed Indication	Short term (up to 5 days) management of moderate to severe pain, as a single agent or in combination with opioids
Intended Population	Adult patients who require short term analgesia

TABLE OF CONTENTS

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Given the approved status of ketorolac tromethamine injection (ANDA 75-222, the current referenced listed drug) and ketorolac tromethamine tablets (ANDA 74,761, the current referenced listed drug), originally markeded as Toradol®, I recommend an **Approval** action for the subject of the current application, Sprix® (ketorolac tromethamine) NDA. I recommend a slightly different indication than that proposed by the Applicant. The indication for which I think the data submitted support approval is "the short term management (maximum 5 days) of moderately severe (b) (4) pain (b) (4) I further recommend that appropriate, strong warnings reflecting the increased risk of postoperative bleeding be included in the label.

This application contains sufficient data from two adequate and well-controlled Phase 3 studies (Study 2003-01 and Study 2005-01) to support a finding of efficacy and safety for the above indication. Both studies demonstrated a statistically significant reduction in postoperative pain using the SPID 6, the primary endpoint, with pain measured on a 100 mm visual analog scale. Efficacy was also established with the SPID at 24 and 48 hours.

The safety profile of this new intranasal formulation of ketorolac is consistent with other NSAIDs except for the added risk of nasal adverse events related to the route of administration and an increased risk of postoperative bleeding. In general, nasal adverse events appeared to be self-limited in subjects under 65 years of age. For subjects 65 years of age and older an insufficient number of nasal exams were performed to fully assess nasal safety but the available data suggests that nasal adverse events in the elderly are also self-limited.

All NSAIDs can increase bleeding and this effect was observed in the two pivotal postsurgical pain studies where the incidence of SAEs due to bleeding was increased. The proposed label does not contain an adequate warning regarding the risk of bleeding. The approved label for ketorolac provides a more acceptable Boxed Warning that states ketorolac tromethamine inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding. The label should also indicate that serious adverse events due to bleeding occurred more frequently with Sprix compared to placebo and sometimes required blood transfusion and/or additional surgery.

As discussed in Section 7 (page 99) of this review, postoperative bleeding has been a concern with ketorolac tromethamine since at least 1994. As discussed in Section 2.3 (page 13) of this review, Toradol has undergone a postmarketing safety review on at least two occasions. The risks of postoperative bleeding have not been well defined. Given the long history of use of the ketorolac moiety, I do not believe that the risks of ketorolac use outweigh the benefits. However, the label should clearly reflect the increased risk of postoperative bleeding and the need to exclude subjects with a propensity for bleeding or unable to tolerate bleeding complications.

The recommendation for restricting Sprix use to an inpatient setting is based on safety concerns and lack of adequate outpatient safety and efficacy data. The outpatients most likely to use Sprix, those with poor oral intake, were not studied and run a greater risk of developing renal failure. The approved label for ketorolac cautions against administering the drug to volume depleted subjects due to the risk of renal failure. Subjects with poor oral intake are likely to be volume depleted and therefore at risk for developing renal failure. The outpatient safety database was too small to assess this risk since only 59 subjects received intransal ketorolac as outpatients for an average of 3.4 doses.

Outpatient use of Sprix may also result in a greater risk of serious GI bleeding. A large postmarketing observational study involving IV/IM ketorolac tromethamine demonstrated that the risk of clinically serious gastrointestinal bleeding was dose dependent. Exposure from intranasal ketorolac falls within the range achieved with 15 mg to 30 mg of IM administration and exceeds oral exposure. The currently approved label specifically recommends use of the minimum effective dose. Outpatient use of Sprix will result in higher exposure than oral ketorolac and thus place subjects at increased risk for gastrointestinal bleeding.

The Applicant has recommended that each nasal spray bottle be discarded within 24 hours of taking the first dose to ensure consistency in delivery since less drug may be delivered after 24 hours. This does not appear to pose a safety issue but may adversely impact efficacy. It is unlikely that all subjects will follow the recommendation to discard the spray bottle withing 24 hours of initial use. However, restricting Sprix to inpatient use will eliminate the need to rely on the subject to discard partially used bottles of Sprix.

The inpatient efficacy findings for Sprix cannot be automatically extrapolated to the outpatient setting since in the inpatient studies essentially unlimited concomitant opioid use was allowed whereas with outpatient use access to opioids would likely be either limited or unavailable. Although some subjects received intranasal ketorolac as outpatients, efficacy was only assessed during the inpatient portion of the study. There is no direct evidence to support the assertion that IN ketorolac is better tolerated than oral ketorolac. NSAIDs can cause nausea and Sprix has the added problem of causing nasal symptoms that resulted in approximately six percent of subjects discontinuing drug. Since Sprix has a high incidence of nasal and other local adverse events (41%) compared to placebo (19%), the inpatient efficacy findings may over estimate outpatient efficacy if outpatients without the support of health care professionals are more likely to discontinue Sprix treatment due to local nasal adverse events.

Given the potential safety concerns with the outpatient use of Sprix and lack of direct evidence of outpatient efficacy, I believe that Sprix should be restricted to inpatient use. For subjects requiring continued treatment with ketorolac following discharge from the hospital, oral ketorolac is available. The relatively infrequent use of Sprix by outpatients during the pivotal studies is probably an indication that other readily available analgesics were better suited for outpatient use. If the applicant believes that intranasal ketorolac has a role in the management of outpatient acute pain, they should undertake an appropriately designed study to demonstrate efficacy and safety in a relevant outpatient population.

If the indication is restricted to inpatient use, I recommend a Complete Response action at this time to allow the Agency and Applicant to negotiate a Risk Evaluation and Mitigation Strategy.

1.2 Risk Benefit Analysis

Roxro submitted NDA 22-382 [Sprix® (ketorolac tromethamine nasal spray)], on Decemeber 5, 2008 [under 505(b)(1) of the Federal Food, Drug, and Cosmetic Act] to support a claim of short term (up to 5 days) management of moderate to severe pain, as a single agent or in combination with opioids. The applicant's proposed indication for "moderate to severe pain" should be changed to "moderately severe pain" based on the efficacy of the product and for consistency with the approved label for other ketorolac products. While this application is technically a 505(b)(1), ketorolac tromethamine, a non-steroidal anti-inflammatory drug, initially approved on November 30, 1989 as an injectable (IV/IM) formulation (NDA 19-698) has been relevant to my evaluation of Sprix. In 1996, a Boxed Warning was added to the package insert highlighting concerns about bleeding and renal effects.

Benefit
Efficacy was demonstrated in two adequate and well-controlled (i.e., randomized, double-blind, placebo-controlled) Phase 3 postoperative pain studies (Study 2003-01 and Study 2005-01). Roxro also submitted an additional Phase 2 study in postoperative pain and a single dose Phase 2 study in dental pain that supported the finding of efficacy. The primary efficacy assessments for both pivotal studies were completed in the hospital. No significant evidence of outpatient efficacy was provided.

Risk
The duration of intranasal ketorolac exposure was adequate to assess the short-term (up to 5 days) safety of IN ketorolac in postoperative patients in an inpatient setting. However, there were only 59 subjects who received intranasal ketorolac at home for a mean of 3.4 doses. There were no deaths in the Sprix or placebo groups. There was a greater incidence of serious adverse events (SAEs), adverse events leading to discontinuation, and adverse events in the Sprix group.

The most serious risks associated with the NSAID class of drugs are peptic ulcers, gastrointestinal bleeding and/or perforation, hemorrhage, renal toxicity, anaphylactoid reactions, increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke. In the safety database for intranasal ketorolac, there was evidence of increased bleeding but no clear-cut safety signal for other serious events often associated with NSAID use. This may have been related to the short duration of treatment and/or the controlled inpatient setting (e.g. inpatient subjects may have been less likely to be volume depleted and at risk for renal failure). There were reports of increased creatinine and oliguria but review of these cases did not reveal any significant persistent changes in renal function. There were no significant anaphylactioid reactions although there were more adverse events due to rashes in the Sprix group. There was no evidence to suggest that IN ketorolac resulted in cardiovascular events or delayed wound healing. There was a higher incidence of adverse events due to elevated transaminases in the Sprix group (2.2%) than placebo group (1.4%) but no subjects discontinued the study due to abnormal liver function tests. One subject with marked elevation of ALT (438 U/L) and AST (275 U/L) but normal bilirubin discontinued for another reason. There were slightly more adverse events due to edema peripheral in the Sprix group (4.6%) compared to the placebo group (3.4%).

There was evidence of nasal irritation and erosions related to Sprix use both by history and examination. The nasal symptoms and erosions appeared to be self limited and do not pose a major safety issue for use of Sprix up to five days in subjects less than 65 years old. Adequate data does not exist to fully assess the nasal safety in subjects 65 years of age or older since only seven nasal exams were performed in this age group in Study 2003-01, a five day study. An additional 13 subjects 65 years of age or older had a nasal exam in Study 2001-03, a two day study. No subjects 65 years of age or older had a two week follow-up nasal exam. Of the twenty nasal exams performed in subjects 65 years of age or older, one subject in Study 2003-01 had an abnormal nasal exam after nine doses of Sprix due to a nasal ulcer. None of the 34 subjects under the age of 65 in Study 2003-01 had an abnormal nasal exam. Results from the limited number of nasal exams in the elderly suggest a possible increase in the risk of nasal mucosal injury. This would be consistent with the apparent age related increase in epistaxis in the Sprix group.

A greater proportion of patients in the Sprix group, compared to the placebo group, experienced serious adverse events due to bleeding and required additional surgery or a transfusion. Review of the individual case report forms often resulted in difficulty assigning a definite etiology to the postoperative bleeding. However, since it is well known that NSAIDs can result in platelet inhibition and increased bleeding, it is reasonable to conclude that the difference in rates and severity of bleeding between Sprix and placebo groups was due at least in part to the use of Sprix.

Risk Benefit Analysis
The most serious risk identified with the short term use of Sprix is bleeding. The risk of bleeding can be appropriately managed through proper labeling that excludes subjects at increased risk of bleeding or at greater potential for harm from bleeding. The Applicant's proposed label does not provide a sufficient warning regarding the risk of bleeding. However, the approved label for oral and IV/IM ketorolac contains the following Boxed Warning:

> "Name of NSAID" inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding (See WARNINGS and PRECAUTIONS).

The label should also indicate that serious adverse events due to bleeding occurred more frequently with Sprix compared to placebo and sometimes required blood transfusion and/or additional surgery.

The nasal symptoms appeared to be self limited and do not impact on the overall safe use of this product when used as intended for a maximum of five days in adults under 65 years of age. For subjects 65 years of age or older there was limited information on nasal safety. There was no evidence to suggest more serious nasal events occur in the elderly but there was some evidence to suggest that they occur more frequently. There was no apparent safety signal for significant renal toxicity, intestinal bleeding and other typical serious NSAID associated adverse events except for bleeding. However, given the relatively small safety dataset for Sprix, it is impossible to conclude that the risks associated with other NSAIDs do not occur with Sprix. In fact other ketorolac containing formulations have been associated with serious renal and gastrointestinal adverse events and have

required a Black Box Warning. A weak signal was present for elevated transaminases in the Sprix group compared to placebo group. This is a known effect of NSAIDs and the approved label for ketorolac states that borderline elevations of liver function tests may occur in subjects treated with NSAIDs in up to 15% of patients. The increased incidence of subjects with adverse events due to peripheral edema and rash are also known to occur with NSAIDs. The risks associated with NSAIDs whether identified in the Sprix safety dataset or not will be adequately addressed by the standard NSAID class labeling that will apply to Sprix. Also, restricting Sprix use to five days in an inpatient setting will reduce the risk of adverse events.

The data provided support a positive risk benefit analysis for inpatient use, provided that patients are appropriately selected from the perspective of bleeding propensity. There is inadequate outpatient data to make an informed risk benefit analysis. No efficacy data was provided for outpatients and the inpatient efficacy findings cannot be automatically extrapolated to outpatients given the large amount of concomitant opioid use during the inpatient studies. The size of the outpatient safety database is small and the inpatient safety findings may not reliably predict outpatient safety. For example, there is no evidence of significant renal toxicity with Sprix but this is more likely to occur in subjects that are volume depleted e.g. subjects with poor oral intake. Hospitalized subjects with poor oral intake have access to IV fluids and, therefore, are less likely to be volume depleted. Although theoretically subjects with reduced oral intake would be ideal candidates for an intranasal analgesic, they would also be at potentially greater risk for developing renal toxicity from Sprix due to hypovolemia.

In summary, the effectiveness and safety of Sprix for acute postoperative pain was established for inpatients in two adequate and well-controlled studies. The data provided support a positive risk benefit analysis for inpatient use. The primary safety concern with IN ketorolac was increased bleeding. By appropriate labeling, subjects with the greatest risk for bleeding or unable to tolerate bleeding complications can be excluded. The other serious safety issues associated with NSAIDs were not observed in the IN ketorolac safety dataset, possibly due to the short duration of therapy (≤ 5 days) and/or from the use of the product under controlled conditions in a hospital. The potential adverse events associated with other NSAIDs but not identified in the Sprix dataset will be adequately covered by the NSAID class labeling. For approval of this product in an outpatient setting, the applicant should establish in an appropriate outpatient population efficacy and safety.

1.3 Recommendations for Postmarket Risk Management Activities

If approved for inpatient use only, a risk evaluation and mitigation strategies (REMS) program will be necessary.

1.4 Recommendations for Postmarket Studies/Clinical Trials

The applicant will have to fulfill the requirements of the Pediatric Research Equity Act.

2 Introduction and Regulatory Background

Sprix is an intranasal formulation of ketorolac tromethamine, a nonsteroidal anti-inflammatory drug (NSAID). The product is intended for dosing every 6 to 8 hours for the short term management of moderately severe pain. The applicant purports that the intranasal formulation benefits subjects by avoiding the need for painful injections or intravenous access and allows patients who are nauseated and unable to take oral medications to receive ketorolac.

2.1 Product Information

Trade Name (established name): Sprix® (ketorolac tromethamine)

Indication
Approved Indication
Information obtained from the product label for ketorolac tromethamine injection (Bedford Laboratories, revised Jan, 2009):

> "Ketorolac tromethamine is indicated for the short-term (≤5 days) management of *moderately severe* acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with IV or IM dosing of ketorolac tromethamine, and oral ketorolac tromethamine is to be used only as continuation treatment, if necessary.
> The total combined duration of use of ketorolac tromethamine injection and oral ketorolac tromethamine is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses. Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.
> Ketorolac tromethamine injection has been used concomitantly with morphine and meperidine and has shown an opioid sparing effect. For breakthrough pain, it is recommended to supplement the lower end of the ketorolac tromethamine injection dosage range with low doses of narcotics prn, unless otherwise contraindicated."

Discussion:
The preceding statement pertaining to opioid sparing appears to have been based on the following clinical information in the label:

> **Adult Patients:** In a postoperative study, where all patients received morphine by a PCA device, patients treated with ketorolac tromethamine IV as fixed intermittent boluses (e.g., 30 mg initial dose followed by 15 mg q3h), required significantly less morphine (26%) than the placebo group. Analgesia was significantly superior, at various postdosing pain assessment times, in the patients receiving ketorolac tromethamine IV plus PCA morphine as compared to patients receiving PCA-administered morphine alone.

Proposed Indication:

> "Sprix is indicated in adult patients for the short term (up to 5 days) management of *moderate to severe* pain that requires analgesia at the opioid level.
>
> (b) (4) . (b) (4)

Reviewer's Note:
The approved indication is for "moderately severe" pain.

Dose Regimen:
Approved Dosing Regimen for Ketorolac Tromethamine:
Multiple-Dose Treatment (IV or IM)
Adults (< 65 years of age): The recommended dose is 30 mg ketorolac tromethamine injection every 6 hours. The maximum daily dose should not exceed 120 mg.

Elderly (≥65 years of age, renally impaired patients and patients less than 50 kg): The recommended dose is 15 mg ketorolac tromethamine injection every 6 hours. The maximum daily dose for these populations should not exceed 60 mg."

Single-Dose Treatment (IV or IM)
Adults (< 65 years of age)
IM dosing: one dose of 60 mg
IV dosing: one dose of 30 mg

Elderly (≥65 years of age, renally impaired patients and patients less than 50 kg):
IM dosing: one dose of 30 mg
IV dosing: one dose of 15 mg

(b) (4)

Oral Dose
In adults, the use of oral ketorolac is only indicated as continuation therapy to IV or IM dosing of ketorolac.
Adults (Under 65 years of age): 20 mg PO once followed by 10 mg q4-6 hours prn not >40 mg/day

Elderly (65 years of age and older): 10 mg PO once followed by 10 mg q4-6 hours prn not >40 mg/day

Age <17 years: Oral not approved

Note:
- Oral formulation should not be given as an initial dose
- Use minimum effective dose for the individual patient
- Do not shorten dosing interval of 4 to 6 hours
- Total duration of treatment in adult patients: the combined duration of use of IV or IM dosing of ketorolac tromethamine and oral ketorolac is not to exceed 5 days.

(b) (4)

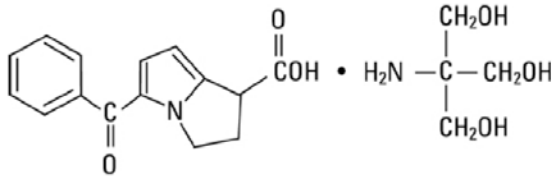
Reviewer Comment: A single-dose study was conducted to compare the pharmacokinetics of Sprix (31.5 mg) in subjects ≥ age 65 to the pharmacokinetics in subjects < age 65. Exposure to ketorolac was increased by 23% for the ≥ 65 population as compared to subjects < 65. Peak concentrations of 2028 ng/mL and 1840 ng/mL were observed for the elderly and nonelderly adult populations, respectively, at 0.75 h after dosing. In the elderly population a slightly longer terminal half-life was observed as compared to the nonelderly adults.

Pediatric Patients: "Sprix has not been shown to be safe and effective in pediatric patients"

Pharmacologic Class: Ketorolac tromethamine is a member of the pyrrolo-pyrrole group of non-steroidal anti-inflammatory drugs (NSAIDs).

Chemistry:

Chemical Formula: (±)-5-benzoyl-2, 3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2- (hydroxymethyl)-1,3-propanediol, and the structural formula is:



2.2 Tables of Currently Available Treatments for Proposed Indications

There are numerous FDA approved products for the management of acute pain. Although many NSAIDs are available, intranasal ketorolac represents a novel route of administration. Table 2.2 summarizes available treatments for acute pain.

Table 2.2: Available Treatments for Acute Pain

Product	Route of Administration	Advantages	Disadvantages
NSAIDs	**Oral**	• **Anti-inflammatory activity** • **No respiratory depression** • **No effect on gastric emptying**	• **Increased bleeding due to platlet inhibition** • **GI damage** • **Renal Impairment** • **Poor bone or wound healing** • **Not as effective for severe pain**
Acetaminophen	**Oral**	• **No respiratory depression** • **No effect on gastric emptying** • **No effect on platelet aggregation**	• **No anti-inflammatory activity** • **Possible hepatic impairment from overdose** • **Not as effective for severe pain**
Opioids	**Oral** **Transdermal** **Intramuscular** **Subcutaneous** **Intravenous** **Sublingual** **Patient Controlled Analgesia (PCA)** **Epidural or intrathecal**	• **Effective for severe pain** • **With epidural or intrathecal use the opioid dose can be reduced**	• **Hypotension** • **Respiratoy depression** • **Nausea and vomiting** • **Delayed gastric emptying and small bowel transit time** • **With epidural/ intrathecal use:** **- Epidural hematoma or Abscess** **- Nerve injury**
Local Anesthetics (Regional and local analgesia)	**Wound infiltration**	• **Postoperative pain**	
	Nerve and plexus blocks	• **Effective for severe pain**	• **Nerve injury**
	Epidural or Intrathecal	• **Effective for severe pain**	• **Epidural hematoma/ abscess** • **Nerve injury**

Opioids are effective for the treatment of severe pain but often result in opioid-related side effects. Some pain specialists believe that multimodal treatment of pain (e.g. an opioid and NSAID) results in improved pain control and less opioid-related side effects due to opioid sparing. Epidural or intrathecal administration of opioids or local anesthetics is effective in the management of severe pain but epidural hematoma or abscess are potential serious complications of this treatment.

In addition to the above approved products, several other therapeutic modalities have been used with varying degrees of success including: acupuncture, transcutaneous electrical nerve stimulation (TENS), therapeutic cold and rest.

2.3 Availability of Proposed Active Ingredient in the United States

Ketorolac was initially approved November 30, 1989 as an injectable formulation (NDA 19-698) and approved as an oral formulation December 20, 1991 (NDA 19-645). Ketorolac is indicated for the short-term (≤5 days) management of moderately severe acute pain that requires analgesia at the opioid level, (b) (4). Therapy should always be initiated with ketorolac IV/IM and oral ketorolac is to be used only as continuation treatment, if necessary. In 1996, a boxed warning pertaining to the following issues was added to the label:

- Gastrointestinal risk: Ketorolac can cause peptic ulcers, gastrointestinal bleeding, and perforation.
- Renal risk: Ketorolac is contraindicated in patients with advanced renal impairment and in patients at risk for renal failure due to volume depletion.
- Risk of bleeding: Ketorolac inhibits platelet function and is therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding. Ketorolac is contraindicated as prophylactic analgesic before any major surgery and is contraindicated intra-operatively when hemostasis is critical because of the increased risk of bleeding.
- Hypersensitivity reactions: Bronchospasm to anaphylactic shock, have occurred and appropriate counteractive measures must be available when administering the first dose of ketorolac IV/IM.
- Labor and delivery: Ketorolac is contraindicated because it may adversely affect fetal circulation and inhibit uterine contractions.
- Concomitant use with NSAIDs: Ketorolac is contraindicated in patients currently receiving ASA or NSAIDs.
- Dosage and Special populations: Ketorolac oral is indicated only as continuation therapy to IV/IM and the combined duration is not to exceed 5 days because of the increased risk of serious adverse events. Dosage should be adjusted for patients 65 years or older, for patients under 50 kg of body weight, and for patients with moderately elevated serum creatinine.

The FDA conducted a safety review of ketorolac tromethamine in 2002. A summary of the safety review by Dr Hertz follows:

> Agency Safety Review
> "On May 15, 2002, the Office of Drug Safety performed a review of postmarketing reports of serious gastrointestinal (GI), renal, and cardiovascular events related to parenteral and oral formulations of Toradol from 1997 to 2002. This review included serious GI and other hemorrhagic events. From the initial marketing in 1989 until April 8, 2002, there were 3952 reports of adverse events to the AERS system. GI hemorrhage, hemorrhage, blood creatinine increased, anemia, dyspnea, and renal failure acute were the top six preferred terms. Of these reports, 2971 (75%) involved parenteral use of ketorolac.
>
> A search for serious cases of hemorrhage, renal failure, and cardiovascular thrombotic events resulted in 195 unduplicated cases. Sixty-two were excluded as there were alternate causes identified or the events were not temporally related to the use of ketorolac. Of the remaining 133 cases, 92 (69%) had received parenteral ketorolac, 21

> (16%) oral ketorolac and the route of administration was unspecified in 20 cases. There were 65 cases of GI hemorrhage temporally associated with the use of ketorolac including 13 deaths. Forty-one cases followed parenteral use, 17 followed oral use, and the route was unspecified in seven cases. There were 40 reports of renal failure-related events temporally associated with ketorolac use including five deaths. The route was parenteral in 30 cases, oral in three cases and not specified in seven cases. The duration of therapy in all of these cases was less than 5 days.
>
> This review commented that, overall, the number of serious events was small, but this could have been due in part to the addition of the boxed warning in 1996, as well as reduced reporting of adverse events that occurs after a product has been on the market for a number of years."

Dr. Hertz in her review identified GI hemorrhage and renal failure as the most common serious adverse events, occurring more often in subjects receiving parenteral than oral ketorolac.

A Safety Review of ketorolac was performed by Roche, the sponsor, on December 14, 2003. The review was based on the Roche Drug Safety Database ADVENT. The Sponsor's Safety Review was reviewed by Dr. Hertz and key points from her review are summarized below:

- The Sponsor estimates that (b) (4) patients have been exposed to Toradol.
- Serious GI and Renal AEs are summarized by age and duration of dosing in Table 2.3. Serious GI and renal adverse events occur more often with dosing over five days but serious adverse events were still observed with dosing for five days or less.
- Serious GI events were primarily gastrointestinal hemorrhage and gastric ulcer, followed by perforation, melena, pain, and hematemesis.
    - Doses ranged from 10 mg to 120 mg/day although the most frequent dosages were 20-40 mg/day.
- Serious renal AEs were primarily renal insufficiency, renal failure acute and renal impairment.
    - For subjects under 65 years, doses ranged from 10 mg to 120 mg/day and were fairly evenly distributed between 20, 30, 40 and 120 mg/day.
    - For subjects 65 years and older, doses ranged form 10 mg to 100 mg per day with most occurring at 20, 30 and 40 mg/day.

Table 2.3: Serious GI and Renal AEs by Age and Duration of Therapy with Toradol as Reported by Roche Based on December 14, 2003 Drug Safety Review

	5 days or less	More than 5 days	Duration of use unknown
Serious GI Adverse Events			
Age <65 years	46	85	48
Age ≥ 65 years	67	69	56
Age not specified	4	15	14
Serious Renal Adverse Events			
Age <65 years	14	11	8
Age ≥ 65 years	5	10	7
Age not specified	4	2	4

Reference: NDA 19-645 (Toradol), Medical Officer Review dated 9/14/2004

A large postmarketing observational, nonrandomized study, involving approximately 10,000 patients receiving injectabale ketorolac tromethamine, demonstrated that the risk of clinically serious gastrointestinal bleeding was dose-dependent (Table 2.3.1). This was particularly true in elderly patients who received an average daily dose greater than 60 mg/day of ketorolac. This dose dependent risk of gastrointestinal bleeding was considered significant enough to warrant inclusion in the approved label.

Table 2.3.1: Bleeding (PUB) After up to 5 Days of Treatment with Ketorolac Tromethamine IV/IM

A. Adult Patients Without History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine IV/IM			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	0.4%	0.4%	0.9%	4.6%
≥65 years of age	1.2%	2.8%	2.2%	7.7%

B. Adult Patients With History of PUB

Age of Patients	Total Daily Dose of Ketorolac Tromethamine IV/IM			
	≤60 mg	>60 to 90 mg	>90 to 120 mg	>120 mg
<65 years of age	2.1%	4.6%	7.8%	15.4%
≥65 years of age	4.7%	3.7%	2.8%	25.0%

Reference: Toradol label (Hoffmann-la Roche, revised 01/2009)

NSAID Boxed Warning

All NSAIDs, including ketorolac, contain the following Boxed Warning for cardiovascular and gastrointestinal risks:

Cardiovascular Risk

• NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction (MI), and stroke, which can be fatal. This risk may increase with

duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS.)
• "Name of NSAID" is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. (See WARNINGS.)

Gastrointestinal Risk
• "Name of NSAID" can cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal (GI) events. (See WARNINGS.)

2.4 Important Safety Issues With Consideration to Related Drugs

Approved NSAIDs including ketorolac are all associated with potentially serious cardiovascular, gastrointestinal and renal risks described in Section 2.3.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2.5.1 displays highlights of the regulatory activity that occurred during the clinical development program for Sprix.

Table 2.5.1: Regulatory Interactions between the FDA and the Applicant

Date Meeting	Topics
3/8/2002 PIND 62,829 Meeting	The Division made several comments to the Applicant: • There needs to be adequate dose-ranging to establish both efficacy and safety. • Adequate number of patients will need to be exposed to the highest dose determined to be effective for 5 days.
4/2002 IND 62,829 opened	• Date of Submission: April 9, 2002 • Date of Receipt: April 10, 2002
3/27/2003 Guidance Meeting	The Division made the following comments: • (b) (4) (b) (4) is not a labeled indication. • Analgesics for acute pain need to be studied in both outpatient and inpatient settings where the single dose analgesic characteristics of onset, peak and duration of effect are studied as well as…the dose and dosing interval for multiple day use beyond day one. • Since this is a new route of administration, this NDA cannot be developed without adequate and well-controlled clinical trials to establish both efficacy and safety. • Drug interaction trials need to include subjects who have moderately severe upper respiratory viral infections.

6/5/2003 Guidance Meeting	The Division made the following comments to the Applicant: • Single dose efficacy needs to be established for patients both off and on PCA. • The open label study design to evaluate the bioavailability of ketorolac in subjects with rhinitis and effects of chronic use of intranasal steroid and single dose of nasal decongestant oxymetazoline hydrochloride is acceptable. • The Agency recommends conducting studies in geriatric patients.
7/17/2004 End of Phase 2 Meeting	The Division made several comments to the Applicant: • Efficacy needs to be established beyond the first dose, and beyond the 24 hours proposed in the draft Phase 3 protocol. • The data from study 2003-05 suggests that the dosing interval is at least every 6 hours (mean time to re-medication is 360 min). • Additional single dose data is needed from patients after major surgery. • Measurements at 8, 24 and 48 hour timepoints, as primary and secondary endpoints. • Occurrence of adverse events due to this new route of administration may require a safety database of more than 400 patients. Rigorous review of safety data would be required before conclusions can be made regarding any safety database. This would include the results of the nasal endoscopic study 2001-04. • The Division suggested that pediatric studies be deferred until more efficacy and safety data are available in the adult population.
12/13/2004 Type B Meeting	The Division made several comments to the Applicant: • As we discussed during our previous meeting, the mean time to remedication in the previous trial was 360 min, it is therefore unclear why the dosing interval is q8 hrs in the pivotal trial. • Primary endpoints need to be clearly defined prior to unblinding the study. • Reduction of morphine consumption as the sole primary endpoint in acute analgesic trials is problematic in that this (b) (4) (b) (4) a manner that demonstrates a clinically meaningful benefit.
3/11/2005 Advice Letter	The Division made several comments to the Applicant: • The proposed clinical trial will not support a dosing regimen for up to 5 days given that regular dosing will only continue for 48 hours. - We encourage you to study the efficacy for longer periods of time. • Not achieving perceptible pain relief within 60 minutes will be problematic for this drug in an acute situation.

5/19/2005 Advice Letter	The Division made several comments to the Applicant: • Provide a sizable proportion of patients with exit ENT exams after 5 full days of regular dosing. - Perform a follow-up ENT exam at 14 days in at least 1/3 of the patients exposed to the drug during the trial. • In order to label the use of the drug for up to 5 days, you must have a sizable proportion of patients with regular dosing for 5 full days; sufficient to allow us to evaluate the drug efficacy and safety.
10/4/2007 Pre-NDA Meeting	The Division made the following comments to the Applicant: • The proposed NDA submission appears adequate in terms of the number and design of studies to be submitted. • The proposed safety data package appears acceptable. - Provide a subgroup assessment of safety in pediatric patients. • The Pediatric Research Equity Act (PREA) is triggered by your application. - However, you may request a deferral for pediatric studies with your NDA submission. • A paper NDA submission is acceptable. - We strongly encourage you to submit an electronic NDA. • Labeling should be submitted in PLR and SPL formats. • Full CRFs should be submitted for all SAEs, in addition to deaths and withdrawals due to adverse events. • Roxro proposed an indication for ketorolac intranasal equivalent to (b) (4) below: (b) (4) We indicated that the proposed approach appears acceptable but the information provided by the applicant pertaining to the approved label was incorrect. The indication for ketorolac tromethamine injectable from the currently approved FDA label is for *moderately severe pain* and not (b) (4) • We agreed with dose reduction (50%) in subjects with low body weight and renally-impaired if the intranasal and intramuscular pharmacokinetics are found to be similar. With respect to the

	elderly, this approach may not be suitable as the intranasal absorption may be different compared to young adults. -PK data for elderly patients must be submitted with the NDA application. • The drug-drug interaction study must be conducted in patients and not healthy individuals.
10/30/2007 Advice Letter	The Division made several comments to the Applicant: • As agreed upon during the March 2002 pre-IND meeting, the Division still agrees that you may reference FDA's findings of safety for Toradol Injectable Solution to support the proposed 505(b)(2) NDA. If unexpected or additional safety concerns develop during manufacturing or during clinical trials, additional toxicological studies may be required. • As per the discussion at the pre-NDA meeting held October 4, 2007, the proposed database package appears acceptable.
4/10/2008 Advice Letter	The Division made several comments to the Applicant regarding the Quantitative Safety Analysis Plan (QSAP): • Provide justifications for the AEs of special interest • Consider the use of MedDRA SMQs or other standardized definitions to identify these AEs. • Provide s;ummaries of AEs after the first 48 hours in addition to the first 48 hours. Provide summaries with a finer partition of age (e.g., 18-55, 55-65, 65-75, ≥ 75).
12/5/2008 NDA submission	• NDA submitted under 505(b)(2). • RLD Toradol from NDA 19-645 and NDA 19-698 (both RLDs discontinued). • Submission contains: - Two Phase 3 efficacy studies (Studies 2005-01 and 2003-01) - Two Phase 2 efficacy studies (Studies 2001-03 and 2003-05) - 11 Phase 1 studies

2.6 Other Relevant Background Information

There are no significant regulatory actions, reported by the applicant, that have been instituted outside of the United States. There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA submission was reasonably well-organized and acceptable for a review. Roxro Pharma's responses to all of FDA's information requests were timely and well-organized. In their response to FDA's information requests, Roxro stated that the following information could not be provided:

1. Initial protocol for Study 2003-01

   Discussion
   The missing original protocol did not effect interpretation of the study results since it preceded enrollment of any patients.

2. The exact amount of morphine sulfate used in Study 2003-01 and Study 2005-01 for subjects who withdrew prematurely

   The Applicant explained that according to the protocol when subjects withdrew from the study, no further efficacy assessments would be obtained which included rescue medication use. Therefore morphine use was extrapolated for subjects who withdrew prematurely.

   Discussion
   Since the percent of subjects requiring extrapolation was similar in both groups any bias introduced from extrapolation would presumably be similar in both groups. Using extrapolation for subjects who discontinued early, there was less rescue opioids used in the intranasal ketorolac group compared to placebo.

3.2 Compliance with Good Clinical Practices

According to Roxro, Study 2003-01 and Study 2005-01 were conducted in accordance with the Declaration of Helsinki. Prior to initiating the studies approval of the IRB was obtained and each subject gave informed consent before any study-related procedures were performed.

The Division of Scientific Investigation (DSI) inspected one site in New Zealand and two sites in the United States. The Division selected Site #81 in New Zealand since all the patients studied in pivotal Study ROX 2003-01 and a substantial number of the subjects in Study 2005-01 were enrolled at this site. For Study 2005-01, study sites #82 and #83 were selected since the highest enrollment in the US was at these two sites.

The DSI inspection of Dr. Neil Singla's site for Protocol 2005-01 was completed and DSI concluded that the study appeared to have been conducted adequately. Results from the DSI investigation of Protocol 2003-01 was pending at the time of this review.

3.3 Financial Disclosures

Roxro submitted FDA Form 3454 certifying that the clinical investigators who supervised clinical studies in support of this application:

- Did not participate in any financial arrangement with the sponsor, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study [as defined in 21 CFR 54.2(a)]:
- Had no proprietary interest in this product or significant equity interest in the sponsor [as defined in 21 CFR 54.2(b)]: and
- Was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)]

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

A detailed discussion of the chemistry issues by Dr. Joseph Leginus, the chemistry reviewer, is contained in the CMC section.

According to Dr. Joseph Leginus, there are no significant chemistry, manufacturing, or control issues with the product when used as labeled. The Applicant recommends that each vial once opened be disposed of after 24 hours due to reduced drug delivery. Dr. Leginus reports that after 24 hours the delivery of active ingredient falls out of specification in 10% of the determinations. He concludes that the applicant's proposal to recommend use of the drug product unit within the same 24 hour period as initial spraying is justified.

Discussion
The variability in drug delivery after 24 hours does not appear to pose a major safety concern, since the amount of drug delivered is less than specified. However, the efficacy of the drug may be reduced in some subjects using the drug product unit beyond the recommended 24 hour period.

4.2 Clinical Microbiology

The microbiology review is pending.

4.3 Preclinical Pharmacology/Toxicology

A detailed discussion of the Pharmacology/Toxicology issues is contained in the review by Dr. Newton Woo, the pharmacology/toxicology reviewer.

The following information was obtained from the FDA Pharmacologist, Dr. Newton Woo. Since this is a new route of administration of an approved product, the Applicant was only required to demonstrate safety for the new intranasal route of administration for ketorolac. The Applicant conducted a local tolerance study in the rabbit and a 28-day study in the rat. No local nasal concerns were identified. The rat study demonstrated GI toxicities that were consistent with the known effects of NSAIDS.

A degradation product, 1-keto, was identified that exceeded the qualification threshold. A genetox assay and general toxicity assay with the degredent were performed. The Ames assay was negative but the in vitro chromosomal aberration study was positive. Pharm Tox concluded that no additional studies would be required considering the intended short-term use of the product (≤ 5 days) and the negative findings from the computational toxicology analysis.

4.4 Clinical Pharmacology

A detailed discussion of the clinical pharmacology issues is contained in the review by Dr. Sayed Al Habet, the pharmacology reviewer.

4.4.1 Mechanism of Action

Ketorolac tromethamine is a potent analgesic nonsteroidal anti-inflammatory drug that inhibits the enzyme cyclooxygenase (COX 1 and 2). This results in reduction in the syntheses of the inflammatory mediators such as prostaglandins, thromboxanes and prostacyclin. In addition to analgesic and anti-inflammatory properties ketorolac also has an anti-pyretic effect.

4.4.2 Pharmacodynamics

The following information on NSAIDs also applies to ketorolac. NSAIDs inhibit platelet function and can prolong bleeding time. NSAIDs may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow which may precipitate renal decompensation.

4.4.3 Pharmacokinetics

The pharmacokinetics of ketorolac following intranasal (IN) and intramuscular (IM) doses were compared in Study 2001-02. The 15.5 and 31.5 mg doses of IN ketorolac were dose proportional but the highest dose of 45 mg was less than proportional. The Cmax occured within 30-60 min similar to that obtained with IM administration. The half-life of ketorolac by the IN route was similar to that of the IM route (4-8 hours). Steady state was achieved within 24 hours after multiple dose administration. The bioavailability of ketorolac by the IN route of administration was approximately 60-75% compared to IM administration (Table 4.4.3.1). A 31.5 mg dose of IN ketorolac resulted in exposure and Cmax between the 15 mg IM and 30 mg IM dose. Roxro did not conduct studies comparing intranasal to oral administration of ketorolac. However, pharmacokinetic information comparing oral, intramuscular and intravenous dosing is contained in the approved label for ketorolac (Table 4.4.3.2). Dosing with oral ketorolac 10 mg (approved dose) results in single dose and steady state Cmax and steady state average plasma concentrations less than obtained with IM 15 mg and IV

15 mg dosing. In general the proposed IN ketorolac dose has pharmacokinetic findings closer to the approved IM/IV dose than oral dose. This similarity in pharmacokinetics suggests that the safety risks for intranasal ketorolac are closer to injectable than oral administration of ketorolac and provides the rationale for having similar dosing recommendations for IN and IV/IM administration.

Table 4.4.3.1: Pharmacokinetic Parameters of Ketorolac Tromethamine after Intramuscular (IM) and Intranasal (IN) Administration

Ketorolac Tromethamine	C_{max} (SD) ng/mL	t_{max} (range) hours	$AUC_{0-\infty}$ (SD) ng.h/mL	$T_{½}$ (SD) hours
30mg IM (1.0 mL of a 30 mg/mL solution)	2382.2 (432.7)	0.75 (0.25-1.03)	11152.8 (4260.1)	4.80 (1.18)
31.5mg IN (100 µL of a 15% w/w solution)	1805.8 (882.8)	0.75 (0.50-2.00)	7477.3 (3654.4)	5.24 (1.33)
15mg IM (0.5 mL of a 30 mg/mL solution)	1163.4 (279.9)	0.75 (0.25-1.50)	5196.3 (2076.7)	5.00 (1.72)
15.5mg* IN (100 µL of a 7.5% w/w solution)	912.6 (292.9)	0.50 (0.25-1.00)	3906.8 (1569.4)	4.76 (1.38)

(b) (4)

C_{max} = maximum plasma concentration; t_{max} = time of C_{max}; $AUC_{0-\infty}$ = complete area under the concentration-time curve; $T_{½}$ = half-life; SD = standard deviation. All values are means, except t_{max}, for which medians are reported.

Table 4.4.3.2: Approximate Average Pharmacokinetic Parameters (Mean±SD) Following Oral, Intramuscular and Intravenous Doses of Ketorolac Tromethamine

Pharmacokinetic Parameters (units)	Oral*	Intramuscular†			Intravenous Bolus‡	
	10 mg	15 mg	30 mg	60 mg	15 mg	30 mg
Bioavailability (extent)	100%					
T_{max}§ (min)	44 ± 34	33 ± 21¶	44 ± 29	33 ± 21¶	1.1 ± 0.7¶	2.9 ± 1.8
C_{max}# (µg/mL) [single-dose]	0.87 ± 0.22	1.14 ± 0.32¶	2.42 ± 0.68	4.55 ± 1.27¶	2.47 ± 0.51¶	4.65 ± 0.96
C_{max} (µg/mL) [steady state qid]	1.05 ± 0.26¶	1.56 ± 0.44¶	3.11 ± 0.87¶	N/AÞ	3.09 ± 1.17¶	6.85 ± 2.61
C_{min}ß (µg/mL) [steady state qid]	0.29 ± 0.07¶	0.47 ± 0.13¶	0.93 ± 0.26¶	N/A	0.61 ± 0.21¶	1.04 ± 0.35
C_{avg}à (µg/mL) [steady state qid]	0.59 ± 0.20¶	0.94 ± 0.29¶	1.88 ± 0.59¶	N/A	1.09 ± 0.30¶	2.17 ± 0.59
Vβè (L/kg)	0.175 ± 0.039				0.210 ± 0.044	

% Dose metabolized = <50
% Dose excreted in feces = 6
% Dose excreted in urine = 91
% Plasma protein binding = 99
*Derived from PO pharmacokinetic studies in 77 normal fasted volunteers
†Derived from IM pharmacokinetic studies in 54 normal volunteers
‡Derived from IV pharmacokinetic studies in 24 normal volunteers
§Time-to-peak plasma concentration
¶Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed C_{max} and T_{max} data
#Peak plasma concentration
ÞNot applicable because 60 mg is only recommended as a single dose
ßTrough plasma concentration
àAverage plasma concentration
èVolume of distribution

Reference: Toradol label (Hoffmann-La Roche Inc., Revised 01/2009)

The dose recommendation for patients 65 years and older in the approved label for injectable ketorolac is a 50% reduction in the dose for subjects under the age of 65. The Division told the Applicant that to support the use of a 50% dose reduction of intranasal ketorolac in the elderly they would need to demonstrate that absorption was similar in young adults and the elderly. Roxro conducted a PK study in the elderly (Study 2007-02). The FDA pharmacologist concluded that intranasal absorption was comparable considering variability in the Cmax of elderly.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A listing of the clinical studies is shown in Tables 5.1.1 and 5.1.2 below.

Table 5.1.1: Phase 1 Studies

DESCRIPTION		Number of Subjects	
		Total	IN ketorolac
Phase 1: Single-dose Studies			
REC 1993-01	Phase 1 PK pilot study to evaluate feasibility of IN administration. Single-dose, crossover bioavailability study of 10 and 30 mg IN and 10 mg IV.	12	12
ROX-2001-01	Phase 1, single-dose, crossover study of IN doses of 20.5 mg ketorolac, ROX-888, and 42.0 mg ketorolac and 31.5 mg IN with an absorption enhancer.	15	15
ROX-2001-02	Phase 1, single-center, 5-way crossover, safety, tolerability and PK study in healthy male and female volunteers with the IM treatments as open-label and the IN treatments as double-blind. Single IN doses of 15.5 mg ketorolac, ROX-888, and 48 mg ketorolac and intramuscular (IM) administration of 15 mg and 30 mg of ketorolac.	15	15
ROX-2006-02	Phase 1, open-label, PK study in pediatric subjects (aged 12 through 17 years) who had undergone general surgery. Single IN dose of 15.75 mg ketorolac for subjects weighing <50 kg and single dose of ROX-888 for subjects weighing ≥50 kg.	20	20
ROX-2007-02	Phase 1, open-label, single-dose, safety and PK study of ROX-888 in elderly (≥65 years) and nonelderly (<65 years) healthy adult subjects.	30	30
ROX-2007-03	Phase 1, open-label, 3-way study in participants with symptomatic allergic rhinitis. Pharmacokinetics were assessed after administration of oxymetazoline and fluticasone.	24	24
Phase 1: Multiple-dose Studies			
ROX-2001-04	Phase 1, double-blind, safety and PK study of ROX-888 vs. placebo every 6 hours for 20 doses.	18	12
ROX-2005-03	Phase 1, steady-state PK study with ROX-888 administered every 8 hours for a total of 7 doses.	20	20
Phase 1: Drug Interaction Studies			
ROX-2006-03	Phase 1, open-label, 3-way drug interaction study with ROX-888 and IN oxymetazoline. Single-dose study in healthy volunteers.	22	22
ROX-2006-04	Phase 1, open-label, 3-way drug interaction study with ROX-888 and IN fluticasone. Single-dose study in healthy volunteers.	36	36
Phase 1 Distribution Study			
ROX-2002-02	Phase 1, randomized 3-way crossover scintigraphic distribution study of single IN doses of 31.5 mg radiolabeled ketorolac in healthy volunteers.	13	13

Reference: Table 2.5.1: Biopharmaceutical and Clinical Pharmacology Studies from Section 2.5 Clinical Overview, Module 2, Volume 1

Table 5.1.2: Phase 2 and 3 Efficacy Studies

Study	Description	Number of Subjects	
		Total	IN Ketorolac
ROX-2001-03	Double-blind, placebo-controlled, efficacy and safety study of 10.0 mg IN ketorolac and ROX-888 in postoperative pain. Study drug was given every 8 hours daily for 2 days. PCA morphine sulfate allowed for additional analgesia.	127	85
ROX-2003-05	Double-blind, placebo-controlled, single-dose study of ROX-888 as monotherapy in dental extraction pain.	80	40
ROX-2003-01	Double-blind, placebo-controlled, efficacy and safety study of ROX-888 given every 8 hours for 48 hours and then 3 times a day for up to 5 days for postoperative pain. PCA morphine sulfate allowed for additional analgesia. A subset of patients received study drug without background PCA to determine onset, peak effect, and duration of efficacy.	300	199
ROX-2005-01	Double-blind, placebo-controlled, efficacy and safety study of ROX-888 given every 6 hours for 48 hours and then 4 times a day for up to 5 days for postoperative pain. PCA morphine sulfate allowed for additional analgesia.	321	214
Total		825	538

Reference: Table 2.5.2: Controlled Efficacy Studies from Section 2.5 Clinical Overview, Module 2, Volume 1

5.2 Review Strategy

Efficacy

Study 2003-01 and Study 2005-01 were reviewed to support the efficacy of Sprix for the short-term management of moderately severe acute pain. Both studies were considered pivotal studies for the following reasons:

- Well-controlled (i.e., randomized, double-blind, placebo-controlled)
- Included a significant number of patients
- Provided for dosing up to five days

The applicant also submitted two Phase 2 studies (Study 2001-03 and 2003-05) that were reviewed to support the findings of the pivotal studies but were not considered pivotal because:

Study 2001-03

- Provided only up to 48 hours of dosing

- Contained insufficient number of subjects (85 subjects received Sprix)
- Inadequate primary endpoint (total morphine sulfate consumption at 24 hours)

Study 2003-05
- Single-dose study
- Contained insufficient number of subjects (40 subjects received Sprix)

Safety
Roxro's integrated safety analyses included safety data from four Phase 2 and 3 studies (Studies 2003-01, 2005-01, 2001-03 and 2003-05). The integrated safety data and safety from 11 individual Phase 1 studies were reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

To support efficacy, the applicant submitted two Phase 3 studies (Study 2003-01 and Study 2005-01) and two Phase 2 studies (Study 2001-03 and Study 2003-05). A review of the controlled efficacy studies follows. (b) (4) (b) (4), the intended dose of 15 mg, 30 mg (b) (4) delivered doses of 15.5 mg, 31.5 mg (b) (4). Throughout this review the term ROX-888 refers to the intranasal ketorolac tromethamine dose of 31.5 mg.

5.3.1 Study 2005-01

The following summary of the design of Study 2005-01 was derived from amendment #4. The first patient was not enrolled in this study until after the changes in this protocol amendment were incorporated into the conduct of the study. The original protocol and Amendment 01 were submitted without the signature pages since the applicant could not locate these pages.

Title: "A Phase 3, Double-Blind, Randomized Study of the Safety, Tolerability, and Analgesic Efficacy of Multiple Doses of Ketorolac Tromethamine Administered Intranasally for Postoperative Pain Following Major Abdominal Surgery"

Dates Conducted: The first subject was enrolled in the study December 13, 2005 and the last subject completed the study February 12, 2007.

Objectives: The primary objective of the study was to evaluate the analgesic efficacy of multiple intranasal (IN) doses of ketorolac administered for up to 5 days. The secondary objective was to evaluate the safety and tolerability of this dosing regimen.

Overall Design: This was a Phase 3, randomized, double-blind, placebo-controlled, multi-center study of IN ketorolac in subjects who underwent major abdominal surgery. Following surgery, subjects exhibiting signs of discomfort were to have received an IV opioid titrated to comfort. Once

subjects were alert and their pain intensity rating was greater than or equal to 40 mm on a 100-mm visual analog scale (VAS), they were to have been randomized 2:1 to receive IN ketorolac 30 mg or IN placebo. Thereafter, subjects were to have received study drug every 6 hours for 48 hours and then up to 4 times daily for up to 5 days total. Subjects discharged before postoperative day 4 were to have been allowed to self-medicate at home through postoperative day 4.

Inclusion Criteria:

Patients were to have met the following criteria:

1. Men or women, age 18 through 64 years
2. Major abdominal surgery by an open procedure
3. Body weight ≥100 pounds and ≤ 300 pounds
4. Women of child bearing potential must have a negative serum pregnancy test result
5. Able to provide written informed consent
6. At least moderate pain as determined by a PI score of ≥ 40 mm on a 100-mn VAS
7. Expected to remain in the hospital for at least 48 hours with the possibility of remaining for 5 days
8. Willing and able to comply with all testing and requirements defined in the protocol
9. Willing and able to complete both posttreatment follow-up visits

Exclusion Criteria

Patients were to be excluded if any of the following applied:

1. Allergy or sensitivity to ketorolac or EDTA(ethylenediaminetetraacetic acid)
2. Allergic reaction to aspirin or other NSAIDs
3. Current upper respiratory tract infection or other respiratory tract condition that could interfere with the absorption of the nasal spray or with the assessment of AEs
4. Use of any IN product within 24 hours prior to study entry
5. Clinically significant abnormality on screening laboratory tests
6. History of cocaine use resulting in nasal mucosal damage
7. Active peptic ulcer disease, recent (defined as within 6 months) history of peptic ulcer disease or gastrointestinal bleeding considered by the investigator to be clinically significant
8. Advanced renal impairment (serum creatinine > 1.5mg/dL) or a risk for renal failure due to volume depletion
9. A history of any other clinically significant medical problem, which in the opinion of the investigator would interfere with study participation
10. Participation within 30 days of study entry or within 5 times the half-life, whichever is longer, in another investigational drug study
11. Allergy or significant reaction to opioids
12. Pregnancy or breastfeeding
13. Previous participation in this study

Study Medication

Throughout this review, the administered dose of ketorolac tromethamine is reported as 30 mg whereas the actual dose delivered was 31.5 mg. (b) (4) which means that two sprays intended to deliver 30 mg, in fact delivered 31.5 mg.

Subjects were to have been randomly assigned, in a ratio of two to one, to receive IN ketorolac tromethamine 30 mg or IN placebo. The ketorolac nasal solutions were to have been provided in a disposable, multidose, metered-spray device. Doses were to have been administered as one spray (100 µL) into each nostril (200 µL total). Each device was to have been used for one calendar day with five devices dispensed to each subject.

Concomitant Medication

Rescue analgesia medication
Rescue medication was to have been allowed with morphine sulfate (MS) via patient-controlled analgesia (PCA) starting at the time of the first dose of study drug. After PCA was no longer required, rescue medication was to have been allowed with non-NSAID analgesics. Acetaminophen and NSAIDs were to have been avoided but their use did not constitute a reason for premature withdrawal from the study. Intraoperative neuraxial opioids and postoperative epidural catheters were not to be used. All concomitant medications were to have been recorded on the Concomitant Medication case report form (CRF).

Reviewer's Note: The design of the protocol allowed for administration of MS via PCA at anytime during the study including immediately before study drug administration.

Study Procedures:

A schedule of assessments is contained in Table 5.3.1.1

Screening Period
Subjects were to have signed an informed consent form prior to performance of any specific tests or evaluations. Screening procedures were to have been completed within 30 days of the day of surgery, with the exception of the serum pregnancy test, which was to have been completed within 1 week of the first dose of study drug.

Double-Blind (DB) Treatment Period (lasting up to 5 days)
Following surgery, subjects were to have been randomly assigned, in a two-to-one ratio, to receive ROX-888 or placebo when their pain intensity rating was at least 40 mm on a 100-mm VAS. For the first 48 hours the study drug was to have been administered every 6 hours. After 48 hours, subjects who continue to require study drug were to receive it up to four times daily for up to five days total. Initially, subjects were to have access to morphine sulfate administered via PCA for pain not relieved by the study drug. When PCA was no longer required rescue medication was to have been another standard (non-NSAID) analgesic such as Hydrocodone/acetaminophen. If subjects were

discharged before postoperative Day 4, they were to have been allowed to continue to self-medicate at home through postoperative Day 4.

At 20, 40, and 60 minutes and at 2, 3, 4, 5, 6, 12, 18, 24, 30, 36, 42, and 48 hours after the first dose, and before each dose given between the 48-hour dose on postoperative day 2 and the 72-hour time point on postoperative day 3, pain intensity (VAS) and quality of analgesia (5-point categorical scale) were to have been conducted. A global assessment of pain control was to have been done once daily at bedtime (sleeping subjects were not to be awakened).

Follow-Up Period
At the end of study drug administration on postoperative day 2, 3, 4, or 5 (whichever corresponded most closely to the end), a complete physical examination (excluding ophthalmic and genitourinary evaluations) and nasal examination using a light to visualize the interior nares were to have been performed. Routine hematology and serum chemistry studies were also obtained. A second follow-up visit was to have been conducted approximately 14 days after the end of dosing. At this visit a questionnaire related to cardiovascular and nasal AEs was to have been administered and a nasal examination was to have been performed.

Criteria for Removal of Subjects from Therapy
Subjects were to have been removed from the study if any of the following events occurred:

1. Allergic reaction to the nasal spray or intolerable irritation, stinging, or burning following application of the nasal spray
2. Development of significant rhinitis or rhinorrhea (eg, secondary to seasonal allergies or upper respiratory tract infection) sufficient to interfere with IN drug delivery

Table 5.3.1.1: Schedule of Assessments in Study 2005-01

Phase	Screening	Treatment				Follow-up	
Study Day	-30 to –1	0	1	2	3 & 4	2 to 5	19±3
Definitions	30 days prior to surgery through the day before surgery	Day of surgery	Postop day 1	Postop day 2	Postop days 3, 4	Postop days 2-5	Last dose +14 days
Informed Consent	X						
Demographics	X						
Medical History	X						
Physical Examination	X					X	
Vital Signs[a]	X	X	X	X		X	
Nasal examination						X	X
Body Weight	X						
Hematology[b]	X					X	
Serum Chemistry[b]	X					X	
Serum β-hCG	X						
Urinalysis	X						
Study Drug[c]		X	X	X	X		
Pain Ratings[d]		X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X

a. Vital signs will be performed at screening, prior to the first dose, every 8 hours after the first dose, and at the follow-up visit. Oxygen saturation will be measured by pulse oximetry during the use of PCA
b. Hematology: hemoglobin, hematocrit, RBC, WBC, differential, platlet count; Chermistry: bilirubin, AST, ALT, BUN, creatinine, albumin, glucose; Urinalysis: pH, glucose, protein, RBC, WBC;
c. Every 6 hours for 48 hours, then up to 4 times daily for up to 5 days total; the frequency of dosing may be reduced after 2 days;
d. Before receiving the study drug, 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; following the 48-hour dose on postoperative day 2, and for all doses given prior to the 72-hour time point on postoperative day 3, assessments will be made immediately before each dose. Whenever subjects no longer require the study drug for analgesia, all pain assessments and MS consumption recording will stop.
Reference: Adapted from Time and Events Table, page 5 Amendment 4 of Protocol 2005-01, Volume 18, Module 5

Efficacy Measures

The following efficacy measures were to have been performed:

1. Pain intensity scores measured on a 100 mm VAS, PID scores and SPID scores:
   a. SPID will be calculated and analyzed at 4 and 6 hours by adding the weighted PID scores over those intervals
   b. Peak relief will be defined as the maximum PID score

2. Quality of analgesia reported on a 5-point categorical scale (O= poor, 1 = fair, 2 = good, 3 = very good, 4= excellent)
3. Global assessment of pain control reported once-daily on a 5-point categorical scale, (0 = poor, 1 = fair, 2 = good, 3 = very good, 4 = excellent)
4. Total MS consumption measured in milligrams by PCA from the start of dosing through 72 hours. For subjects receiving rescue medication in addition to MS by PCA, the amount of additional opioid rescue medication will be converted to a MS equivalent and added to the total MS consumption. Data will be tabulated at 2-hour intervals for the first 12 hours and at 6-hour intervals for the remainder of the first 72 hours.

Efficacy Endpoints:

Primary Efficacy Endpoint: The 6-hour SPID using last observation carried forward (LOCF) was to have been the primary efficacy endpoint.

Secondary Efficacy Endpoints: Secondary efficacy measures were to have included 24-hour, 48-hour, and 72-hour MS consumption, hourly PID scores, quality of analgesia, and the global assessment of pain control.

Safety Assessments: Multiple pre-specified safety assessments were to have been performed including the following:

- Vital signs: BP, heart rate, respiratory rate, and oral temperature were to have been performed at screening, prior to the first dose, every 8 hours after the first dose during the first two days, and at the follow-up visit
- Pulse oximetry: Oxygen saturation was to have been measured during the use of PCA at all times when vital signs were measured. Oxygen saturation below 90% was to have been recorded as an AE.
- Laboratory Tests:
  Hematology: hemoglobin, hematocrit, RBC, WBC, differential, platelet count
  Urinalysis: pH, Glucose, protein, RBC, WBC
  Serum Chemistry: Bilirubin, ALT, AST, BUN, creatinine, albumin, glucose
  Hematology and chemistry evaluations were to have been performed at screening and the termination visit; urinalysis was performed only at screening.
- Nasal mucosa assessment: An assessment of the nasal mucosa was to have been made by a qualified physician, with the use of a light to illuminate the interior nares conducted at or near the time of the first follow-up visit on day 2, 3, 4, or 5 and also 14 days after the end of dosing.
- Safety questionnaire: A questionnaire containing specific questions related to cardiovascular and nasal AEs was to have been administered by telephone 14 days after the end of dosing.

Statistical Methods:

Subject Populations
All subjects receiving study drug were to have been included in the efficacy and safety analyses.

Statistical Analysis
The PID and SPID scores were to have been analyzed using 2-way analysis of covariance with the baseline PI score made prior to study drug administration as the covariate. Factors in the analysis were to have included study center, treatment and site-by-treatment interaction. The PI ratings and MS usage were to have been analyzed using 2-way analysis of variance. The quality of analgesia and the once-daily global evaluation of analgesia were to be analyzed using the Cochran-Mantel-Haenszel row mean score test stratified by study center. No interim analyses were planned.

Missing Data Imputation
Last observation carried forward (LOCF) was to have been used for the hourly pain evaluations. Data was to have been 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 this method of extrapolation, a second method, baseline observation carried forward (BOCF), was to have been used following the first use of supplemental or backup medication. Missing data between time points was to have been linearly interpolated for both methods.

Reviewer's Note:
No pain assessment was required immediately prior to administration of rescue medication. The imputation procedure used could theorectically assign a good score when rescue medication was required.

For subjects receiving rescue medication or other analgesics, the dose was converted to MS equivalents according to the American Pain Society guidelines. The MS equivalent dose was added to the MS usage for the period in which the medication was administered. For subjects who withdraw prematurely, the following convention was to apply to MS analysis:

a. If a subject dropped out after 4 hours but prior to 24 hours, data will be extrapolated to obtain 24-hour MS usage using the average per hour MS usage from the last completed 2 or 6 hour block. The 24 to 48 hour MS use will remain missing, as will the 0 to 48 hour and 0 to 72 hour MS usage.
b. If a subject dropped out prior to 4 hours after surgery, the 24-hour MS usage will be missing, as will be the 24 to 48 hour MS usage and the 0 to 48 hour MS usage and the 0 to 72 hour MS usage.
c. If a subject dropped out between 24 and 48 hours, data will be extrapolated using the average per hour MS usage from the last completed 6-hour block to calculate the 24-to 48-hour usage and the 0- to 48-hour usage. The 0-72 hour MS usage will remain missing
d. If a subject drops out between 48 and 72 hours, data will be extrapolated using the average per hour MS usage from the last completed 6-hour block to get 48 to 72 hour usage and 0 to 72 hour usage.

Safety Analyses
Adverse events were to have been summarized by treatment group with verbatim terms mapped to preferred terms and organ systems using the Medical Dictionary for Regulatory Activities (MedDRA). Event incidences were to have been presented by treatment group. Laboratory data were to have been summarized by change from baseline status.

Protocol Amendments:

Amendment 01, June 8, 2005 (prior to enrollment of first patient)
The following key changes were made to the protocol in this amendment:

- A nasal examination was added to the 14-day follow-up visit.
- The measurement of the onset of pain relief was removed.
- The 15-minute pain evaluation was deleted and evaluations at 20 and 40 minutes and 48, 56, 64, and 72 hours were added to the pain evaluations; and MS consumption data collection was extended from 48 to 72 hours.
- The schedule for collection of MS consumption data was changed from every 4 hours to every 2 hours for the first 8 hours and every 8 hours for the remainder of the first 72 hours.

Amendment 02, October 4, 2005 (prior to enrollment of first patient)
The following key changes were made to the protocol in this amendment:

- The dosing regimen was changed from every 8 hours or 3 times daily to every 6 hours or 4 times daily.
- The age range was changed from 18 years or older to 18 through 64 years, because the more frequent dosing in this study exceeded the daily dose limit for patients 65 years of age or older.
- The title and all references to orthopedic surgery and to hip and knee replacement were removed and replaced by a reference to abdominal surgery, because the orthopedic procedures that were to be targeted originally are performed primarily in an older population, whereas abdominal procedures are more often performed in patients under the age of 65.
- The schedule of efficacy evaluations was changed to drop 7, 8, 16, 32, 40, 56, and 64 hours and add 12, 36 and 60 hours. This change was made based on the corresponding change in dosing regimen from every 8 hours to every 6 hours.
- The number of subjects was increased from 180 to 300 to provide an adequate number of subjects for the 2 US sites.
- The SPID calculations were changed from 4, 6, and 8 hours to 4 and 6 hours. The 8-hour SPID was no longer relevant, because a second dose of study medication was given at 6 hours.
- Instructions for administration and storage of the study drug were changed to reflect the fact that it must be kept refrigerated to provide enhanced shelf stability.
- The sample size calculation was reworded to reflect data from the most recent ROXRO study.
- The statistical sections were rewritten. The original sections were written on the assumption that the study would be conducted at a single site.

Amendment 03, October 17, 2005 (prior to enrollment of first patient)
The following key changes were made to the protocol in this amendment:

- The timing of the first follow-up visit was changed from 2 to 5 days after the start of dosing instead of 5 to 7 days.
- The description of the dosing schedule was expanded from "every 6 hours" to "every 6 hours for 48 hours, then up to 4 times daily" for clarification.

- The schedule of pain assessments was changed to include 6-hourly assessments for the first 48 hours instead of 12-hourly, and to specify that on postoperative Day 3, assessments would be made immediately before each dose. On Day 3, assessments were correlated to dosing, as requested by the FDA.
- Removal of the drug from refrigeration was allowed the night before dosing for convenience. Previously the drug was to be removed at least 2 hours and a maximum of 8 hours before use.
- An example of the alternative analgesic regimen after PCA was added, ie, "such as Hydrocodone/acetaminophen" for clarification and to emphasize the fact that, while acetaminophen was not to be used during the use of PCA, it was permitted after PCA was stopped.

Amendment 04, November 10, 2005 (prior to enrollment of first patient)
This following key changes were made to the protocol in this amendment:

- Statements were added to indicate that the first follow-up visit would be done on a day that most closely corresponded to the day on which study drug was stopped.
- Statements were added to indicate that subjects who were sleeping did not have to be awakened for the efficacy and safety evaluations.

Amendment 05, October 12, 2006 (after enrollment of the first patient)
The following changes were made to the protocol in this amendment:

- Several sentences were added to the statistical section:
  - "The study will be conducted at multiple sites. Prior to summarizing the results by study center or to performing analyses that include center as a factor in the analysis, the smaller sites will be pooled. Details of how sites will be pooled will be specified in the statistical analysis plan."
  - The term "site-by-treatment" was changed to "center-by-treatment" for clarification.
  - "Summary statistics for the primary efficacy variable (SPID6) by pooled study center will be presented."
  - "Sample size determination was also based on power computations based on a smaller ROXRO study, Protocol 2001-03, a Phase 2 study where morphine use was not discontinued before taking the study drug. Power was calculated using the pooled standard deviation derived from the standard deviation for the placebo (SD=93.32, n=42) and the ketorolac 30-mg group (SD=78.42, n=42) for the SPID6 variable. A 2-group t-test with a 0.05 two-sided significance level will have 90% power to detect a difference in means of 34.3, assuming that the pooled or common standard deviation is 86.19 when the sample sizes in the 2 groups are 100 and 200, respectively (a total sample size of 300)."
  - "Assuming an absolute value difference between treatment groups of about 34 to46, the power calculations are similar irrespective of whether we use results from ROXRO Study 2003-01 or 2001-03."
- The original protocol stated that 300 subjects would be enrolled. This protocol amendment provided that a total of 321 subjects would be enrolled (107 placebo and 214 ketorolac subjects).

Amendment 06, November 27, 2006
The applicant states that the purpose of this amendment was to correct internal inconsistencies within Protocol Amendment 05. The following changes were made to the protocol in this amendment:

- The total number of subjects to be enrolled was amended from 300 to 321 in Section 2 (Synopsis), Section 9.1 (Overall Study Design and Plan) and Section 19.1 (Sample Informed Consent Form). The enrollment breakdown into treatment groups was amended from 200 ketorolac and 100 placebo subjects to 214 ketorolac and 107 placebo subjects.

Study Results
Enrollment
A total of 321 patients were enrolled at six sites: 1 in New Zealand, 3 in California and 2 in Texas. Enrollment at each site was as follows:

Table 5.3.1.1: Patient Enrollment in Study 2005-01

Center	Site ID	ROX-888 (N=214)	Placebo (N=107)	Total (N=321)
New Zealand	81	54 (25.2%)	28 (26.2%)	82 (25.5%)
California	82	60 (30.7%)	31 (28.7%)	160 (49.8%)
	84	17 (7.9%)	8 (7.5%)	
	85	30 (14.0%)	14 (13.1%)	
Texas	83	42 (19.6%)	22 (20.6%)	79 (24.6%)
	86	11 (5.1%)	4 (3.7%)	

Table derived from dataset ADSL

Subject Disposition
A total of 84% (180/214) of subjects in the ROX-888 treatment group and 85% (91/107) of subjects in the placebo treatment group prematurely discontinued the study before five days of dosing. The reasons for study discontinuation at end of study are summarized in Table 5.3.1.2 and subject disposition at 24 hours and 48 hours are summarized in Table 6.1.3.2 and Table 6.1.3.3, respectively.

Table 5.3.1.2: Patient Disposition in Study 2005-01

Parameter	ROX-888 (N=214)	Placebo (N=107)	Total (N=321)
Completed 5 Days of Therapy	34 (15.9%)	16 (15.0%)	50(15.6%)
Discontinued Before 5 Days of Therapy	180 (84.1%)	91 (85.0%)	271 (84.4%)
Reason For Study Discontinuation			
Adverse Event/Intercurrent Illness/ Lab Abnormality	43 (20.1%)	13 (12.1%)	56 (17.4%)
Unsatisfactory Response	1 (0.5%)	2 (1.9%)	3 (0.9%)
Subject's Need For Analgesia Decreased	125 (58.4%)	66 (61.7%)	191 (59.5%)
Subject Request	8 (3.7%)	3 (2.8%)	11 (3.4%)
Investigator Decision	1 (0.5%)	2 (1.9%)	3 (0.9%)
Protocol Violation	1 (0.5%)	0 (0.0%)	1 (0.3%)
Other	1 (0.5%)	5 (4.6%)	6 (1.9%)

Reference: Adapted from Final Clinical Study Report of Protocol 2005-01, Module 5, Volume 17, Table 10.1: Summary of Subject Disposition by Treatment Group

Only 50 subjects completed five days of study dosing. The high discontinuation rate prior to completion of the study does not significantly impact on the interpretation of the efficacy findings since the endpoints of primary interest to the FDA are at 48 hours and earlier. Overall, the main reasons for study discontinuation were "Subject's Need for Analgesia Decreased" and "Adverse Event/Intercurrent Illness/Laboratory Abnormality". The percentage of subjects who discontinued early due to an adverse event was higher in the ROX-888 treatment group (20.1%) compared to the placebo treatment group (12.1%). Approximately 45% of subjects in the ketorolac group and 50% in the placebo group completed dosing up to 48 hours (Table 6.1.3.3)

Protocol Violations
The majority of protocol deviations were due to missed procedures and visits or procedures performed outside the window stipulated by the protocol. A total of 24 subjects had dosing violations where study drug was administered early or late or the dose of study drug was not administered at the planned time point. An additional 27 protocol deviations occurred that included inclusion/exclusion criteria, concomitant medication, or informed consent. Some of the specific protocol deviations included: PI score<40mm, allergic to opioids, clinically significant lab results at baseline, subject weighed more than allowed, HIPAA authorization not obtained and positive pregnancy test.

Demographics
The mean age was 45.9 years with a range from 22 to 70 years. The majority of subjects were female (309/321, 96.3%) and white (230/321, 71.7%). All subjects underwent abdominal surgery except for one patient in the ROX-888 treatment group. General anesthesia was used in greater than 98% of the subjects in both treatment groups. The demographic characteristics were similar between both treatment groups for age, gender, height, vital signs, type of surgery and anesthesia (Table 5.3.1.3).

Table 5.3.1.3: Demographics and Baseline Characteristics in Study 2005-01

Parameter		ROX-888 N=199	Placebo N=101
Age	Mean (SE)	45.6 (0.58) years	46.4 (0.87) years
	Range	22-64 years	28-70 years
Gender	Male, n (%)	8 (3.7%)	4 (3.7%)
	Female, n (%)	206 (96.3%)	103 (96.3%)
Race	White, n (%)	154 (72.0%)	76 (71.0%)
	Black, n (%)	23 (10.7%)	11 (10.3%)
	All other, n (%)	37 (7.3%)	20 (18.7%)
Weight (kg)	Mean (SE)	77.0 (1.29) kg	79.7 (1.71) kg
	Range	45-141	49-126
Height (cm)	Mean (SE)	164.0 (0.50) cm	165.1 (0.84) cm
	Range	145-188	147-191
Systolic BP (mmHg)	Mean (SE)	126.1(1.27)	126.6 (1.73)
	Range	90-220	96-185
Diastolic BP (mmHg)	Mean (SE)	73.1 (0.83)	72.4 (1.25)
	Range	40-120	34-101
Pulse Rate (beats/min)	Mean (SE)	78.3 (0.88)	75.2 (1.10)
	Range	54-124	48-113
Respiration (breaths/min)	Mean (SE)	17.1 (0.15)	16.7 (0.20)
	Range	10-24	8-22
Type Of Surgery	Abdominal	213 (99.5%)	107 (100%)
	Other	1 (0.5%)	0 (0.0%)
Type Of Anesthesia	General Only	211 (98.6%))	105 (98.1%)
	Spinal Only	1 (0.5%)	0 (0.0%)
	General And Spinal	0 (0.0%)	1 (0.9%)
	Other only	1 (0.5%)	1 (0.9%)
	General and other	1 (0.5%)	0 (0.0%)

Parameter		ROX-888 N=199	Placebo N=101
Age	Mean (SE)	45.6 (0.58) years	46.4 (0.87) years
	Range	22-64 years	28-70 years
Gender	Male, n (%)	8 (3.7%)	4 (3.7%)
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	Black, n (%)	23 (10.7%)	11 (10.3%)
	All other, n (%)	37 (7.3%)	20 (18.7%)
Weight (kg)	Mean (SE)	77.0 (1.29) kg	79.7 (1.71) kg
	Range	45-141	49-126
Height (cm)	Mean (SE)	164.0 (0.50) cm	165.1 (0.84) cm
	Range	145-188	147-191
Systolic BP (mmHg)	Mean (SE)	126.1(1.27)	126.6 (1.73)
	Range	90-220	96-185
Diastolic BP (mmHg)	Mean (SE)	73.1 (0.83)	72.4 (1.25)
	Range	40-120	34-101
Pulse Rate (beats/min)	Mean (SE)	78.3 (0.88)	75.2 (1.10)
	Range	54-124	48-113
Respiration (breaths/min)	Mean (SE)	17.1 (0.15)	16.7 (0.20)
	Range	10-24	8-22
Type Of Surgery	Abdominal	213 (99.5%)	107 (100%)
	Other	1 (0.5%)	0 (0.0%)
Type Of Anesthesia	General Only	211 (98.6%))	105 (98.1%)
	Spinal Only	1 (0.5%)	0 (0.0%)
	General And Spinal	0 (0.0%)	1 (0.9%)
	Other only	1 (0.5%)	1 (0.9%)
	General and other	1 (0.5%)	0 (0.0%)

Reference: Adapted from Final Clinical Study Report of Protocol 2005-01, Module 5, Volume 17, Table 11.1: Summary of Baseline Demographic Characteristics

Efficacy Results

Primary Endpoint:

The protocol-specified primary efficacy endpoint was the 6-hour SPID following the first dose of study drug on the day of surgery. The sponsor determined that the ketorolac group had a significantly higher mean 6-hour SPID score (115.6) compared to the placebo group (92.6). The least square means (SE) for the SPID6 was 117.4 for ROX-888 and 89.9 for placebo, p=0.032.

Secondary Endpoints:

Morphine Sulfate Consumption: The mean total amount of morphine used from 0 to 24 hours, 24 to 48 hours and 0 to 48 hours was statistically less for the ROX-888 treatment group compared to the placebo treatment group (Table 5.3.1.4). The mean amount of morphine used for subjects on ROX-888 was approximately 26% less compared to placebo for the 0 to 48 hour time period. The differences between treatment groups for the time intervals of 48 to 72 hours and 0 to 72 hours were not statistically significant.

Table 5.3.1.4: Morphine Usage in Study 2005-01

	Amount of Morphine Used (mg)		
Time Interval	**ROX-888**	**Placebo**	**P value**
0 to 24 Hours			
Mean (SE)	42.4 (2.04)	54.0 (3.49)	0.003[a]
n	210	106	
24 to 48 Hours			
Mean (SE)	23.1 (2.25)	31.3 (3.53)	0.041[a]
n	140	80	
0 to 48 Hours			
Mean (SE)	66.7 (4.43)	89.7 (7.23)	0.004[a]
n	140	80	
48 to 72 Hours			
Mean (SE)	14.7 (8.84)	13.0 (6.47)	0.955[a]
n	9	13	
0 to 72 Hours			
Mean (SE)	81.5 (24.42)	121.1 (36.44)	0.304[a]
n	10	13	

Note 1: Total morphine usage (mg) was calculated by adding all IV-PCA morphine usage and morphine equivalents for other analgesic medications administered for that time period using the American Pain Society guidelines.
a. By 2-way ANOVA
Reference: Adapted from Final Clinical Study Report of Protocol 2005-01, Module 5, Volume 17, Table 11.3: Summary of PCA Morphine Usage

Global Assessment of Pain Control: The global assessment of pain control was not statistically significant on Days 0, 2, 3, and 4.

Quality of Analgesia: The quality of analgesia was rated as significantly better in the ROX-888 treatment group compared to placebo at most time points from 20 minutes to 24 hours. At 30, 36, 42, 48 and 72 hours the difference between treatment groups was not significant.

Additional Endpoints Requested by FDA

SPID 24 and SPID 48

As noted earlier, the protocol-specified primary endpoint was the SPID6. The standard for approval is a demonstration of efficacy over at least 48 hours. Thus, the Agency requested that the Applicant conduct an analysis using SPID 24 and SPID 48 as endpoints which were reported as positive. The FDA statistician, Feng Li, Ph.D., also determined that the SPID 24 and SPID 48 were statistically significant when LOCF or BOCF imputation methods alone were used but not when combined LOCF/BOCF imputation methods were used. The usual imputation method used by the Division for dropouts due to adverse events is BOCF. Using BOCF imputation for the SPID 24 and SPID 48, the difference in least square means was 112.1 and 242.6, respectively (Table 6.1.4.2).

Table 6.1.4.2: SPID 24 and SPID 48 for Study 2005-01

Imputation	Endpoint	Stat	placebo	Ketorolac	P_Value
LOCF	spid24h	LEAST SQUARE MEANS (SE)	514.5 (47.19)	630.3 (34.36)	0.043
		Difference in Means	115.8		
		95% Confidence Interval	3.8 - 227.8		
		Number of non-missing	107	213	
		Number of Extrapolation	51 (48%)	88 (41%)	
	spid48h	LEAST SQUARE MEANS (SE)	1096.7 (101.46)	1347.1 (73.89)	0.042
		Difference in Means	250.5		
		95% Confidence Interval	9.7 - 491.3		
		Number of non-missing	107	213	
		Number of Extrapolation	98 (92%)	182 (85%)	
BOCF	spidb24h	LEAST SQUARE MEANS (SE)	454.9 (42.08)	567.0 (30.65)	0.028
		Difference in Means	112.1		
		95% Confidence Interval	12.2 - 212		
		Number of non-missing	107	213	
		Number of Extrapolation	51 (48%)	88 (41%)	
	spidb48h	LEAST SQUARE MEANS (SE)	613.5 (65.89)	856.1 (47.99)	0.002
		Difference in Means	242.6		
		95% Confidence Interval	86.2 - 398.9		
		Number of non-missing	107	213	
		Number of Extrapolation	98 (92%)	182 (85%)	

Reference: Dr. Feng Li

5.3.2 Study 2003-01

The following summary of the design of Study 2003-01 was derived from amendment #1 of Protocol 2003-01. The first patient was not enrolled until the changes in protocol amendment #1 (May 1, 2003) were incorporated into the conduct of the study. Therefore the applicant did not include the initial protocol in the NDA submission since it was never used in the conduct of the clinical trial.

Title: "A Phase 3, Double-blind, Randomized Study of the Safety,Tolerability, and Analgesic Efficacy of Multiple Doses of Ketorolac Tromethamine Administered Intranasally for Postoperative Pain"

Dates Conducted: The first subject was enrolled in the study June 30, 2003 and the last subject completed the study June 15, 2005.

Objectives: The primary objective of the study was to evaluate the analgesic efficacy of multiple intranasal (IN) doses of ketorolac administered for up to 5 days. The secondary objective was to evaluate the safety and tolerability of this dosing regimen.

Overall Design: This was a Phase 3, randomized, double-blind, placebo-controlled, single-center study of IN ketorolac in subjects who underwent major surgery. Following surgery, subjects exhibiting signs of discomfort were to have received an IV opioid titrated to comfort. Once subjects were alert and their pain intensity rating was greater than or equal to 40 mm on a 100-mm visual analog scale (VAS), they were to have been randomized 2:1 to receive IN ketorolac 30 mg or IN placebo. Thereafter, subjects were to have received study drug every 8 hours for 48 hours and then up to 3 times daily for up to 5 days total. Subjects discharged before Day 4 were to have been allowed to self-medicate at home through Day 4.

The evaluation of onset, peak, and duration of analgesia was to have been done on the first postoperative day after the PCA was discontinued 3 hours before the morning dose. When subjects reported a VAS score of at least 40, the dose of IN ketorolac or placebo was to have been administered.

Inclusion Criteria

Patients were to have met the following criteria:

1. Men or women, age 18 or older
2. Body weight ≥100 pounds and ≤ 300 pounds
3. Women of child bearing potential must have a negative serum pregnancy test result
4. Able to provide written informed consent
5. At least moderate pain as determined by a PI score of ≥ 40 mm on a 100-mn VAS
6. Expected to remain in the hospital for at least 48 hours with the possibility of remaining for 5 days
7. Willing and able to comply with all testing and requirements
8. Willing and able to complete the posttreatment visit

Exclusion Criteria

Patients were to be excluded if any of the following applied:

1. Allergy or sensitivity to ketorolac or ethylene diamine tetraacetic acid (EDTA)
2. Allergic reaction to aspirin or other NSAIDs
3. Current upper respiratory tract infection or other respiratory tract condition that could interfere with the absorption of the nasal spray or with the assessment of AEs
4. Use of any IN product within 24 hours prior to study entry
5. Clinically significant abnormality on screening laboratory tests
6. History of cocaine use resulting in nasal mucosal damage
7. Active peptic ulcer disease, recent (defined as within 6 months) history of peptic ulcer disease or gastrointestinal bleeding considered by the investigator to be clinically significant
8. Advanced renal impairment (serum creatinine > 1.5mg/dL) or a risk for renal failure due to volume depletion
9. A history of any other clinically significant medical problem, which in the opinion of the investigator would interfere with study participation
10. Participation within 30 days of study entry or within 5 times the half-life in another investigational drug study
11. Allergy or significant reaction to opioids
12. Pregnancy or breastfeeding
13. Previous participation in this study

Study Medication

Throughout this review, the administered dose of ketorolac tromethamine is reported as 30 mg whereas the actual dose delivered was 31.5 mg. This discrepancy is due to (b) (4) (b) (4), which means that two sprays intended to deliver 30 mg, in fact delivered 31.5 mg.

Subjects were to have been randomly assigned, in a ratio of two to one, IN ketorolac tromethamine 30 mg or IN placebo. The ketorolac nasal solutions were to have been provided in a disposable, multidose, metered-spray device. Doses were to have been administered as one spray (100 µL) into each nostril (200 µL total). Each device was to have been used for one calendar day with five devices dispensed to each subject.

Concomitant Medication

Rescue analgesia medication
Continuous background analgesia (morphine sulfate (MS) via patient-controlled analgesia (PCA)) was permitted, starting at the time of the first dose of study drug and continuing for the first 48 hours after surgery. After PCA was no longer required, rescue medication was to have been allowed with non-NSAID analgesics. All concomitant medications were to have been recorded on the Concomitant Medication case report form (CRF).

Prohibited medications:
The only absolute prohibition during the study was to have been the use of any NSAID other than the study drug.

Study Procedures:

A schedule of assessments is contained in Table 5.3.2.1

Screening Period
Informed consent was to have been obtained prior to performance of any protocol driven evaluations or treatments. Screening procedures were to have been completed within 30 days of the day of surgery, with the exception of the serum pregnancy test, which was to have been completed within 1 week of the first dose of study drug.

Double-Blind (DB) Treatment Period (lasting up to 5 days)
Subjects were to have been randomly assigned in a two to one ratio to receive ROX-888 or placebo when the pain intensity score was at least 40 mm on a 100-mm VAS. Subjects were to have received study drug every eight hours for 48 hours and then 3 times daily for up to 5 calendar days in total. The frequency of dosing could be reduced after 48 hours. Rescue medication/background analgesia was to have been allowed with morphine sulfate (MS) via patient-controlled analgesia (PCA) starting at the time of the first dose of study drug and continuing for the first 48 hours after surgery. After PCA was no longer required, rescue medication was to have been allowed with non-NSAID analgesics. If subjects were discharged before postoperative Day 4, they were to have been allowed to continue to self-medicate at home through postoperative Day 4.

On the first postoperative day, evaluation of onset, peak, and duration of analgesia was to have been assessed. The PCA was to have been discontinued 3 hours before the morning dose. When subjects reported a VAS score of at least 40, the dose of IN ketorolac or placebo was to have been administered. If the dose was before 8:00 AM on Day 1, the second dose could be used. A single stopwatch was to have been used to measure the onset of "meaningful" analgesia. Subjects were to have been provided a stopwatch at the time of the morning dose of study drug on the first postoperative day and instructed to press the button when they have experienced "meaningful" pain relief.

Follow-Up Period
Subjects were to have a follow-up visit on postoperative Day 4 or 5 or within 5 days of the end of dosing. Protocol Amendment 2 provided for a nasal examination. A safety follow-up evaluation conducted by telephone approximately 14 days after the end of dosing in a subset of subjects was added in Protocol Amendment 3.

Criteria for Removal of Subjects from Therapy
Subjects were to have been removed from the study if any of the following events occurred:

1. Allergic reaction to the nasal spray or intolerable irritation, stinging, or burning following application of the nasal spray
2. Development of significant rhinitis or rhinorrhea (eg, secondary to seasonal allergies or upper respiratory tract infection) sufficient to interfere with IN drug delivery

Table 5.3.2.1: Schedule of Assessments in Study 2003-01

Visit Number	1	2				3
Phase	SCREENING	MEDICATION				FOLLOW-UP
Study Day	-30 to 0	0	1	2	3 & 4	4 to 9
Definitions	30 days prior to surgery through the day of surgery	Day of surgery	Postoperative day 1	Postoperative day 2	Postoperative days 3 & 4	Postoperative days 4-9
Informed Consent	X					
Demographics	X					
Medical History	X					
Physical Examination	X					X
Vital Signs[a]	X	X	X	X		X
Body Weight	X					
Hematology[b]	X					X
Serum Chemistry[b]	X					X
Serum β-hCG	X					
Urinalysis	X					
Study Drug[c]		X	X	X	X	
Pain Ratings[d]		X	X	X	X	
Concomitant Medications	X	X	X	X	X	X
Adverse Events		X	X	X	X	X
Termination						X

a. Vital signs will be performed at screening, prior to the first dose, every 8 hours after the first dose, and at the termination (follow-up) visit. Oxygen saturation will be measured by pulse oximetry during the use of PCA.
b. See Section 9.5.1.4 for a list of specific tests.
c. Every 8 hours for 48 hours, then 3 times daily for up to 5 days total; the frequency of dosing may be reduced after 48 hours.
d. Before receiving the study drug, and at 8, 16, 24, 32, 40, and 48 hours after the first dose. In addition, after the morning dose on postoperative day 1, at 30 minutes, and at 1, 2, 3, 4, 5, 6, and 8 hours. After 48 hours, only the global assessment will be made at bedtime daily.

Reference: From Amendment 1 of Protocol 2003-01, NDA Amendment submitted January 28, 2009, page 6, Time and Events Table

Reviewer's Note: Footnote d in the above table describes subjects undergoing pain ratings at 8 hours on postoperative day 1. However, the protocol in Section 9.5.3.2 Study Evaluations does not include an 8 hour pain evaluation on the first postoperative day. The 8 hour pain evaluation was not added until later in Amendment 02.

Efficacy Measures

The following efficacy measures were to have been performed:

1. Pain Intensity measured on a 100-mm VAS
    a. Pain Intensity Difference (PID)
        1. Peak relief defined as the maximum PID score prior to restarting the PCA
    b. Sum of Pain Intensity Difference (SPID) on the first postoperative at 4 and 6 hours. *Amendment 02* included SPID at 4, 6 and 8 hours.
2. Onset of pain relief defined two ways:
    c. Measured with a stopwatch on the first postoperative day. Patients were instructed to press the button when they experienced "meaningful" pain relief.
    d. Time to onset of at least "good" pain control measured on a 5-point scale (0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent)
3. Duration of Analgesia defined as the time to the first request to restart the PCA following the first dose of study medication on the first postoperative day
4. Quality of Analgesia measured on a 5-point categorical scale (0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent)
5. Global Evaluation of Pain Control assessed by the following question, "How was your pain control overall?" measured on a 5-point categorical scale (0 = poor, 1 = fair, 2 = good, 3 = very good, and 4= excellent) once daily at bedtime.
    After 48 hours the only pain assessments were the bedtime global evaluations.
6. Total MS consumption measured at 4-hour intervals for the first 48 hours. For subjects receiving opioid rescue medication in addition to MS by PCA, the amount of additional opioid rescue medication was converted to a MS equivalent and added to the total MS consumption.

Timing of efficacy evaluations
Subjects were to have been assessed immediately before receiving the study drug and immediately before each subsequent dose during the first 48 hours of the study, at 8, 16, 24, 32, 40, and 48 hours. On the first postoperative day (day 1) subjects were to have been assessed before the first dose of study drug and at 30 minutes and 1, 2, 3, 4, 5, and 6 hours after the morning dose. Protocol Amendment 02 provided for subjects to have another evaluation at 8 hours.

Efficacy Endpoints

Primary Efficacy Endpoint: There is no explicit identification of a primary endpoint in Amendment 01. The sponsor in Amendment 02 states that no primary endpoint was previously identified and now identifies the SPID 6 as the primary endpoint. According to the applicant, the identification of a primary endpoint occurred as the result of a meeting with the FDA, who requested the identification of a primary efficacy measure. However, there is circumstantial evidence to suggest that the patients'

global assessment of pain may have been the primary endpoint since this measure was the basis for determining power and sample size. The sponsor states in Section 9.7.2 (Determination of Sample Size) that the sample size was based on mean scores of subjects' global evaluations at the end of day 2 from Roxro study 2001-03. In addition the position of "patients' global assessment of pain control" as the first efficacy variable in Section 9.7.1.3 Efficacy Analyses of Amendment 01 and its separation from all of the other efficacy variables suggests that this efficacy variable was of more importance i.e. the primary efficacy endpoint (see below):

> "9.7.1.3 Efficacy Analyses
>
> The measure of overall efficacy is the patients' global assessment of pain control at the end of day 2. The global assessment of pain control will be measured on a 5-point categorical scale where O=poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent.
>
> Other efficacy variables for this study will be:
> (1) Pain relief defined in two ways:
> a. Time to …"

Assuming that selection of the SPID 6 as the primary endpoint in Amendment 02 was done under blinded conditions, interpretation of the efficacy findings would not be affected. The acceptability of selecting a primary endpoint once the study is in progress is supported by the following FDA comment made in the, December 13, 2004, End of Phase 2 Meeting for this NDA:

> However, primary endpoints need to be clearly defined prior to unblinding the study.

Use of a VAS pain intensity measure which the SPID is based on is an acceptable endpoint in the assessment of analgesic efficacy. However, the SPID 6 does not provide information about the durability of analgesic effect beyond six hours. In the Type B Meeting on July 16, 2004, the Division stated that:

> Efficacy also needs to be established beyond the first dose, and beyond the 24 hours proposed in the draft Phase 3 protocol; for example, Toradol is currently approved for use up to 5 days.

For a further discussion of endpoints and the efficacy analysis the reader is referred to Section 6, Review of Efficacy.

Secondary Efficacy Endpoints: Secondary efficacy measures (specified in Amendment 02) included 24-hour and 48-hour MS consumption, hourly PID scores, quality of analgesia, the global assessment of pain control, and onset and duration of pain relief.

Safety Assessments: Multiple pre-specified safety assessments were to have been performed including the following:

- Vital signs: BP, heart rate, respiratory rate, and oral temperature were to have been done every 8 hours for the first 48 hours
- Oxygen saturation: Pulse oximetry was to have been measured during the use of PCA when vital signs were measured. An oxygen saturation below 90% was recorded as an AE.

- Nasal mucosa assessment: As provided in Amendment 02, an assessment of the nasal mucosa was to have been conducted at or near the time of the follow-up visit in a subset of subjects.
- Laboratory Tests:
  Hematology: hemoglobin, hematocrit, RBC, WBC, differential, platelet count
  Urinalysis: pH, Glucose, Protein, RBC, WBC
  Serum Chemistry: Bilirubin, ALT, AST, BUN, creatinine, albumin, glucose
  Hematology and chemistry evaluations were performed at screening and the termination visit; urinalysis was performed only at screening.
- Safety questionnaire: As provided in Amendment 03, a questionnaire containing specific questions related to cardiovascular and nasal AEs was administered by telephone 14 days after the end of dosing.

Statistical Methods:

Statistical Plan
The two treatment groups were to have been compared statistically to evaluate the comparability of the groups at baseline and to compare efficacy between the groups. The PI ratings and hourly PID scores, SPID scores, and MS usage were to have been analyzed using a one-way ANOVA model. The onset of pain relief and the duration of analgesia were to have been summarized using Kaplan-Meier methods, and treatment group differences were to have been analyzed using the log-rank test. The quality of analgesia data and the once-daily global evaluation of analgesia were to have been analyzed using the Cochran-Mantel-Haenszel raw mean score test. All statistical tests were to have been two-tailed and statistical significance declared at the .05 alpha level. All subjects receiving study drug were to have been included in the efficacy and safety analyses. The measurement of overall efficacy was the patients' global assessment of pain control at the end of day 2. Other efficacy variables for this study are described in the section on Efficacy Measures. Missing pain intensity data between time points were to have been linearly interpolated. Data on MS consumption were to be collected in 4-hour intervals. For subjects receiving rescue medication or other analgesics, the dose was converted to MS equivalents according to the American Pain Society guidelines. The MS equivalent dose was added to the MS usage for the period in which the medication was administered. For subjects who withdraw prematurely, the following convention was to apply to MS analysis:

> a. If a subject dropped out after 4 hours but prior to 24 hours, data will be 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 will remain missing, as will the 0- to 48-hour MS usage.
> b. If a subject dropped out prior to 4 hours after surgery, the 24-hour MS usage will be missing, as will be 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 will be 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.

There was no identification of a specific primary endpoint in Amendment 01. The sponsor in Amendment 02 states that no primary endpoint was previously identified and identified the SPID 6 as the primary endpoint. However, as noted previously in the review on efficacy endpoints there is circumstantial

evidence to suggest that the patients' global assessment of pain may have been the endpoint of primary interest to the Applicant.

Amendment 02 Changes
The 6-hour SPID was identified as the primary efficacy measure in this protocol amendment. A total of 240 patients was originally planned for the study based on Roxro Study 2001-03. In this amendment the total enrollment was increased to 300 patients with the following explanation by the sponsor:

> This change resulted from a request from the FDA to collect data on local nasal mucosal tolerance with nasal examinations, which were not a part of the original protocol.

Amendment 03 Changes
Methods for the Primary Efficacy Endpoint: This amendment added that the single-dose hourly PID and SPID scores will be analyzed using the analysis of covariance with the baseline PI rating made prior to the single-dose study drug administration as a covariate in the model. The amendment also included how missing data will be handled for the primary endpoint as follows:

> For the hourly pain evaluations, data will be 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 will be examined. For this alternative method, missing data will be handled as follows. For the hourly pain evaluations, data will be 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 will be linearly interpolated for both methods.

In Protocol Amendment 03 power was recalculated using the SPID6 results from Roxro Study 2001-03.

> Power was recalculated using the pooled standard deviation (sd = 86.19) derived from the standard deviation for the placebo (sd = 93.32, n =42) and the ketorolac 30 mg (sd = 78.42, n= 42) groups, respectively. A 2-group t-test with a .052-sided significance level will have 90% power to detect a difference in means of 34.3, assuming that the common standard deviation is 86.19, when the sample sizes in the 2 groups are 100 (placebo) and 200 (ketorolac 30 mg), respectively (a total sample size of 300).
>
> The actual difference in means using the means of the placebo and ketorolac 30 mg group from study 2001-03 was 64.9 (placebo mean = -130.60 and ketorolac 30mg mean =-195.50). A 2-group t-test with a .05 2-sided significance level will have greater than 99% power to detect a difference in means of 64.9, assuming that the common standard deviation is 86.19, when the sample sizes in the 2 groups are 100 and 200, respectively (a total sample size of 300).

Populations
All subjects receiving study drug were included in the efficacy and safety analyses.

Safety Analyses
Adverse events were summarized by treatment group and provided as data listings. Verbatim terms were mapped to preferred terms and organ systems using the Medical Dictionary for Regulatory Activities (MedDRA). Event incidences were presented by treatment group.

percentages were calculated for each treatment group. Laboratory data were summarized by treatment group in terms of change from baseline status.

Key Protocol Amendments:

Amendment 01, May 1, 2003 (prior to enrollment of first patient):
The following changes were made to the protocol in this amendment:

- Wording was changed to clarify that the pain intensity and quality of analgesia ratings would not continue after 48 hours. The following sentence was added "After 48 hours, the only pain assessments will be the bedtime global evaluation"

- The hourly evaluations following the first dose on the day of surgery were eliminated and replaced by evaluations every 8 hours; hourly examinations were instead done on the first postoperative day (Day 1), following discontinuation of the PCA. The applicant states that this modification was done to accommodate the FDA's request for efficacy data from treatment with ketorolac alone.

- The dosing schedule was changed to allow for less frequent dosing after 48 hours. This change was intended to reflect the possibility that analgesic requirements may diminish with time.

- The exclusion criteria "expected to remain in the hospital for 5 days" was changed to "expected to remain in the hospital for at least 48 hours with the possibility of remaining for 5 days."

Amendment 02, January 6, 2005:
The following changes were made to the protocol in this amendment:

- The number of subjects was increased from 240 (80 in placebo group and 160 in ketorolac group) to 300.

- A nasal examination was added to the termination examination at the request of the FDA.

- The 6-hour SPID was identified as the primary efficacy variable .

- An 8-hour pain evaluation was added to the 6-hour evaluations on the first postoperative day .

- The SPID analysis was changed from 4 and 6 hours to 4, 6, and 8 hours.

Amendment 03, March 14, 2005:
The following changes were made to the protocol in this amendment:

- A telephone contact 14 days after the end of dosing was added and a questionnaire for use during the telephone contact was added at the request of the FDA.

- The statistical section was changed to add 2 new elements requested by the FDA:
  1) analysis of the primary endpoint (6-hour SPID) using both LOCF and BOCF and
  2) the covariate of baseline pain score was to be used for PID and SPID analyses

The SAP indicated that normal laboratory reference ranges according to the Chernecky and Berger reference were used when in fact the reference ranges used were according to Harrison's Principles of Internal Medicine.

Study Results

Enrollment

Three hundred patients were enrolled in a single-center in New Zealand. A total of 199 subjects received at least one dose of ROX-888 and 101 subjects received placebo treatment.

Subject Disposition

A total of 31% (61/199) of subjects in the ROX-888 treatment group and 29% (29/101) of subjects in the placebo treatment group prematurely discontinued the study before five days of dosing. The reasons for study discontinuation at the end of the study are summarized in Table 5.3.2.2 and subject disposition at 24 hours and 48 hours are summarized in Table 6.1.3.2 and Table 6.1.3.3, respectively. Approximately 75% of subjects in the ketorolac group and 81% in the placebo group completed dosing up to 48 hours (Table 6.1.3.3).

Table 5.3.2.2: Patient Disposition in Study 2003-01

Reason For Study Discontinuation	ROX-888 (N=199)	Placebo (N=101)	Total (N=300)
Completed 5 Days of Therapy	138 (69.3%)	72 (71.3%)	210(70.0%)
Discontinued Before 5 Days of Therapy	61 (30.7%)	29 (28.7%)	90 (30.0%)
Adverse Event/Intercurrent Illness/ Lab Abnormality	34 (17.1%)[1]	15 (14.9%)[2]	49 (16.3%)
Unsatisfactory Response	0 (0.0%)	2 (2.0%)	2 (0.7%)
Subject's Need For Analgesia Decreased	4 (2.0%)	0 (0.0%)	4 (1.3%)
Subject Request	22 (11.1%)	8 (7.9%)	30 (10.0%)
Investigator Decision	1 (0.5%)	1 (1.0%)	2 (0.7%)
Other	0 (0.0%)	3 (3.0%)	3 (1.0%)

1 Includes Subject 176 originally coded as "Subject Request"
2 Includes Subject 754 originally coded as "Investigator Decision"
Reference: Adapted from Final Clinical Study Report of Protocol 2003-01, Module 5, Volume 15, Table 2A: Subject Disposition and Termination

Due to the relatively large number of study discontinuations due to "Subject Request", the accuracy of coding this term was checked by comparing the "ISS Reason for Discontinuation" variable name "DSREAS" to the, "Original Reason for Discontinuation" variable name "DSREASO" in the analysis dataset "ADSL". "Subject Request" was consistent with the "Original Reason for Discontinuation" as coded in the dataset except for possibly two patients:

Subject 017 in the ROX-888 treatment group was coded as "Patient did not want nasal spray anymore"

Subject 093 in the placebo treatment group was coded as "Patient feeling miserable"

Subject 017 and Subject 093 coded as "Subject Request" appear to have discontinued due to an adverse event that was not fully elicited at the time the CRF was completed. However, this potential coding difference would not affect the overall conclusions and it is noted that one of the patients was in the placebo treatment group and the other in the ROX-888 treatment group. There were no apparent discrepancies in the coding of the other subjects when comparing discontinuations due to "Subject Request" and the "Original Reason for Discontinuation" but this does not exclude the possibility of the investigator inadequately eliciting the true reason for discontinuation or not recording the reason appropriately in the CRF. In fact the applicant identified two subjects (Subject 176 and Subject 754) that were coded in the dataset as primary termination reasons were "Subject request" and "Investigator decision" respectively but actually had adverse events. Subject 176 in the ROX-888 treatment group withdrew consent following 1 dose of study drug after experiencing nasal irritation. The appropriate box was checked by the investigator in the adverse event section of the CRF but in the section on study drug discontinuation the wrong box was checked i.e. "Patient request". The sponsor found this error and the subject is included in subjects who discontinued due to an adverse event in the table above. The investigator decided to discontinue Subject 754 in the placebo treatment group because the subject was incoherent. As in the case above, the appropriate box was checked in the adverse event section of the CRF but not in the section on study drug discontinuation. Both of these subjects were considered to have discontinued the study due to adverse events by the applicant. The correction of these coding errors reflects that the applicant has attempted to review and correct at least obvious coding errors. The FDA statistician recalculated efficacy assuming that all the subjects coded as discontinued due to "Subject Request" actually discontinued to "Adverse Event." Using the LOCF/BOCF imputation method the p value remained statistically significant but changed from 0.008 to 0.023.

The overall completion and dropout rates were similar in the two treatment groups with slightly more discontinuations in the ROX-888 treatment group compared to the placebo treatment group. More subjects in the ROX-888 treatment group discontinued due to nasal irritation (discussed in Section 7 Review of Safety).

Protocol Violations
The most common protocol deviation was in study drug dosing. Sixteen subjects took NSAIDs: nine in the placebo group and seven in the ketorolac group.

Demographics
The mean age of subjects in the trial was 51.5 years, with a range from 19 to 81 years. Of the 300 subjects, 31 % were male and 69% female. The majority of patients 75% were White (Non-Hispanic and Non-Latino), 21.3% were Polynesian. The demographic characteristics were similar between treatment groups for age, sex, ethnicity, height and type of surgery. Statistically significant differences were found by the applicant between the two treatment groups in weight. The average

weight in the ketorolac treated group was 86.8 kg vs. 82.2 kg in the placebo group. This difference does not appear to have any clinical significance.

Table 5.3.2.2: Demographics and Baseline Characteristics in Study 2003-01

	Parameter	ROX-888 N=199	Placebo N=101
Age[1]	Mean (SE)	51.7 (0.92) years	51.0 (1.20) years
	Median	50.3 years	49.5 years
	Range	19-81 years	22-73 years
	Age < 65, n (%)	161 (81%)	85 (84%)
	Age ≥ 65, n (%)	38 (19%)	16 (16%)
Gender	Male, n (%)	55 (28%)	37 (37%)
	Female, n (%)	144 (72%)	64 (63%)
Race	Caucasian (Non-Hispanic and Non-Latino), n (%)	147 (74%)	78 (77%)
	Polynesian, n (%)	44 (22%)	20 (20%)
	Hispanic or Latino, n (%)	4 (2%)	0 (0%)
	Asian, n (%)	2(1%)	2 (2%)
	Other, n (%)	2(1%)	1 (1%)
Weight (kg)	Mean (SE)	82.2 (1.26) kg	86.8 (1.82) kg
	Median	80.0 kg	85.8 kg
Height (cm)	Mean (SE)	167.1 (0.70) cm	169.2 (0.99) cm
	Median	166.4 cm	167.3 cm
Systolic BP (mmHg)	Mean (SE)	135 (1.43)	141 (2.56)
	Median	135	138
Diastolic BP (mmHg)	Mean (SE)	76 (0.74)	81 (1.38)
	Median	76	81
Pulse Rate (beats/min)	Mean (SE)	73.4 (0.86)	72.4 (1.14)
	Median	72	72
	Range	48-128	49-112
Respiration (breaths/min)	Mean (SE)	16.1 (0.11)	15.9 (0.14)
	Median	16.0	16.0
	Range	12-22	12-20
Type Of Surgery	Abdominal	102 (51%)	54 (54%)
	Orthopedic	96 (48%)	43 (43%)
	Other	1 (0.5%)	4 (4%)
Type Of Anesthesia	General Only	152 (76%))	80 (79%)
	Spinal Only	40 (20%)	19 (19%)
	General And Spinal	7 (3.5%)	2 (2.0%)

1 Age < 65 and ≥ 65 derived from dataset ADSL
Reference: Adapted from Final Clinical Study Report of Protocol 2003-01, Module 5, Volume 15, Table 1: Demographics and Other Baseline Characteristics

Efficacy Results

Primary Endpoint: The protocol-specified primary efficacy endpoint was the 6-hour SPID using the LOCF. The applicant found that for subjects who were eligible for the single-dose portion of the study the ketorolac group had a significantly higher mean 6-hour SPID score (83.3) compared to the

placebo group (37.2), p=0.007. Baseline VAS Pain Intensity scores were comparable for the two treatment groups, 54.0 for the ketorolac group and 53.6 for the placebo treatment group.

Secondary Endpoints:
Morphine Sulfate Consumption: The mean total amount of morphine used from 0 to 24 hours, 24 to 48 hours and 0 to 48 hours was statistically less for the ROX-888 treatment group compared to the placebo treatment group (Table 5.3.2.4). The mean amount of morphine used for subjects on ROX-888 was approximately 33% less compared to placebo for the 0 to 48 hour time period. Morphine sulfate use was not followed beyond 48 hours.

Table 5.3.2.4: Morphine Usage in Study 2003-01

Time Post-dose	ROX-888	Placebo
Total Usage 0 to 24 Hours		
Mean (SE)	34.0 (1.64)	48.4 (2.93)
Median	29.0	42.0
N	199	101
Total Usage 24 to 48 Hours		
Mean (SE)	18.8 (1.51)	29.2 (2.61)
Median	15.0	22.5
N	166	87
Total Usage 0 to 48 Hours		
Mean (SE)	51.4 (2.75)	77.4 (5.28)
Median	44.8	64.5
N	166	87

Note 1: Total morphine usage (mg) was calculated by adding all IV-PCA morphine usage and morphine equivalents for other analgesic medications administered for that time period using the American Pain Society guidelines.
Note 2: The ketorolac group used significantly less morphine than placebo group for all the time intervals, all P values <0.0005.
Reference: Adapted from Final Clinical Study Report of Protocol 2003-01, Module 5, Volume 15, Table 6A: PCA Morphine Usage Results

Global Assessment of Pain Control: The global assessment of pain control was statistically significant in favor of the ketorolac group on Days 3 and 4.

Quality of Analgesia: The quality of analgesia was rated as significantly better in the ketorolac treatment group compared to placebo at 0.5, 1, 2, 3, 4 and 5 hours. At 6 hours there was a trend in favor of the ketorolac group but not statistically significant. For the subset of 31 subjects that also were evaluated at 8 hours, no statistically significant differences were detected between treatment groups.

Additional Endpoints Requested by FDA
SPID 24 and SPID 48: The FDA statistician, Feng Li, determined that the SPID 24 and SPID 48 were statistically significant for the ITT population using multiple imputation methods including combined LOCF/BOCF (Table 5.3.2.5).

Table 5.3.2.5: SPID 24 and SPID 48 for Study 2003-01

Imputation Method	Endpoint	Stat	placebo	Ketorolac	P_Value
LOCF	spid24h	LEAST SQUARE MEANS (SE)	613.6 (35.14)	781.5 (25.03)	0
		Difference in Means	167.9		
		95% Confidence Interval	83 - 252.9		
		Number of non-missing	101	199	
		Number of Extrapolation	10 (10%)	29 (15%)	
	spid48h	LEAST SQUARE MEANS (SE)	1384.3 (69.08)	1624.2 (49.21)	0.005
		Difference in Means	239.9		
		95% Confidence Interval	73 - 406.9		
		Number of non-missing	101	199	
		Number of Extrapolation	41 (41%)	78 (39%)	
BOCF	spidb24h	LEAST SQUARE MEANS (SE)	586.1 (35.86)	743.0 (25.54)	0
		Difference in Means	157		
		95% Confidence Interval	70.3 - 243.6		
		Number of non-missing	101	199	
		Number of Extrapolation	10 (10%)	29 (15%)	
	spidb48h	LEAST SQUARE MEANS (SE)	1167.7 (72.65)	1392.2 (51.75)	0.012
		Difference in Means	224.4		
		95% Confidence Interval	48.8 - 400		
		Number of non-missing	101	199	
		Number of Extrapolation	41 (41%)	78 (39%)	

Reference: Dr. Feng Li.

5.3.3 Study 2003-05

Title: "A randomized, double-blind, placebo-controlled, parallel, single-dose study of IN ketorolac in the treatment of pain secondary to dental impaction surgery"

Objectives: The primary objective was to evaluate the analgesic efficacy of a single dose of ROX-888 after dental extraction surgery. The secondary objective was to evaluate the safety and tolerability.

Overall Design: This was a randomized, double-blind, placebo-controlled, Phase 2 study in subjects undergoing extraction of 3 or 4 third molars, with at least 1 extraction being a mandibular partial or complete bony impaction. Subjects were randomized in equal numbers to receive a single dose of ROX-888 or placebo. Subjects were assessed immediately before receiving the study drug and at 20 and 40 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after the dose of study drug. Subjects who required rescue medication were withdrawn from the study.

Efficacy Endpoints

Primary Efficacy Endpoint
The primary efficacy endpoint was the SPID score at 8 hours (SPID8).

Secondary Efficacy Endpoints
Secondary efficacy endpoints included SPID scores at 4 and 6 hours; TOTPAR scores through 4, 6, and 8 hours; PID scores and pain relief scores, onset of pain relief (as measured by time to both perceptible and meaningful relief), peak relief (as measured by both maximum PID scores and maximum pain relief scores), duration of analgesic effect (as measured by the time to use of rescue medication), and global pain control.

Results as reported by the applicant

Enrollment
A total of 80 subjects were enrolled in the study equally divided into placebo and ROX-888 treatment groups with 40 subjects in each group.

Efficacy Results
SPID: The mean SPID4, SPID6 and SPID8 (primary endpoint) all showed statistically significant analgesic efficacy compared to placebo (Table 5.3.3.1).

Peak Relief (as measured by maximum PID): The mean peak PID score was statistically significantly higher in the ROX-888 group compared to the placebo group (Table 5.3.3.1).

Table 5.3.3.1: Summed Pain Intensity Difference Scores and Peak Relief in Study 2003-05

Parameter	Placebo n=40	ROX-888 n=40	*P*-value[a]
SPID4, mean (SE)	-46.7 (13.5)	90.3 (16.4)	<0.001
SPID6, mean (SE)	-76.7 (21.1)	120.5 (24.7)	<0.001
SPID8[b], mean (SE)	-105.2 (29.1)	136.7 (33.0)	<0.001
Peak PID, mean (SE)	4.6 (3.7)	38.4 (4.3)	<0.001

a. Statistical significance of t-test (pooled estimate of variance).
b. Primary endpoint

Reference: Applicant's Table 1.2.7, page 13 of ISE, Volume 19, Module 5

Time to use of rescue medication: The median time to use of rescue medication was significantly longer in the ROX-888 group compared to placebo, 360 min and 95.5 min respectively (Table 5.3.3.2). The time to use of rescue medication in the ROX-888 group supports the proposed six hour dosing interval.

Time to perceptible and meaningful pain relief: The times to perceptible and meaningful pain relief were significantly shorter for the ROX-888 group compared to placebo (Table 5.3.3.2).

Table 5.3.3.2: Median Time to Perceptible Pain Relief, Meaningful Pain Relief, and Rescue Analgesics for Study 2003-05

Median time in minutes to:	Placebo n=40	ROX-888 n=40	*P*-value[a]
Perceptible pain relief	64.5	19.5	<0.001
Meaningful pain relief	90.0	65.5	<0.001
Rescue analgesics	95.5	360.0	<0.001

a. Statistical significance of log-rank test.
Reference: Applicant's Table 1.2.12, page 16 of ISE, Volume 19, Module 5

5.3.4 Study 2001-03

Title: "A Phase 2, double-blind, randomized study of the safety, tolerability and analgesic efficacy of multiple doses of ketorolac tromethamine administered intranasally for postoperative pain"

Objectives: The primary objective of this study was to compare the analgesic efficacy of multiple doses of 10 mg IN ketorolac or ROX-888 (31.5 mg IN ketorolac) over 2 days. Doses were selected to explore the range of the lowest approved and highest approved multiple dose of ketorolac.

Overall Design: This was a randomized, double-blind, placebo-controlled, Phase 2 study in postoperative pain following major abdominal or orthopedic surgery. Following surgery, subjects were randomly assigned to receive IN ketorolac 10 mg, ROX-888, or placebo when PI scores were at least 40 on a 100-mm VAS. Subjects were dosed every eight hours with the last dose given at 40 hours. Subjects had access to MS administered via PCA. Subjects were assessed immediately before receiving the study drug, at 30 and 60 minutes, and 2, 3, 4, 5, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours after the first dose of study drug.

Efficacy Endpoints

Primary Efficacy Endpoint
The primary efficacy measure was total MS consumption at 24 hours.

Secondary Efficacy Endpoints
Secondary efficacy measures included MS consumption at 48 hours, PID scores, SPID scores, quality of analgesia, and global pain control.

Results as reported by the applicant

Enrollment
A total of 127 subjects were enrolled in the study: 50 had abdominal surgery (10 in the 10 mg group, 22 in the ROX-888 group and 18 in the placebo group) and 77 had orthopedic surgery (32 in the 10 mg group, 21 in the ROX-888 group and 24 in the placebo group).

Efficacy Results
Morphine Consumption 0 to 24 hours (primary endpoint): The difference in morphine consumption was statistically significant between the ROX-888 treatment group and the 10-mg and placebo groups. Mean PCA MS use during the first 24 hours was 56.45 mg in the placebo group, 54.32 mg in the 10-mg group, and 37.77 mg in the ROX-888 group. The difference between the 10-mg and placebo groups was not significant.

Morphine Consumption 24 to 48 hours: The difference in morphine consumption was not statistically significant between the ROX-888 treatment group and the placebo treatment group by ANOVA but was statistically significant by the Kruskal-Wallis test.

SPID
The SPID scores at 4, 6 and 8 hours were statistically significant for the ROX-888 group compared to the placebo and the 10-mg groups.

Pain Intensity (PI) Scores
Mean PI values were significantly lower in the ROX-888 group than in the placebo group starting at 1 hour postdose through 6 hours postdose. No differences were observed between the 10-mg group and the placebo group during this time period.

6 Review of Efficacy

Efficacy Summary

The Applicant conducted two pivotal studies (Study 2003-01 and Study 2005-01) in support of the efficacy of Sprix for the short term (up to 5 days) management of moderate to moderately severe pain. The findings of both studies in postoperative pain demonstrated a statistically significant difference in effect between Sprix and placebo on the primary endpoint, the SPID 6, when assessed using a 100-mm visual analog pain scale score. The current standard of the Division is to require evidence of efficacy beyond six hours. The FDA statistician examined efficacy based on additional endpoints at 24 and 48 hours and concluded that the SPID 24 and 48 demonstrated statistical significance in both studies. Secondary outcome measures were also supportive of the primary efficacy findings.

Roxro also conducted two Phase 2 studies that were supportive of the efficacy findings in the pivotal studies. Study 2001-03 in postoperative pain showed decreased morphine consumption, the primary

endpoint, during the first 24 hours. Study 2003-05 a single dose study in dental pain demonstrated statistical significance for the SPID 8, the primary endpoint.

Key Issues
Two major issues impacting on the interpretation of the efficacy findings were the use of continuous background opioid analgesia and a predominantly inpatient population in both pivotal studies. For Studies 2005-01 and 2003-01, concomitant opioid use was allowed throughout the study except during the single dose portion of Study 2003-01 when the SPID 6, the primary endpoint, was assessed. The use of opioid rescue medication can affect a subject's *individual* pain score and thus potentially invalidate the efficacy findings. However, the difference in pain scores between placebo and Sprix *groups* should be valid since opioids were allowed under the same rules in both groups and in fact more opioids were used in the placebo group. In addition the efficacy of Sprix was demonstrated without background opioid use in the single dose portion of Study 2003-01 and in the single-dose Phase 2 dental pain study (Study 2003-05).

In the four controlled efficacy studies only 59 subjects received dosing at home and no efficacy data was collected on these subjects during the outpatient portion of the study. The data provided is insufficient to support efficacy in an outpatient setting and does not support extrapolating the inpatient efficacy findings to the outpatient setting. Inpatient efficacy for Sprix was demonstrated in the setting of widespread opioid use which is not likely to be available to outpatients. The efficacy findings from single-dose inpatient use of Sprix without rescue opioid use cannot be extrapolated with certainty to predict multiple-dose outpatient efficacy.

In summary, the Applicant has provided sufficient data from adequate and well-controlled studies to conclude that Sprix is effective in the treatment of moderate to moderately severe pain in an inpatient setting. The applicant has not provided convincing evidence to support the efficacy of multiple-dosing of Sprix in an outpatient setting.

(b) (4)

6.1 Indication

Proposed Indication
Roxro's proposed indication is the following:

"Sprix is an intranasal formulation of ketorolac, a nonsteroidal anti-inflammatory drug. Sprix is indicated in adult patients for the short term (up to 5 days) management of moderate to severe pain that requires analgesia at the opioid level.

(b) (4)
(b) (4) , (b) (4)

Approved Indication
Ketorolac is approved in both an oral formulation and IV/IM formulation. The approved indication for **oral ketorolac** is the following:

> "Toradol oral is indicated for the short-term (≤5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with IV or IM dosing of ketorolac tromethamine, and Toradol oral is to be used only as continuation treatment, if necessary."

The approved indication for **IV or IM ketoroalc** is the following:

> "Ketorolac tromethamine is indicated for the short-term (≤5 days) management of moderately severe, acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with IV or IM ketorolac tromethamine, and the oral dosage form is to be used only as continuation treatment, if necessary.
> The total combined duration of use of ketorolac tromethamine injection and oral ketorolac tromethamine is not to exceed 5 days of use because of the potential of increasing the frequency and severity of adverse reactions associated with the recommended doses. Patients should be switched to alternative analgesics as soon as possible, but ketorolac tromethamine therapy is not to exceed 5 days.
> Ketorolac tromethamine injection has been used concomitantly with morphine and meperidine and has shown an opioid sparing effect. For breakthrough pain, it is recommended to supplement the lower end of the ketorolac tromethamine injection dosage range with low doses of narcotics prn, unless otherwise contraindicated."

Discussion
Several differences exist between the proposed indication for intranasal ketorolac and the approved indication for oral and parenteral ketorolac. The proposed indication for management of "*moderate to severe pain*" suggests efficacy for more painful conditions than covered by the approved indication of "*moderately severe pain*." The approved indication is for "*acute* pain" but the proposed indication does not include the word "acute."

6.1.1 Methods

The applicant has submitted four controlled efficacy studies to support a finding of efficacy for the indication of Sprix for the management of moderately severe (b) (4) pain. Two studies were adequate and well-controlled (i.e., randomized, double-blind, placebo-controlled) Phase 3 postoperative pain studies. The primary efficacy measure, pain on a 100 mm visual analog scale (VAS), was

acceptable. The pre-specified primary endpoint, SPID 6, was not considered adequate to demonstrate durability of effect but using the VAS as a primary efficacy measure for pain, the SPID 24 and 48 could be calculated.

Roxro also submitted a Phase 2 study in postoperative pain (Study 2001-03) and a single dose Phase 2 study in dental pain (Study 2003-05). These two studies were not considered to primarily support a finding of efficacy for the following reasons. For Study 2003-05 only 40 subjects received a single-dose of Sprix. For Study 2001-03 the primary efficacy endpoint was not a measure of pain intensity but morphine sulfate use and only 85 subjects received Sprix with maximum dosing duration of up to 48 hours.

The study design for both pivotal studies (Study 2003-01 and Study 2005-01) allowed for use of opioid rescue medication without any provision for adjusting subsequent pain scores. The background use of opioid medication makes it difficult to interpret individual pain scores, but not the difference in pain scores between placebo and ketorolac groups since opioid rescue was allowed in both groups. The use of more opioid medication in the placebo group but lower pain scores in the intranasal ketorolac group suggest that efficacy was not due solely to use of opioids. In addition the single dose portion of Study 2003-01 and the single dose Phase 2 dental pain study (Study 2003-05) were conducted without the use of concomitant opioids. There were no outpatient pain scores in any of the four efficacy studies.

See Section 5.3 (Discussion of Individual Studies/Clinical Trials) for a detailed description of the study design, protocol amendments, statistical analyses and results of the pivotal efficacy studies.

6.1.2 Demographics

The overall demographic and baseline characteristics for all subjects treated with IN ketorolac 10 mg, ROX-888, or placebo for the four efficacy studies are summarized in Table 6.1.2 below. The individual demographics for Study 2005-01 and Study 2003-01 are summarized in Section 5.

Table 6.1.2: Demographics and Baseline Characteristics for all 4 Efficacy Studies*

	IN Ketorolac 10 mg	ROX-888	Placebo	Total
Number of Subjects	43	495	290	828
Age				
Mean (SE)	50.1 (2.11)	47.1 (0.60)	46.5 (0.86)	47.0 (0.48)
Median	48.0	46.1	46.7	46.5
Range	22 - 78	18 - 81	18 - 78	18 - 81
Age Category				
18 to <55	27 (62.8%)	370 (74.7%)	208 (71.7%)	605 (73.1%)
55 to <65	10 (23.3%)	74 (14.9%)	46 (15.9%)	130 (15.7%)
65 to <75	4 (9.3%)	44 (8.9%)	31 (10.7%)	79 (9.5%)
≥75	2 (4.7%)	7 (1.4%)	5 (1.7%)	14 (1.7%)
Sex				
Male	11 (25.6%)	95 (19.2%)	77 (26.6%)	183 (22.1%)
Female	32 (74.4%)	400 (80.8%)	213 (73.4%)	645 (77.9%)
Race				
Caucasian	31 (72.1%)	373 (75.4%)	216 (74.5%)	620 (74.9%)
Non-Caucasian	12 (27.9%)	119 (24.0%)	72 (24.8%)	203 (24.5%)
Other	0 (0.0%)	3 (0.6%)	2 (0.7%)	5 (0.6%)
Weight (kg)				
Mean (SE)	81.4 (2.79)	79.5 (0.82)	83.1 (1.10)	80.9 (0.64)
Median	83.0	76.2	81.8	79.0
Range	50 - 124	45 - 141	49 - 144	45 - 144
Type of Surgery				
Abdominal	22 (51.2%)	333 (67.3%)	171 (59.0%)	526 (63.5%)
Orthopedic	21 (48.8%)	120 (24.2%)	75 (25.9%)	216 (26.1%)
Dental Extraction	0 (0.0%)	40 (8.1%)	40 (13.8%)	80 (9.7%)
Other	0 (0.0%)	2 (0.4%)	4 (1.4%)	6 (0.7%)

* Includes Studies 2005-01, 2003-01, 2003-05 and 2003-01
Reference: Table 1.2 Demographics and Baseline Characteristics from ISS page 12, Module 5

Demographic characteristics were similar between treatment groups. The mean age for placebo (46.5 years) and for ROX-888 (47.1 years) and the percent of subjects 65 years of age or greater (36/290 (12.4%) for placebo and 51/495 (10.3%) for ROX-888 were similar. Patients were predominantly female with 80.8% (400/495) women in the ROX-888 group and 73.4% (213/290) women in the placebo group. Of the 51 subjects 65 years of age or greater 38 were in Study 2003-01 and 13 were in Study 2001-03. No subjects 65 years of age or greater were in pivotal Study 2005-01.

6.1.3 Subject Disposition

The integrated subject disposition for all subjects treated with IN ketorolac 10 mg, ROX-888, or placebo for the four efficacy studies are summarized in Table 6.1.3 below. The subject disposition for Study 2005-01 and Study 2003-01 at 24 and 48 hours are summarized in Tables 6.1.3.2 and 6.1.3.3.

Table 6.1.3: Summary of Subject Disposition for all 4 Efficacy Studies

	IN ketorolac 10 mg	ROX-888	Placebo	Total
Number of Subjects	43	495	290	828
Was Study Drug Discontinued Early?				
No	32 (74.4%)	242 (48.9%)	163 (56.2%)	437 (52.8%)
Yes	11 (25.6%)	253 (51.1%)	127 (43.8%)	391 (47.2%)
Primary Reason for Early Discontinuation				
Adverse Event [a]	5 (11.6%)	79 (16.0%)	31 (10.7%)	115 (13.9%)
Unsatisfactory Response (efficacy)	0 (0.0%)	1 (0.2%)	4 (1.4%)	5 (0.6%)
Protocol violation	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Subject request	0 (0.0%)	31 (6.3%)	11 (3.8%)	42 (5.1%)
Patient's need for analgesia decreased	0 (0.0%)	129 (26.1%)	66 (22.8%)	195 (23.6%)
Investigator decision	0 (0.0%)	2 (0.4%)	4 (1.4%)	6 (0.7%)
Other[b]	6 (14.0%)	10 (2.0%)	11 (3.8%)	27 (3.3%)

Source: Table 28

a. This includes intercurrent illness or lab abnormalities.

b. Other included: IV occluded and subject did not want it reinserted (2), PCA IV nonfunctional, NSAID inadvertently given to subject (3), need for nasogastric tube, backache, lost to follow-up (2), subject needed to undergo an intravenous pyelogram, attending surgeon took subject off study, subject's need for analgesia decreased and subject was unable to switch to oral medication, subject did not want to take study drug home (2), subject was discontinued earlier than planned due to nursing error in interpreting physician's orders, subject's request, subject had nicotine withdrawal symptoms, subject was discharged early (2), subject did not wish to continue taking study drug (6), and subject was a smoker and wanted PCA disconnected.

* Includes Studies 2005-01, 2003-01, 2003-05 and 2003-01

Reference: Table 1.3 Summary of Subject Disposition from ISS page 14, Module 5

There were slightly more discontinuations in the ROX-888 treatment group 51% (253/495) compared to the placebo treatment group 44% (127/290). More subjects discontinued in the ROX-888 group due to adverse events. The relatively large number of study discontinuations due to "Subject Request" was largely due to Study 2003-01 where 22 subjects in the ROX-888 group discontinued for this reason. This issue was reviewed in Section 5.3.2 under the heading Subject Disposition for Study 2003-01 and revealed no obvious coding error between the "Original Reason for Discontinuation" and the "ISS Reason for Discontinuation" but this does not exclude the possibility of the investigator inadequately eliciting the true reason for discontinuation. If one assumed that all the subjects in the four efficacy studies that were coded as discontinued due to "Subject Request" actually discontinued due to "Adverse Event" there would only be an additional 2.5% discontinuations due to "Adverse Event" in the ROX-888 group compared to placebo group. For Study 2003-01 which had the greatest number of discontinuations due to "Subject Request," the FDA statistician recalculated efficacy assuming that all the subjects in this group discontinued due to "Adverse Event." Using the LOCF/BOCF combined imputation method the p-value remained statistically significant but changed from 0.008 to 0.023.

For Study 2003-01 approximately 75% of subjects in the ROX-888 group completed at least 48 hours of dosing. For Study 2005-01 only 45% of subjects completed 48 hours of dosing in the ROX-888 group but 33% dropped out due to decreased need for analgesia. The number of subjects completing 48 hours of dosing is adequate for assessing efficacy at 48 hours.

Table 6.1.3.2: Subject Disposition for Study 2005-01 and 2003-01 at 24 Hours

Subject Disposition at 24 Hours				
	Study 2005-01		**Study 2003-01**	
	Placebo	Ketorolac	Placebo	Ketorolac
Number of Subjects	107	214	101	199
Completed 24 Hours Dosing?				
No	9 (8.4%)	33 (15.4%)	9 (8.9%)	28 (14.1%)
Yes	98 (91.6%)	181 (84.6%)	92 (91.1%)	171 (85.9%)
Discontinuation Reason				
AE	5 (4.67%)	28 (13.1%)	6 (5.9%)	18 (9.1%)
Unsatisfactory	1 (0.9%)	1 (0.5%)		
Decreased Need for Analgesia				2 (1.0%)
Protocol Violation		1 (0.5%)		
Subject Request	1 (0.9%)	3 (1.4%)	1 (1.0%)	7 (3.5%)
Investigator Decision	1 (0.9%)		1 (1.0%)	1 (0.5%)
Other	1 (0.9%)		1 (1.0%)	

Table 6.1.3.3: Subject Disposition for Study 2005-01 and 2003-01 at 48 Hours

Subject Disposition at 48 Hours				
	Study 2005-01		Study 2003-01	
	Placebo	Ketorolac	Placebo	Ketorolac
Number of Subjects	107	214	101	199
Completed 24 Hours Dosing?				
No	53 (49.5%)	118 (55.1%)	19 (18.8%)	49 (24.6%)
Yes	54 (50.5%)	96 (44.9%)	82 (81.2%)	150 (75.4%)
Discontinuation Reason				
AE	12 (11.2%)	39 (18.2%)	12(11.9%)	30 (15.1%)
Unsatisfactory	1 (0.9%)	1 (0.5%)		
Decreased Need for Analgesia	33 (30.8%)	70 (32.7%)		3 (1.5%)
Protocol Violation		1 (0.5%)		
Subject Request	2 (1.9%)	6 (2.8%)	4 (4.0%)	15 (7.5%)
Investigator Decision	1 (0.9%)	1 (0.5%)	2 (2.0%)	1 (0.5%)
Other	1 (0.9%)		1 (1.0%)	

6.1.4 Analysis of Primary Endpoint(s)

Choice of Endpoints

Applicant's Primary Endpoints for Pivotal Studies

The primary efficacy variable for Study 2005-01 and 2003-01 was pain intensity as assessed on a 100 mm visual analog scale (VAS). The primary efficacy endpoint for both Phase 3 studies was the time-interval weighted sum of pain intensity difference (SPID) for the 0 to 6 hour interval following dosing. For Study 2003-01 SPID 6 was determined on the first postoperative day. Opioid medication was not allowed throughout the six hour period following dosing but was allowed at all other times during the study. For Study 2005-01 the SPID 6 was determined on the day of surgery following the initial dose. Concomitant opioid use was allowed throughout the entire study.

Applicants Primary Endpoints for Phase 2 Studies

For Study 2003-05, the single-dose pain study following dental impaction surgery, the primary efficacy endpoint was the SPID score at 8 hours (SPID 8).

For Study 2001-03, a postoperative pain study, the primary efficacy measure was total MS consumption at 24 hours.

Acceptability of Applicant's Primary Endpoints

The primary outcome measure, pain intensity measured on a 100 mm VAS, is acceptable. However, the primary endpoint, SPID 6, used in both Phase 3 studies does not adequately measure durability of effect. In the past the SPID 6 was considered an acceptable primary endpoint for acute pain but the Division now requires efficacy be demonstrated for at least 24 to 48 hours. Therefore additional efficacy analyses using the SPID 24 and SPID 48 were performed by the FDA statistician.

Reduction of morphine consumption, the primary endpoint for Study 2001-03, is problematic for the Division as a sole primary endpoint. The Division needs any opioid-sparing effect to correlate with a reduction of opioid-related side effects in a manner that demonstrates a clinically meaningful benefit. The Division's concern with opioid consumption as a primary endpoint was discussed with the Applicant during a Type B Meeting on December 13, 2004.

Efficacy Results

Study 2005-01

SPID 6

For the primary endpoint, the SPID 6, the difference in least square means between placebo and ROX-888 was 27.6 and statistically significant (Table 6.1.4.1). The FDA statistician, Feng Li, verified the values obtained by the applicant were similar to his findings.

Table 6.1.4.1: Summary of SPID6 Scores (Study 2005-01)

	ROX-888 n = 213	Placebo n = 107	*P*-value
Mean (SE)	115.6 (7.98)	92.6 (11.08)	
Median	110.8	99.0	
Range	-179.0 – 429.7	-234.0 – 363.1	
Least square means (SE)	117.4 (7.71)	89.9 (10.59)	0.032[a]
Difference in means		27.6	
95% CI		2.5 – 52.7	

a. The 2-way ANCOVA with the Day 0 predose PI score as a covariate in the model was used to analyze differences between the 2 treatment groups.

Reference: Table 1.2.19 Summary of SPID6 Scores (Study 2005-01) from ISE page 24

SPID 24 and SPID 48

The FDA statistician, determined that the SPID 24 and SPID 48 were statistically significant when LOCF or BOCF alone were used but not when combined LOCF/BOCF imputation methods were used. Using BOCF imputation for the SPID 24 and SPID 48 the difference in least square means was 112.1 and 242.6, respectively (Table 6.1.4.2). The usual imputation method used by the Division for dropouts due to adverse events is BOCF.

Table 6.1.4.2: SPID 24 and SPID 48 for Study 2005-01

Imputation	Endpoint	Stat	placebo	Ketorolac	P_Value
LOCF	spid24h	LEAST SQUARE MEANS (SE)	514.5 (47.19)	630.3 (34.36)	0.043
		Difference in Means	115.8		
		95% Confidence Interval	3.8 - 227.8		
		Number of non-missing	107	213	
		Number of Extrapolation	51 (48%)	88 (41%)	
	spid48h	LEAST SQUARE MEANS (SE)	1096.7 (101.46)	1347.1 (73.89)	0.042
		Difference in Means	250.5		
		95% Confidence Interval	9.7 - 491.3		
		Number of non-missing	107	213	
		Number of Extrapolation	98 (92%)	182 (85%)	
BOCF	spidb24h	LEAST SQUARE MEANS (SE)	454.9 (42.08)	567.0 (30.65)	0.028
		Difference in Means	112.1		
		95% Confidence Interval	12.2 - 212		
		Number of non-missing	107	213	
		Number of Extrapolation	51 (48%)	88 (41%)	
	spidb48h	LEAST SQUARE MEANS (SE)	613.5 (65.89)	856.1 (47.99)	0.002
		Difference in Means	242.6		
		95% Confidence Interval	86.2 - 398.9		
		Number of non-missing	107	213	
		Number of Extrapolation	98 (92%)	182 (85%)	

Reference: Dr. Li

Study 2003-01

SPID 6

For the primary endpoint, the SPID 6, the difference in least square means was statistically significant between ROX-888 and placebo, 50.4 and 35.7 using LOCF and BOCF imputation methods, respectively (Table 6.1.4.3). The FDA statistician verified that the Applicant's results were similar to his findings.

Table 6.1.4.3: Primary Efficacy Results (Study ROX-2003-01)

Endpoint	Imputation	Stat	Placebo	ROX-888	p-value
SPID6			N= 101	N=199	
Applicant's	LOCF	Least square means	34.6	85.0	0.003
		Difference in means	50.4		
		95% confidence interval	17.4 - 83.4		
		Number of non-missing	73	115	
	BOCF	Least square means	49.0	84.7	0.006
		Difference in means	35.7		
		95% confidence interval	10.2 - 61.2		
		Number of non-missing	74	115	

Reference: Dr. Li

SPID 24 and SPID 48

The FDA statistician determined that the SPID 24 and SPID 48 were statistically significant when LOCF, BOCF or combined LOCF/BOCF imputation methods were used. Using BOCF imputation for the SPID 24 and SPID 48 the difference in least square means was 157 and 224, respectively. The results summarized in Table 6.1.4.4 are slightly different than more recent calculations by the statistician but the conclusions remain the same.

Table 6.1.4.4: SPID 24 and SPID 48 for Study 2003-01

Imputation Method	Endpoint	Stat	placebo	Ketorolac	P_Value
LOCF	spid24h	LEAST SQUARE MEANS (SE)	613.6 (35.14)	781 5 (25.03)	0
		Difference in Means	167.9		
		95% Confidence Interval	83 - 252.9		
		Number of non-missing	101	199	
		Number of Extrapolation	10 (10%)	29 (15%)	
	spid48h	LEAST SQUARE MEANS (SE)	1384.3 (69.08)	1624.2 (49.21)	0.005
		Difference in Means	239.9		
		95% Confidence Interval	73 - 406.9		
		Number of non-missing	101	199	
		Number of Extrapolation	41 (41%)	78 (39%)	
BOCF	spidb24h	LEAST SQUARE MEANS (SE)	586.1 (35.86)	743.0 (25.54)	0
		Difference in Means	157		
		95% Confidence Interval	70.3 - 243.6		
		Number of non-missing	101	199	
		Number of Extrapolation	10 (10%)	29 (15%)	
	spidb48h	LEAST SQUARE MEANS (SE)	1167.7 (72.65)	1392.2 (51.75)	0.012
		Difference in Means	224.4		
		95% Confidence Interval	48.8 - 400		
		Number of non-missing	101	199	
		Number of Extrapolation	41 (41%)	78 (39%)	

Reference: Dr. Li

Efficacy Results for Elderly in Study 2003-01
The SPID 6, SPID 24 and SPID 48 were numerically superior for subjects 65 years of age or older but the studies were not powered to show statistical significance for this subgroup analysis.

Study 2003-05 (Phase 2 Study)
SPID 8
The primary efficacy endpoint, the SPID 8, was statistically significant (Table 6.1.4.5). The FDA statistician obtained similar results.

Table 6.1.4.5: SPID Scores for Study 2003-05

Parameter	Placebo n=40	ROX-888 n=40	*P*-value[a]
SPID4, mean (SE)	-46.7 (13.5)	90.3 (16.4)	<0.001
SPID6, mean (SE)	-76.7 (21.1)	120.5 (24.7)	<0.001
SPID8[b], mean (SE)	-105.2 (29.1)	136.7 (33.0)	<0.001
Peak PID, mean (SE)	4.6 (3.7)	38.4 (4.3)	<0.001

a. Statistical significance of t-test (pooled estimate of variance).
b. Primary endpoint

Reference: Table 1.2.7 Summed Pain Intensity Difference Scores and Peak Relief (Study ROX-2003-05) Module 5, Integrated Summary of Efficacy, page 13

Study 2001-03 (Phase 2 Study)
Morphine Sulfate Consumption at 24 hours
The primary efficacy measure, total MS consumption at 24 hours, was 56 mg in the placebo group, 54 mg in the 10-mg group, and 37 mg in the ROX-888 group. The FDA statistician verified that the difference in overall morphine sulfate use between the ROX-888 group and placebo group was statistically significant. The statistician determined that male subjects in both ketorolac groups used more morphine sulfate than male subjects in the placebo group (Table 6.1.4.6) but the difference between ROX-888 and placebo was minimal.

Table 6.1.4.6: Morphine Sulfate Use by Subgroup (Study 2001-03)

	Placebo		IN Ketorolac 10 mg		ROX-888	
Endpoint	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**mean**
PCA024						
Gender						
Female	24	61.1 (34.6)	30	42.6 (27)	28	30.7 (19.3)
Male	17	**49.9** (24)	11	**86.2** (54.8)	13	**53** (46.8)
Race						
Caucasian	32	57.4 (29.4)	30	52.3 (36.4)	35	35.9 (29)
Non-Caucasian and Other	9	52.9 (37.2)	11	59.7 (52.5)	6	48.7 (47.6)
Age						
<65 years	23	67.4 (33.4)	35	58.4 (42.3)	28	39.2 (36.1)
≥ 65 years	18	42.4 (20.5)	6	30.4 (17.3)	13	34.7 (21.1)

Reference: Dr. Li

Efficacy Results for Elderly in Study 2001-03
The 24 hour morphine sulfate use for elderly subjects was 34.7 mg on ROX-888 and 42.4 mg on placebo. Although morphine sulfate use trended in the right direction the study was not powered to show statistical significance

6.1.5 Analysis of Secondary endpoint(s)

Study 2005-01
Morphine Sulfate Consumption: The mean total amount of morphine used from 0 to 24 hours, 24 to 48 hours and 0 to 48 hours was statistically less for the ROX-888 treatment group compared to the placebo treatment group (Table 6.1.5.1). The mean amount of morphine used for subjects on ROX-888 was approximately 21% less compared to placebo for the 0 to 24 hour time period and 26% less for the 24 to 48 hour time period. The difference between treatment groups for the time intervals of 48 to 72 hours and 0 to 72 hours was not statistically significant. The statistician verified the accuracy based on the Applicant's data and method of extrapolation for morphine consumption.

Table 6.1.5.1: Morphine Usage in Study 2005-01

Time Interval	Amount of Morphine Used (mg)		
	ROX-888	Placebo	P value
0 to 24 Hours			
Mean (SE)	42.4 (2.04)	54.0 (3.49)	0.003[a]
n	210	106	
24 to 48 Hours			
Mean (SE)	23.1 (2.25)	31.3 (3.53)	0.041[a]
n	140	80	
0 to 48 Hours			
Mean (SE)	66.7 (4.43)	89.7 (7.23)	0.004[a]
n	140	80	
48 to 72 Hours			
Mean (SE)	14.7 (8.84)	13.0 (6.47)	0.955[a]
n	9	13	
0 to 72 Hours			
Mean (SE)	81.5 (24.42)	121.1 (36.44)	0.304[a]
n	10	13	

Note 1: Total morphine usage (mg) was calculated by adding all IV-PCA morphine usage and morphine equivalents for other analgesic medications administered for that time period using the American Pain Society guidelines.
a. By 2-way ANOVA
Reference: Adapted from Final Clinical Study Report of Protocol 2005-01, Module 5, Volume 17, Table 11.3: Summary of PCA Morphine Usage

Study 2003-01

Morphine Sulfate Consumption: The mean total amount of morphine used from 0 to 24 hours, 24 to 48 hours and 0 to 48 hours was statistically less for the ROX-888 treatment group compared to the placebo treatment group (Table 6.1.5.2). The mean amount of morphine used for subjects on ROX-888 was approximately 30% less compared to placebo for the 0 to 24 hour time period and 33% less for the 0 to 48 hour time period. The analysis of overall opioid use by the FDA statistician was similar but a subpopulation analysis based on race showed that for Non-Caucasians there was slightly more opioid use in the ROX-888 group than placebo group (Table 6.1.5.3).

Table 6.1.5.2: Morphine Usage in Study 2003-01

Time Post-dose	ROX-888	Placebo
Total Usage 0 to 24 Hours		
Mean (SE)	34.0 (1.64)	48.4 (2.93)
Median	29.0	42.0
N	199	101
Total Usage 24 to 48 Hours		
Mean (SE)	18.8 (1.51)	29.2 (2.61)
Median	15.0	22.5
N	166	87
Total Usage 0 to 48 Hours		
Mean (SE)	51.4 (2.75)	77.4 (5.28)
Median	44.8	64.5
N	166	87

Note 1: Total morphine usage (mg) was calculated by adding all IV-PCA morphine usage and morphine equivalents for other analgesic medications administered for that time period using the American Pain Society guidelines.
Note 2: The ketorolac group used significantly less morphine than placebo group for all the time intervals, all P values <0.0005.
Reference: Adapted from Final Clinical Study Report of Protocol 2003-01, Module 5, Volume 15, Table 6A: PCA Morphine Usage Results

Table 6.1.5.3: Efficacy Results by Subgroup (Study 2003-01)

	Placebo		ROX-888	
Endpoint	**n**	**Mean (SD)**	**n**	**Mean (SD)**
PCA048				
Gender				
Female	58	68.1 (46.8)	123	48.5 (36)
Male	29	91.2 (50.6)	43	54.2 (31.8)
Race				
Caucasian	66	82.3 (50.3)	124	47.3 (33.2)
Non-Caucasian and Other	21	**55.3** (39.3)	42	**58.1** (39)
Age				
<65 years	75	77.7 (49)	133	53.7 (36)
≥ 65 years	12	64.1 (49.6)	33	35.1 (25.9)

Reference: Dr. Li

Onset of Pain Relief
There was no difference in time to meaningful pain relief between ROX-888 and placebo groups as measured by a single stopwatch with the median time to meaningful analgesia 0.3 hours for both groups. However, the PID scores were statistically significantly superior for ROX-888 at 0.5, 1, 2

and 3 hours. Although the PID scores are not a measure of meaningful painrelief, they do support that ROX-888 had an analgesic effect within one hour of administration.

Study 2003-05 (Phase 2 Study)
SPID 4 and SPID 6
The SPID 4 and SPID 6, secondary efficacy endpoints, in addition to the primary efficacy endpoint the SPID 8 were statistically significant compared to placebo (Table 6.1.4.5).

Time to use of rescue medication
The median time to use of rescue medication was significantly longer in the ROX-888 group compared to placebo, 360 min and 95.5 min respectively (Table 5.3.3.2). At the End of Phase 2 Meeting, the Division concluded that the time to rescue medication supported a dosing interval of every six hours or less (dosing interval had been every 8 hours).

Time to perceptible and meaningful pain relief
The time to perceptible and meaningful pain relief were significantly shorter for the ROX-888 group compared to placebo (Table 6.1.5.3). The Division requires an acute analgesic to have an onset of action within 60 minutes. For ROX-888 the median time to onset of perceptible pain relief was 19.5 minutes.

Table 6.1.5.3: Median Time to Perceptible Pain Relief, Meaningful Pain Relief, and Rescue Analgesics for Study 2003-05

Median time in minutes to:	Placebo n=40	ROX-888 n=40	*P*-value[a]
Perceptible pain relief	64.5	19.5	<0.001
Meaningful pain relief	90.0	65.5	<0.001
Rescue analgesics	95.5	360.0	<0.001

a. Statistical significance of log-rank test.
Reference: Applicant's Table 1.2.12, page 16 of ISE, Volume 19, Module 5

Study 2001-03
Morphine Sulfate Consumption
The difference in the mean total amount of morphine sulfate used from 0 to 24 hours between the placebo group (56.5 mg) and the ROX-888 group (37.8 mg) was 33% and statistically significant. The amount of morphine sulfate used for 24 to 48 hours was less in the ROX-888 group (23.1 mg) compared to placebo group (32.6 mg) but not statistically significant by ANOVA.

SPID
The SPID scores at 4, 6 and 8 hours were statistically significant for the ROX-888 group compared to the placebo and the 10-mg groups.

Pain Intensity (PI) Scores
Mean PI values were significantly lower in the ROX-888 group than in the placebo group starting at 1 hour postdose through 6 hours postdose. No differences were observed between the 10-mg group and the placebo group during this time period.

6.1.6 Other endpoint(s)

Not applicable.

6.1.7 Subpopulations

The FDA statistician verified that the efficacy findings were not significantly affected by age, sex, and race with the exception of opioid use. The statistician determined that opioid use in Study 2001-03 was influenced by sex with less opioids used in women in the ROX-888 group but slightly more opioids used in men in the ROX-888 group compared to placebo (Table 6.1.4.6). There was also a difference in opioid use by race in study 2003-01. In Caucasians there was less opioid use in the ROX-888 group but in the Non-Caucasian group there was slightly more opioid use in the ROX-888 group compared to placebo (Table 6.1.7).

Table 6.1.7: Efficacy Results by Subgroup (Study 2003-01)

	Placebo		ROX-888	
Endpoint	**n**	**Mean (SD)**	**n**	**Mean (SD)**
PCA048				
Gender				
Female	58	68.1 (46.8)	123	48.5 (36)
Male	29	91.2 (50.6)	43	54.2 (31.8)
Race				
Caucasian	66	82.3 (50.3)	124	47.3 (33.2)
Non-Caucasian and Other	21	**55.3** (39.3)	42	**58.1** (39)
Age				
<65 years	75	77.7 (49)	133	53.7 (36)
≥ 65 years	12	64.1 (49.6)	33	35.1 (25.9)

Reference: FDA Statistician Table 14: Efficacy Results by Subgroup (Study ROX-2003-01)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The proposed dosing recommendations for Sprix are supported by PK and efficacy studies conducted by the Applicant and the approved dosing regimen for oral and parenteral ketorolac. The

pharmacokinetic data from Study 2001-02 indicate that ROX-888 achieves Cmax and AUC values between that obtained with IM ketorlac doses of 15 mg and 30 mg (Table 6.1.8.1). The proposed dosing regimen for Sprix is every six hours, the same as the approved dosing regimen for IM and IV ketorolac. Study 2003-05 also supports the six hour dosing regimen since the median time to use of rescue medication in that study was six hours. ROX-888 (31.5 mg) was shown to be an effective dose but 10 mg failed to demonstrate efficacy in Study 2001-03. Roxro did not conduct studies comparing intranasal to oral administration of ketorolac. However, pharmacokinetic information in the approved label for oral ketorolac shows that for a10 mg oral dose the Cmax and steady state average plasma concentrations are less than obtained with IM and IV (Table 6.1.8.2). The Cmax and AUC for Sprix are higher than that obtained with oral dosing and the 15 mg IM dose. In general the proposed IN ketorolac dose has pharmacokinetic findings more similar with approved IM and IV dosing than oral dosing. This similarity in pharmocokinetics suggests that dosing recommendations for Sprix be based on the IM and IV ketorolac recommendations.

Dosing in Elderly
The dosing of IV and IM ketorolac in the elderly is 50% of the dose in subjects less than 65 years old. The Division told the Applicant that to justify use of a 50% dose reduction for Sprix in the elderly they would need to demonstrate that absorption was similar to young adults. Roxro conducted a PK study in the elderly, Study 2007-02. The FDA pharmacologist concluded that intranasal absorption was comparable in the young and elderly considering variability in the Cmax of elderly. Therefore it is reasonable to reduce the dose of Sprix in subjects 65 years of age or older by 50%.

Study 2001-02
- Title: A Phase I, Randomized, 5-Way Crossover Study of the Pharmacokinetics of Single Doses of Ketorolac Tromethamine by Intranasal Administration Compared to Intramuscular Administration in Healthy Volunteers
- Objectives: To compare the safety, tolerability, and PK parameters of single doses of 15.5 mg ketorolac, ROX-888, and 48 mg ketorolac administered IN to those achieved with IM administration of 15 mg and 30 mg of ketorolac.

Results
The pharmacokinetic parameters for the 15 subjects (6 males and 9 females) enrolled in the study are summarized in Table 6.1.8.1.

Table 6.1.8.1: Mean (±SD) Pharmacokinetic Parameters following Intranasal and Intramuscular Ketorolac in Healthy Subjects

Ketorolac Treatment	C_{max} (ng/mL)	t_{max} (h)[a]	AUC_{0-t} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{½z}$ (h)	MRT (h)
15 mg IM (0.5 mL of 30 mg/mL)	1163.4 (279.9)	0.75 (0.25-1.50)	4955.6 (1920.5)	5196.3 (2076.7)	5.00 (1.72)	5.79 (1.70)
15.5 mg IN (7.5% Solution)	912.6 (292.9)	0.50 (0.25-1.00)	3723.1 (1483.3)	3906.8 (1569.4)	4.76 (1.38)	5.96 (2.07)
31.5 mg IN (15% Solution)	1805.8 (882.8)	0.75 (0.50-2.00)	7141.1 (3465.8)	7477.3 (3654.4)	5.24 (1.33)	6.31 (2.45)
48 mg IN (22.5% Solution)	2245.5 (1240.4)	0.50 (0.25-1.02)	8246.8 (3106.4)	8669.7 (3173.4)	5.73 (2.03)	6.53 (2.19)
30 mg IM (1.0 mL of 30 mg/mL)	2382.2 (432.7)	0.75 (0.25-1.03)	10770.3 (3885.5)	11152.8 (4260.1)	4.80 (1.18)	5.51 (1.48)

[a] Median and range reported
Reference: Table 15, page 50 of Clinical Study Report Addendum for Protocol 2001-02, Volume 3, Module 5

The 15.5 and 31.5 mg doses of IN ketorolac were approximately dose proportional. The half-life of ketorolac by the IN route was similar to that of the IM route. The bioavailability of ketorolac by the IN route of administration was approximately 60-75% compared to IM administration. A 31.5 mg dose of IN ketorolac results in an exposure and Cmax between the 15 mg IM and 30 mg IM dose.

Table 6.1.8.2: Pharmacokinetic Parameters of Oral, IM and IV Ketorolac Tromethamine

Table 1 Table of Approximate Average Pharmacokinetic Parameters (Mean± SD) Following Oral, Intramuscular and Intravenous Doses of Ketorolac Tromethamine

Pharmacokinetic Parameters (units)	Oral*	Intramuscular†			Intravenous Bolus‡	
	10 mg	15 mg	30 mg	60 mg	15 mg	30 mg
Bioavailability (extent)	100%					
T_{max}§ (min)	44 ± 34	33 ± 21¶	44 ± 29	33 ± 21¶	1.1 ± 0.7¶	2.9 ± 1.8
C_{max}# (µg/mL) [single-dose]	0.87 ± 0.22	1.14 ± 0.32¶	2.42 ± 0.68	4.55 ± 1.27¶	2.47 ± 0.51¶	4.65 ± 0.96
C_{max} (µg/mL) [steady state qid]	1.05 ± 0.26¶	1.56 ± 0.44¶	3.11 ± 0.87¶	N/Aþ	3.09 ± 1.17¶	6.85 ± 2.61
C_{min}ß (µg/mL) [steady state qid]	0.29 ± 0.07¶	0.47 ± 0.13¶	0.93 ± 0.26¶	N/A	0.61 ± 0.21¶	1.04 ± 0.35
C_{avg}à (µg/mL) [steady state qid]	0.59 ± 0.20¶	0.94 ± 0.29¶	1.88 ± 0.59¶	N/A	1.09 ± 0.30¶	2.17 ± 0.59
Vβè (L/kg)	0.175 ± 0.039				0.210 ± 0.044	

% Dose metabolized = <50
% Dose excreted in feces = 6
% Dose excreted in urine = 91
% Plasma protein binding = 99
*Derived from PO pharmacokinetic studies in 77 normal fasted volunteers
†Derived from IM pharmacokinetic studies in 54 normal volunteers
‡Derived from IV pharmacokinetic studies in 24 normal volunteers
§Time-to-peak plasma concentration
¶Mean value was simulated from observed plasma concentration data and standard deviation was simulated from percent coefficient of variation for observed C_{max} and T_{max} data
#Peak plasma concentration
þNot applicable because 60 mg is only recommended as a single dose
ßTrough plasma concentration
àAverage plasma concentration
èVolume of distribution

Reference: Oral Toradol label, Revised 01/2008

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy was demonstrated in both pivotal studies with the SPID at 24 and 48 hours. This is consistent with the current Division's requirement for demonstrating evidence of efficacy for a minimum of 24 to 48 hours for an acute pain indication.

Tolerance is not an issue for the NSAID class of drugs which includes Sprix.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

Exposure: The controlled safety database consisted of 495 subjects that received at least one dose of ROX-888. A total of 172 subjects (35%) received at least five days of treatment. The majority of subjects studied were in the hospital with only 59 subjects receiving intranasal ketorolac at home for a mean number of 3.4 doses.

Major Safety Results: There were no deaths. The overall safety profile of Sprix is consistent with other NSAIDs except for the added risk of nasal adverse events related to the route of administration and an increased risk of postoperative bleeding. The incidence of serious adverse events due to bleeding was approximately three fold higher in the ROX-888 group with 1.5% (7/455) in the ROX-888 group and 0.4% (1/250) in the placebo group. Six of the seven subjects in the ROX-888 group with a bleeding SAE underwent a follow-up surgical procedure and four of the subjects received a blood transfusion whereas none of the subjects in the placebo group required follow-up surgery and one subject received a blood transfusion. There was approximately a three fold increase in the number of subjects at follow-up with hemoglobin less than 7 mg/dl in the ROX-888 group 12/455 (2.6%) compared to placebo group 2/250 (0.8%). There was a higher incidence of adverse events due to elevated transaminases in the ROX-888 group (2.2%) than placebo group (1.4%) but this is a kown effect of NSAIDs. No subject discontinued the study due to abnormal liver function tests but one subject with marked elevation of ALT (438 U/L) and AST (275 U/L) and normal bilirubin discontinued for another reason. There were slightly more adverse events due to edema peripheral in the ROX-888 group (4.6%) compared to the placebo group (3.4%). There were reports of increased creatinine and oliguria but review of these cases did not reveal any significant persistent changes in renal function. There were no significant anaphylactioid reactions although there were more adverse events due to rashes in the ROX-888 group. There was no evidence to suggest that IN ketorolac resulted in cardiovascular events or delayed wound healing.

New Safety Concerns: Nasal related adverse events occurred as a result of using intranasal ketorolac. The nasal symptoms and erosions appeared to be self limited and do not appear to pose a major safety issue for use of Sprix up to five days in subjects less than 65 years old. Adequate data does not exist to fully assess the nasal safety in subjects 65 years of age or older but suggests an increased frequency of nasal events.

Postoperative bleeding with ketorolac although a known side effect was the most serious adverse event in the controlled safety database and is discussed in the section above on major safety results.

Safety by Duration and by Dose Analyses: In the Sprix group there appeared to be a weak dose response relationship between the number of doses administered and an abnormal nasal exam. Abnormal nasal exam occurred with as few as two doses of Sprix.

Need for Risk Management: If approved for inpatient use only, a risk evaluation and mitigation strategies (REMS) program will be necessary.

Limitations of Available Data: The safety database consisted of only 59 outpatients that received an average of 3.4 doses. There were only 20 subjects 65 years of age or older that had nasal exams and only seven of these subjects had nasal exams in the five-day study (Study 2003-01) with the remaining nasal exams performed in the two-day study (Study 2001-03).

7.1 Methods

Studies/Clinical Trials Used to Evaluate Safety

In support of this NDA, the Applicant submitted eleven Phase 1 studies and four Phase 2 and 3 studies. Roxro's integrated safety analyses included safety data from 828 subjects enrolled in the four Phase 2 and 3 studies (Study 2003-01, 2005-01, 2005-03 and 2001-03). The safety dataset was considered adequate since it contained:

- Well-controlled (i.e., randomized, double-blind, placebo-controlled) studies
- An adequate number of patients, 495, who received Sprix
- An adequate number of patients, 172, who receive Sprix for 5 days (maximum duration of dosing)

Safety findings were reviewed for the eleven Phase 1 studies. Studies 2006-03 and 2006-04 were drug interaction studies and the results are discussed in Section 7.5.5. Study 2002-02 was a distribution study and the results are discussed in Section .

The safety dataset for outpatients consisted of 59 subjects who received a mean of 3.4 outpatient doses of Sprix. This reviewer considers the outpatient safety dataset too small to adequately assess outpatient safety without relying on the inpatient findings.

Categorization of Adverse Events

Roxro's categorization of adverse events with preferred terms is consistent with the investigator's reported terms for the adverse events.

Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As noted in section 7.1.1 the safety dataset was comprised of pooled data from four well-controlled studies.

7.2 Adequacy of Safety Assessments

A total of 495 subjects received at least one dose of ROX-888 in the controlled safety database. Safety assessments included adverse events, laboratory evaluations (hematology and biochemistry), vital signs, nasal examinations and cardiovascular and nasal 14-day follow-up questionnaires. The Applicant's submitted data was of adequate quality and completeness to allow for a comprehensive safety review with the following exceptions:

- An insufficient number of nasal exams were performed on subjects 65 years or older. A total of 20 subjects age 65 or older on ROX-888 had nasal exams but only 7 subjects in the 5-day study with the remaining in a 2-day study.
- Only 59 subjects were dosed as outpatients.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 7.2.1 displays the duration of exposure for IN ketorolac in the pooled efficacy studies. A total of 495 subjects received at least one dose of ROX-888 in the controlled safety database of which 172 subjects (35%) received at least five days of treatment. However, only 59 subjects received outpatient dosing with a mean number of outpatient doses of 3.4 per patient.

Table 7.2.1: Duration of Study Drug Exposure in all Four Efficacy Studies

	IN ketorolac 10 mg	ROX-888	Placebo	Total
Number of Subjects	43	495	290	828
Single Dose [a]		40 (8.1%)	40 (13.8%)	80 (9.7%)
Multiple Dose Studies				
2001-03 (Phase 2)	43 (100.0%)	42 (8.5%)	42 (14.5%)	127 (15.3%)
2003-01 (Phase 3)		199 (40.2%)	101 (34.8%)	300 (36.2%)
2005-01 (Phase 3)		214 (43.2%)	107 (36.9%)	321 (38.8%)
No. of Doses Received [b]				
1 - 4	7 (16.3%)	118 (23.8%)	64 (22.1%)	189 (22.8%)
5 - 8	36 (83.7%)	144 (29.1%)	96 (33.1%)	276 (33.3%)
9 - 12	0 (0.0%)	94 (19.0%)	54 (18.6%)	148 (17.9%)
13 - 16	0 (0.0%)	136 (27.5%)	73 (25.2%)	209 (25.2%)
17 - 20	0 (0.0%)	3 (0.6%)	3 (1.0%)	6 (0.7%)
Mean (SE)	5.4 (0.20)	8.4 (0.20)	8.2 (0.26)	8.2 (0.15)
Median	6.0	8.0	8.0	8.0
Range	1 - 6	1 - 17	1 - 18	1 - 18
No. of Days of Exposure [c] **Multiple-Dose Studies Only**				
1	2 (4.7%)	23 (4.6%)	6 (2.1%)	31 (3.7%)
2	6 (14.0%)	65 (13.1%)	23 (7.9%)	94 (11.4%)
3	35 (81.4%)	170 (34.3%)	114 (39.3%)	319 (38.5%)
4	0 (0.0%)	25 (5.1%)	18 (6.2%)	43 (5.2%)
5	0 (0.0%)	171 (34.5%)	89 (30.7%)	260 (31.4%)
6	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.1%)
Mean (SE)	2.8 (0.08)	3.6 (0.06)	3.6 (0.07)	3.5 (0.04)
Median	3.0	3.0	3.0	3.0
Range	1 - 3	1 - 6	1 - 5	1 - 6

Source: Table 2

a. Study ROX-2003-05 dental extraction surgery Phase 2 study.

b. The frequency count includes subjects from Study ROX-2003-05 who received only 1 dose.

c. Days of exposure = last dose date minus first dose date plus 1. Subjects in Study ROX-2003-05 (the single dose study) were exposed for 1 day. Subject 83054 (Study ROX-2005-01) was the only subject exposed to 6 days of study medication.

Reference: Sponsor's Table 1.4 Extent of Study Drug Exposure, page 15 ISS, Volume 19, Module 5

7.2.2 Explorations for Dose Response

The number of doses and relationship to adverse events specifically renal, cardiovascular, gastrointestinal and bleeding were assessed. Tabular data in the Integrated Summary of Safety summarizing the incidence of adverse events related to number of doses was reviewed.

There appeared to be a small dose response relationship with nasal symptoms and abnormal nasal exam. There was no apparent evidence of a dose response relationship for other adverse events.

7.2.3 Special Animal and/or In Vitro Testing

According to Dr. Newton Woo, the FDA pharmacologist, the previously submitted toxicology studies were adequate to support this NDA application submitted as a 505(b)(2).

7.2.4 Routine Clinical Testing

In Studies 2003-01, 2005-01, and 2001-03 the following tests were performed during the Treatment Period

- Vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Serum chemistry
- Hematology
- Nasal examination
- Cardiac and nasal questionnaire (not obtained in Study 2001-03)

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the Clinical Pharmacology Review

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The NSAID class of drugs has been associated with potentially serious cardiovascular, gastrointestinal and renal risks described in Section 2.3. The causality assessment of these adverse events can be difficult to determine in a postoperative population since these patients have underlying medical issues and receive multiple concomitant medications that can also cause or contribute to these adverse events. In attempting to determine whether ROX-888 resulted in adverse events associated with other NSAIDs, the difference in incidence between adverse events in placebo and ROX-888 groups was analyzed.

7.3 Major Safety Results and Discussion

7.3.1 Deaths

No deaths were reported during the clinical development program of intranasal ketorolac.

7.3.2 Nonfatal Serious Adverse Events

In the four pooled efficacy studies, a total of 28/828 subjects (3.4%) reported 38 SAEs: 2/43 (4.7%) in the 10-mg IN ketorolac group, 18/495 (3.6%) in the ROX-888 group, and 8/290 (2.8%) in the placebo group. In the single-dose dental study (Study 2003-05) no subjects reported a SAE. When Study 2003-05 is removed from the pooled data, a total of 28/748 subjects (3.7%) reported 38 SAEs: 2/43 (4.7%) in the 10-mg IN ketorolac group, 18/455 (4.0%) in the ROX-888 group and 8/250 (3.2%) in the placebo group. Of the 38 SAEs reported, six led to discontinuation in the ROX-888 group, one in the 10-mg IN ketorolac group and none in the placebo group. The SAEs leading to study discontinuation as recorded in the CRF by the term AEDECOD (Dictionary Term – Preferred Term) included: vaginal hemorrhage (Subject 81906 in the 10-mg group), wound complication the reported term was wound hematoma (Subject 81515 in the ROX-888 group), postprocedural hemorrhage (Subject 81555 in the ROX-888 group), postprocedural hemorrhage (Subject 81563 in the ROX-888 group), small intestinal hemorrhage (Subject 83039 in the ROX-888 group), postprocedural hematoma (Subject 83056 in the ROX-888 group), and postprocedural hemorrhage and anemia (Subject 84013 in the ROX-888 group). As summarized by the applicant, the most commonly reported SAE by the term AEDECOD was postprocedural hemorrhage, experienced by 3 (0.6%) subjects in the ROX-888 group and no subjects in the 10-mg IN ketorolac or placebo groups. However, including discontinuations due to SAEs from any bleeding complication (i.e. vaginal hemorrhage, wound hematoma, postprocedural hemorrhage, intestinal hemorrhage and post procedural hematoma) in the three multiple-dose efficacy studies resulted in the following: 6/455 (1.3%) subjects in the ROX-888 group and 1/43 (2.3 %) subjects in the 10-mg IN ketorolac group and no subjects in the placebo group.

The available information about each serious adverse event was thoroughly reviewed in all 20 subjects receiving IN ketorolac (18 subjects in the ROX-888 group and 2 subjects in the 10 mg group). For the two subjects with a SAE of pulmonary embolus (Subject 81903 in the 10 mg group and Subject 81908 in the ROX-888 group) the role of IN ketorolac could be reasonably excluded as a cause and therefore summaries of these patients were not done. Summaries for the remaining 18 subjects with SAEs are provided below. The information provided by the applicant in the CRFs and patient narratives was often insufficient to determine an exact cause for the SAE and in some cases lacked basic details of the SAE. Narratives for placebo subjects with SAEs were not submitted but the CRFs were provided.

<u>Individual Serious Adverse Event Summaries</u>

Subject 81906 (Study 2001-03/ 10 mg)
The subject, a 42 year old woman, underwent total hysterectomy and bilateral salpingoophrectomy on (b) (6) She was assigned to receive IN ketorolac (10 mg) and started taking study drug at 11:30 on the day of surgery. No follow-up doses were administered. On (b) (6) she experienced the SAE of severe vaginal hemorrhage (start time 14:20) approximately three hours after taking study drug. She required surgical intervention that day (no details provided). The event was reported as resolved on (b) (6) at 19:00, and was considered probably not related to the study drug by the investigator. The patient also had AEs of anemia and nausea.

Her past medical history included varicosities of the left leg, bilateral foot operation, ectopic pregnancy, menorrhagia, tubal ligation ([redacted] (b) (6) Perioperative medications administered on [redacted] (b) (6) for anesthesia included midazolam, fentanyl, propofol, vecuronium, morphine, isoflurane, and nitrous oxide. Other perioperative medications included cefazolin for antibiotic prophylaxis, Maxolon for nausea prophylaxis, and fentanyl for prestudy titration (at 10:50).

Impression
The likely cause of her postoperative bleeding was poor surgical hemostasis. However, given the timing of her postoperative bleeding approximately three hours after receiving 10 mg intranasal ketorolac, the antiplatlet effect of ketorolac cannot be completely excluded as a contributory cause. The bleeding was of sufficient severity to require a surgical procedure.

Subject 81091 (Study 2003-01/ ROX-888)
Subject 81091 is a 31 year old woman status post total abdominal hysterectomy on [redacted] (b) (6) assigned to receive ROX-888. She started taking study drug on [redacted] (b) (6) at 11:50 and was administered follow-up doses at 19:55 on [redacted] (b) (6), at 3:50, 9:05, and 19:55 on [redacted] (b) (6) at 3:05, 11:50, and 20:00 on [redacted] (b) (6), at 9:15, 15:15, 21:00 on [redacted] (b) (4) and at 8:00 and 14:05 on [redacted] (b) (6)

On [redacted] (b) (6), according to the CRF, she experienced the SAE of moderate wound infection requiring medication. However, review of the concomitant medication list indicates that the antibiotics gentamycin and ampicillin/clavulonic acid were started for a chest infection. She received one dose of gentamycin on [redacted] (b) (6) and ampicillin/clavulonic acid from [redacted] (b) (6) through [redacted] (b) (6). Additional adverse events listed in the CRF include: mild wound bruising, moderate constipation epistaxis and nasal irritation. The subject's medical history included: dental abscess (May 2003), sinusitis (2000), intermittent chest infections, intermittent shortness of breath, productive cough related to smoking, headaches, forgetfulness, anemia, eczema, depression, insomnia, daily tobacco use, chronic alcoholism and substance abuse prior to 2002, menorrhagia and dysmenorrhea. Perioperative medications administered on [redacted] (b) (6) for anesthesia included: midazolam, fentanyl, propofol, vecuronium, albuterol, isof1urane, nitrous oxide, cefazolin, morphine (9:55 to 10:45), neostigmine, and glycopyrrolate. Other perioperative medications included fentanyl pre study titration (10:55 to 11:40). Concomitant medications received include: low molecular weight heparin, ondansetron, paracetamol, ampicillin/clavulonic acid, codeine phosphate multiple doses, lactulose, gentamicin, and metoclopramide.

Impression
This subject appears to have been coded incorrectly for an SAE of wound infection when in fact she had a chest infection. The term chest infection may have referred to a lung infection but given the lack of details it is impossible to know for certain. However, it appears unlikely that this was a wound infection, given the typical location of a hysterectomy incision. IV ampicillin/clavulonic acid was used which could be appropriate for either a respiratory tract infection or skin infection. Assuming that this was a lung infection, the subject's past medical history of smoking, productive cough and intermittent chest infections is sufficient to explain her developing a postoperative lung infection.

Discussion of IN ketorolac benefit: The use of IN ketorolac did not prevent this subject from consuming large quantities of oral and parenteral opioids which may have contributed to her developing constipation requiring the use of lactulose. Although it is unlikely that the infection was due to ketorolac, she developed wound bruising, epistaxis and nasal irritation which were likely due at least in part to her use of IN ketorolac. The use of IN ketorolac for this subject did not appear to mitigate against opioid-related side effects but instead resulted in side effects attributable to both opioids and NSAIDs.

Subject 81515 (Study 2003-01/ ROX-888)
Subject 81515 is a 47 year old woman who underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy on (b) (6) She received her first dose of ROX-888 the day of surgery at 18:10. She was administered follow-up doses the next day, (b) (6), at 8 and 16 hours at 2:10 and 8:25. On (b) (6), she experienced the SAE of wound hematoma (start time 8:45), which required a surgical procedure (no details provided). The wound hematoma was reported as resolved at 18:40 on (b) (6), and was considered possibly related to the study drug by the investigator. On (b) (6) she experienced concurrent AEs of nausea and vomiting. Laboratory values at screening were hemoglobin 14 g/dl, hematocrit 42 and platlets 257. Laboratory values at the follow-up exam 5 days after surgery were hemoglobin 10.6, hematocrit 32 and platlets 219.

Her medical history included tonsillectomy, varicose veins, celiac disease, nausea, iron deficiency anemia, dizziness, headaches, lightheadedness, gluten allergy, and menorrhagia. Perioperative medications administered on (b) (6) included fentanyl, midazolam, propofol, rocuronium, nitrous oxide, desflurane, and morphine (15:15 to 16:00). Other perioperative medications included morphine prestudy titration (16:40 to 17:35), ondansetron for nausea (at 16:55), tramadol pre study titration 50 mg IV (at 17:45), and metoclopramide for nausea (at 18:00).

Impression
This subject developed a wound hematoma after receiving three doses of ROX-888. Although the likely primary cause of her postoperative bleeding was inadequate wound hemostasis, a contributory role of the antiplatlet effect of IN ketorolac cannot be completely excluded. Her bleeding was of sufficient severity to necessitate a repeat surgical procedure. There was a 24% drop in hemoglobin form the time of her screening visit to her follow-up visit.

Subject 81555 (Study 2003-01/ ROX-888)
Subject 81555, a 31-year-old woman, underwent total abdominal hysterectomy on (b) (6) and received her initial dose of ROX-888 on the day of surgery at 18:10. No other follow-up doses of study drug were administered. On (b) (6) she experienced the SAE of moderate postprocedural hemorrhage which required a surgical procedure. The event was reported as resolved on (b) (6) at 1:30, and was considered as probably not related to the study drug by the investigator. On (b) (6), she experienced concurent AEs of mild nausea and mild tachycardia. The subject was withdrawn from the study due to the SAE of postprocedural hemorrhage. Pertinent laboratory values at screening were the following: hemoglobin 11.3 g/dl, hematocrit 36 and platlets 282. Laboratory values at the follow-up exam were as follows: hemoglobin 9.3, hematocrit 29 and platlets 181.

Her medical history included childhood asthma, indigestion, alcoholic gastritis (b) (6) backache, iron deficiency anemia, post-traumatic stress disorder, drug abuse (b) (6) tobacco use, penicillin allergy, kidney infection (b) (6) dyspareunia, menorrhagia, and colposcopy (b) (6) (b) (6)

Perioperative medications administered on (b) (6) for anesthesia included midazolam, fentanyl, nitrous oxide, propofol, rocuronium, sevoflurane, atropine, and neostigmine. Other perioperative medications included fentanyl postoperative titration 110 mcg (17:20 to 17:45) and cefazolin for prophylaxis. She also received metoclopramide, "Gelofusine" (volume expansion), PCA morphine, (thiopentone, suxamethonium, vecuronium, morphine, sevoflurane, nitrous oxide, 1 unit red blood cells, phenylephrine, ondansetron, neostigmine, glycopyrrolate, vitamin K, cefazolin, paracetamol, cefaclor, and tramadol 50 mg po on (b) (6)

Impression
This subject within six hours of receiving ROX-888 developed postoperative hemorrhage that necessitated a surgical procedure and transfusion. There was approximately an 18% drop in hematocrit from the time of her screening visit to the time of her follow-up visit which occurred after receiving one unit of packed red blood cells. She was treated with "IV vitamin" for an increased INR but no values or details were provided.

Subject 81563 (Study 2003-01/ ROX-888)
The subject was a 49-year-old woman who underwent a total abdominal hysterectomy and bilateral salpingo-oophrectomy on (b) (6). Her first dose of ROX-888 was on (b) (6) at 16:00 and follow-up dose on (b) (6) at 8 hours at 00:01. On (b) (6) she experienced the SAE of moderate postprocedural hemorrhage which required a surgical procedure. The event was reported as resolved on (b) (6) at 5:40, and was considered as probably not related to the study drug by the investigator. She experienced the concurrent AEs of tachycardia, hyperkalemia, possible pseudocholinesterase deficiency, and T-wave elevation. The subject was withdrawn from the study on (b) (6) due to the SAE of postprocedural hemorrhage. At screening, hemoglobin was 11.4 g/dL, hematocrit 37 and platlets 454. At the follow-up exam hemoglobin was 10.4 (after 1 unit packed RBCs), hematocrit 32 and platlets 268.

Her past medical history included iron deficiency anemia, tobacco use, laparoscopic tubal ligation and menorrhagia. Perioperative medications administered on (b) (6) for anesthesia included neostigmine, midazolam, fentanyl, alfentanil, propofo1, atracurium, dexamethasone, atropine, morphine, isoflurane and glycopyrrolate. Other perioperative medications included cefazolin for prophylaxis and one unit red blood cells administered the day after surgery.

Impression
The subject developed postoperative hemorrhage within eight hours of receiving ROX-888. She received one unit of red blood cells and required a surgical procedure. There was a 9% drop in hemoglobin from the time of the screening visit to the follow-up visit but she received one unit of packed red blood cells prior to her follow-up visit. The postoperative hemorrhage was likely due to

inadequate hemostatsis during the initial surgical procedure but a contributory role by IN ketorolac cannot be excluded.

Subject 81743 (Study 2003-01/ ROX-888)
Subject 81743, a 75-year-old man, underwent left total hip replacement on (b) (6) and started ROX-888 on the same day of surgery at 13:00. He was administered follow-up doses at 8 hours at 21:00 on (b) (6), at 16, 24, and 32 hours at 5:00, 11:20, and 21:00 on (b) (6), and at 40 hours at 5:00 on 06 (b) (4) On (b) (6), he experienced the SAE of moderate wound secretion ("wound ooze") which did not require any medical intervention. This event was considered an SAE due to the need to prolong hospitalization for wound care. The event was reported as resolved on (b) (6) and was considered as probably not related to the study drug by the investigator. On (b) (6), the subject experienced the concurrent AEs of mild ileus paralytic (stop date (b) (6)) and tachypnea (start time 13:00; stop date/ time (b) (6)/15:00). On (b) (6) (b) (6), the subject experienced the concurrent AEs of mild pyrexia (start time 20:30; stop date/ time (b) (6)/2:15) and mild diarrhea (stop date (b) (6)). On (b) (6), the subject experienced the concurrent AEs of mild dyspnea (stop date (b) (6)) and mild vomiting (stop date (b) (6)). The subject was withdrawn from the study on (b) (6) due to the AE of ileus paralytic.

His medical history included blood clot left inner ear ((b) (6) right ear hearing deficiency, indigestion from NSAIDs, appendectomy ((b) (6) osteoarthritis, urinary frequency, and leptospirosis ((b) (6) Perioperative medications administered on (b) (6) for anesthesia included remifentanil, propofol, vecuronium, desflurane, ephedrine, morphine (11:20 to 11:45), and neostigmine. Other perioperative medications included midazolam for premedication , metaclopraminde for premedication, cephazolin for prophylaxis, gentamicin for prophylaxis, and fentanyl for prestudy titration (2:15 to 12:55).
Concomitant medications received included diclofenac, cephazolin, metoclopramide, dalteparin sodium, ondansetron, an oral antacid, paracetemol, and ondansetron wafer.

Impression
Insufficient details were provided in the CRF to fully assess this adverse event. However, the use of a low molecular weight heparin and IN ketorolac may have contributed to oozing from the wound.

Subject 81009 (Study 2005-01/ROX-888)
Subject 81009, a 56 year old women, underwent a laporatomy for left salpino-oopherectomy on (b) (6) (b) (6) Her past medical history included cough, severe postoperative nausea following a cholecystectomy (b) (6) headaches, insomnia, left ovarian cyst, hysterectomy (b) (6) and abdominal pain.

She started taking ROX-888 on (b) (6) at 11:30. She was administered two follow-up doses at 6 and 12 hours on (b) (6) at 17:30 and 23:30, respectively. On (b) (6) she experienced the SAE of a moderate pelvic hematoma that required surgical treatment. This event resolved on (b) (6) (b) (6), and was considered probably not related to the study drug by the investigator. On (b) (6) (b) (6), at 16:30, she experienced the SAE of moderate atrial fibrillation that required medical intervention. This event resolved at 9:00 on (b) (6), and was considered to be probably not

related to the study drug by the investigator. Also on (b) (6), the subject experienced the SAE of moderate wound dehiscence that required surgical treatment. This event resolved on (b) (6) and was considered to be probably not related to the study drug by the investigator. On (b) (6) she experienced concurrent AEs of mild pyrexia (start time 19:45; stop date/time (b) (6)/1 :00), mild tachypnea (start time 7:45; stop date/time (b) (6)/1:00), mild hypokalemia (start time 21:30; stop date/time (b) (6)/22:30). On (b) (6), she experienced the concurrent AE of mild diarrhea and moderate retching. On (b) (6), she experienced the concurrent AEs of moderate abdominal pain, moderate wound infection, and moderate wound ooze (stop date (b) (6) (b) (6). She was treated with ampicillin/clavulonic acid for her wound infection. All concurrent AEs were considered probably not related to the study drug by the investigator except for the severe vomiting which was considered possibly related. The study drug was discontinued on (b) (6) due to the AE of nausea as recorded on the CRF.

During her screening exam on (b) (6), the day prior to surgery, she had tachypnea with a respiratory rate of 22 breaths/minute. Laboratory results from the screening visit were as follows: hemoblobin 14.1 g/dL, hematocrit 44% and platelets 148 x 10^6/mL. Laboratory results at follow-up on (b) (4) were the following: Hemoglobin 7.9, Hematocrit 25% and platlets 140 x 10^6/mL.

Perioperative medications administered on (b) (6) for anesthesia included droperidol (at 9:40), ondansetron (at 9:40), fentanyl (9:40 to 10: 10), propofol (9:40 to 10:25), atropine (9:45 to 10: 15), metaraminol (at 10:05), atracurium (at 10:07), neostigmine (at 10:30), and glycopyrrolate (at 10:30). Morphine was also administered from 10:35 to 11:10, as needed for pre study titration. Concomitant medications received included paracetamol, buscopan (hyoscine butylbromide an antispasmodic for treatment of abdominal pain and cramps), omeprazole, gelofusine, tramadol, metoclopramide, morphine PCA, cyclizine, potassium chloride, ampicillin/clavulonic acid, oral potassium, heparin, cefuroxime, metronidazole, amiodarone, red blood cells, furosemide, metoprolol, enoxaparin, magnesium hydroxide, aspirin, and clotrimazole. The patient required IV heparin for her atrial fibrillation and a unit of red blood cells on (b) (6)

Impression
The SAE of pelvic hematoma approximately 48 to 72 hours after her last dose of IN ketorolac is most likely due to poor surgical hemostasis but a contributory role of IN ketorolac cannot be completely excluded. She required additional surgery for her pelvic hematoma and wound dehiscence. There was approximately a 44% drop in hemoglobin from the time of screening visit to her follow up visit. The IV heparin she received for atrial fibrillation and enoxaprin were both started after she developed her hematoma. The occurrence of atrial fibrillation does not appear to be related to IN ketorolac. There are insufficient details to fully asses her wound dehiscence that occurred four days after her last dose of IN ketorolac but a contributory effect of IN ketorolac cannot be completely excluded.

Subject 81017 (Study 2005-01/ROX-888)
Subject 81017, a 35-year-old female, underwent total abdominal hysterectomy on (b) (6) and started ROX-888 at 13:00 on the day of surgery. She was administered three follow-up doses at 6 hours on (b) (6) at 19:00 and at 12 and 18 hours on (b) (6) at 1:00 and 7:00. On (b) (6) (b) (6) she was readmitted to the hospital for the SAE of incision site cellulitis. She was treated with

IV cefuroxime and metronidazole for one day and then switched to oral formulations of these antibiotics. This event was reported resolved on (b) (6) Her past medical history and medications are non-contributory.

Of note the subject discontinued study drug on (b) (6) after the administration of her 4th dose at 7:00 dose due to nasal stinging. She also reported nasal stinging following all three of her previous doses.

Impression
This subject was diagnosed with surgical site cellulitis four days after receiving her last dose of IN ketorolac. It is unlikely that intranasal ketorolac contributed to her wound infection. This subject also experienced nasal stinging with all four doses of IN ketorolac that eventually resulted in her discontinuing the drug after the fourth dose.

Subject 82055 (Study 2005-01/ROX-888)
This 55 year old man underwent radical prostatectomy and pelvic lymphadenectomy on (b) (6) (b) (6) He received two doses of ROX-888 on the day of surgery and his third dose the following day. On (b) (6), he experienced the SAE of moderate ileus that required medication. This event resolved on (b) (6), and was considered to be probably not related to the study drug by the investigator.

Impression
The reported occurrence of ileus on the second postoperative day is probably related to surgery and not intranasal ketorolac.

Subject 83010 (Study 2005-01/ROX-888)
Subject 83010, a 48-year-old female, underwent a total abdominal hysterectomy and umbilical hernia repair on (b) (6) She received a total of nine doses of ROX-888 with her last dose on (b) (6) at 15:00. On (b) (6) she experienced the SAE of postoperative ileus that required medication and resolved on (b) (6). On (b) (6) she experienced the concurrent AE of severe constipation (stop date (b) (6) According to the CRF the subject was discontinued early from the study with the last dose of study drug on (b) (6) because the subject's need for analgesia decreased. Pertinent concomitant medications included: hydrocodone/acetaminophen 500/5 x1 on (b) (6) at 14:10 (approximately 50 minutes prior to her 24 hour pain assessment) and hydrocodone/acetaminophen 1000/10 x 1 at 19:50 (approximately one hour prior to her 30 hour pain assessment) on (b) (6) and Hydrocodone/acetaminophen 1000/10 x 1 on (b) (6) at 9:10 (approximately 6 hours prior to her 48 hour pain assessment) and at 18:30 (3.5 hours after her last dose of IN ketorolac). Her past medical history included hypertension, hyperlipidemia, menorrhagia, pelvic pain,

Impression
The post-op ileus in this patient was probably related to surgery but opioid use may have been a contributing factor. The use of IN ketorolac did not prevent her from developing GI symptoms possibly related to opioid use.

Unrelated to her SAE, the pain assessments at 24, 30 and 48 hours were potentially influenced by use of opioid rescue medication. The CRF lists the reason for discontinuing study drug as "Patient's need for analgesia decreased." However, the subject required opioid rescue medication approximately 3.5 hours after her final dose of IN ketorolac. The use of opioid rescue medication in this study potentially confounds interpretation of the efficacy findings for this patient.

Subject 83024 (Study 2005-01/ROX-888)
Subject 83024, a 41 year old woman, underwent total abdominal hysterectomy and placement of bilateral ureteral stents on (b) (6). She receive 13 doses of ROX-888 (last dose on postpone day #3). On (b) (6) she was coded in the CRF as experiencing the SAE of severe postprocedural complication for which the verbatim term was postoperative small bowel distension. There is no indication that any intervention was required. The resolution date for this event is left blank. It is unclear from the CRF why this event was considered an SAE. On (b) (6), she experienced the concurrent AE of a mild epistaxis. The subject was discontinued from study drug on (b) (6) because her need for analgesia decreased.

Her past medical history included hypertension, hypothyroidism, anemia, anxiety, uterine fibroid, tubal ligation, abdominal pain, menorrhagia, and complex pelvic mass. Perioperative medications administered on (b) (6) for anesthesia included midazolam, lidocaine, propofol, fentanyl, Cisatracurium, sevoflurane, Anectine, prostigmine, and atropine. The subject also received Ondansetron nausea prophylaxis. Concomitant medications received included Feosol, Levoxyl, Topamax, Ceftriaxone, Diphenhydramine, Hydrocodone/acetaminophen, Mylicon, Phenergan, Propoxyphene/acetaminophen, Mylanta gas, Milk of Magnesia, Meperidine, lorazepam, and Docusate.

Impression
There is no reason to suspect that IN ketorolac played a role in her developing postoperative small bowel distension.

Subject 83039 (Study 2005-01/ROX-888)
Subject 83039, a 31year old woman, underwent laparoscopic sigmoid colectomy with wedge resection of liver lesion on (b) (6), according to the patient narrative provided by the applicant. The CRF indicates that the surgical procedure was an open revision of gastric bypass to duodenal switch. She received her first dose of ROX-888 on the day of surgery at 11:03. She was administered one follow-up dose at 6 hours on (b) (6) at 17:07. On (b) (6), at 17:50, she experienced the SAE of severe small intestinal hemorrhage that required surgery (no additional details of the bleed were provided). This event resolved at 0:00 on (b) (6), and was considered to be probably not related to the study drug by the investigator. The subject was discontinued early from the study on (b) (6) due to the SAE of small intestinal hemorrhage. Laboratory results from the screening visit were as follows: hemoblobin 9.9 g/dL, hematocrit 30% and platelets 372 x 10^6/mL. Laboratory results at the follow-up visit on (b) (6) were the following: Hemoglobin 8.4 (after 2 units packed red blood cells), Hematocrit 25% and platlets 249 x 10^6/mL.

Her medical history included cholecystectomy, abdominoplasty, gastric bypass ([redacted] (b) (6) sickle cell trait, alpha-thalassemia, anemia, hyperglycemia, depression, tubal ligation, and recurrent morbid obesity. Perioperative medications administered on [redacted] (b) (6) for anesthesia included fentanyl, midazolam, lidocaine, propofol, Rocuronium, Anectine, sevof1urane, neostigmine, and glycopyrrolate. In addition, the subject was administered the following medications perioperatively: Metoclopramide for nausea prophylaxis, Ceftriaxone for infection prophylaxis, Labetalol for hypertension, 2 units packed red blood cells (from 9:15 to 10:30 - prior to the administration of IN ketorolac), Ondansetron for nausea prophylaxis, and morphine for pre study titration.

Impression
Insufficient information has been provided to exclude IN ketorolac as a contributing factor in this patient's intestinal bleed. It is unclear whether the bleeding was at the site of the initial surgical procedure and due to inadequate hemostasis or whether the bleeding developed de novo. However, the timing of the hemorrhage occurring on the same day as the initial surgery suggests that it was related to the surgery. The patient underwent emergency surgery approximately two hours after her second dose of IN ketorolac. There is no indication in the CRF as to whether the IN ketorolac may have had an effect on intraoperative bleeding. There was approximately a 15% drop in hemoglobin from the time of her screening visit to the time of her follow-up exam but she received two units of packed red blood cells during the initial surgery prior to administration of IN ketorolac.

Subject 83056 (Study 2005-01/ROX-888)
Subject 83056, a 36 year old woman, underwent a total abdominal hysterectomy with bilateral salpingo-oopherectomy on [redacted] (b) (6) She received her first dose of ROX-888 at 10:00 on the day of surgery and was administered one follow-up dose on [redacted] (b) (6) at 16:00. On [redacted] (b) (6), at 17:02, she experienced the SAE of severe postprocedural hematoma that required surgery. This event resolved at 19:30 on [redacted] (b) (6) On [redacted] (b) (6) she experienced the concurrent AE of mild tachycardia (start time 16:00; stop date/time [redacted] (b) (6)/20:25). The study drug was discontinued early due to the SAE of severe postprocedural hematoma. Her screening hemoglobin was 13.1 g/dL, hematocrit 37% platlets 250 x 10^6/mL. Follow-up labs on [redacted] (b) (6) were significant for a hemoglobin of 7.5 g/dL, hematocrit 21% and platlets 196 x 10^6/mL.

Her medical history included hypertension, laparoscopic appendectomy, migraine headaches, penicillin allergy, menorrhagia, and pelvic pain. Perioperative medications administered on [redacted] (b) (6) [redacted] (b) (6) for anesthesia included midazolam, lidocaine, propofol, fentanyl, rocuronium, Pepcid, ephedrine, ondansetron, neostigmine, and glycopyrrolate. Other perioperative medications included Metoclopramide and Ceftriaxone for infection prophylaxis. Concomitant medications received included irbesartan, sodium topiramate, metoclopramide, ceftriaxone, two units packed red blood cells on [redacted] (b) (6), conjugated estrogens, acetaminophen, Ketorolac, loratadine, and Propoxyphene/acetaminophen.

Impression
The postoperative hematoma and subsequent surgical procedure and blood transfusion were most likely primarily due to poor surgical hemostasis. However, the two doses of ROX-888 that she received the day that she developed her hematoma cannot be excluded as a contributing factor.

There is no indication in the CRF as to whether there was increased bleeding from IN ketorolac during the emergency surgical procedure. However, she required a transfusion for a drop in hemoglobin of over 40% from her screening value.

Subject 84003 (Study 2005-01/ROX-888)
Subject 84003, a 52 year old woman, underwent bilateral salpingo-oopherectomy on (b) (6) (start 7:45, stop 9:05). She received her initial dose of ROX-888 at 9:30 in the morning the day of surgery. She was administered follow-up doses at 6 and 12 hours on (b) (6) at 15:35 and 21:30, at 18, 24, 30, and 36 hours on (b) (6) at 3:30, 9:30, 15:30, and 21:30, and at 42 and 48 hours on (b) (6) at 3:30 and 9:45. On (b) (6), at 1:00 she experienced the SAEs of severe nausea, severe vomiting, and severe upper abdominal pain for which she apparently went to the ER. The nausea required medication with Ondansetron. These events resolved at 15:00 on (b) (6) (b) (6) and were considered to be possibly related to the study drug by the investigator. According to the CRF, the subject was discontinued early from the study with the last dose of study drug on (b) (6) due to decreased need for analgesia. However, review of the concomitant medications in the CRF indicate that the subject was administered Hydrocodone/acetaminophen numerous times over the time period from (b) (6) and also received 3 mg IV morphine on (b) (6). The pain assessments in this subject do not reflect the efficacy of IN ketorolac alone but appear to be influenced by the use of opioids. Other adverse events reported include nasal burning and constipation. The nasal exam at the 14-day follow-up showed no clinically significant findings.

Her medical history included tonsillectomy, asthma, peptic ulcer, bilateral knee arthroscopies, pelvic pain, right ovarian cyst, hysterectomy, and bladder repair. Perioperative medications administered on (b) (6) for anesthesia included Midazolam, Cisatracurium, Propofol, Xylocaine, and desflurane. Other peri-operative medications included Metoclopramide for nausea prophylaxis, Cefazolin for infection prophylaxis, Fentanyl for prestudy titration, Ondansetron for nausea prophylaxis, and morphine (at 9:25) for prestudy titration. The following is a summary of postoperative opioid use excluding PCA: Morphine 3 mg IV on (b) (6) at 9:31; Hydrocodone/acetaminophen 2 tabs po once on (b) (6) at 14:25; Hydrocodone/acetaminophen 10/1000 once on (b) (6) at 19:30; Hydrocodone/acetaminophen 10/1000 po once on (b) (6) (b) (6) at 7:05 (the subject reported a pain intensity score of 0 on the 48 hour pain assessment conducted at 9:45); Hydrocodone/acetaminophen 5/500 on (b) (6) at 12:20. It is unclear whether the subject received Hydrocodone/acetaminophen 10/1000 on (b) (6) at 16:41.

Impression
The exact etiology of the subject's postoperative nausea and vomiting approximately 6 days after surgery and 5 days after her last dose of ROX-888 is unclear. However, a contributory role of NSAIDs cannot be excluded.

The use of rescue opioids in this patient makes it difficult to interpret her efficacy findings. The subject's use of opioids may have partly contributed to her developing constipation. She appears to have benefited minimally if at all from IN ketorolac but suffered nasal burning form use of the product. The possibility that IN ketorolac contributed to her postoperative nausea and vomiting cannot be completely excluded.

Subject 84013 (Study 2005-01/ROX-888)
Subject 84013, a 28 year old woman, underwent an exploratory laportomy and right oopherectomy on (b) (6) She received her first dose of ROX-888 at 9:20 on the day of surgery. She was administered follow-up doses at 6 and 12 hours on (b) (6) at 15:17 and 21:15 and at 18 and 24 hours on (b) (6) at 3:15 and 9:15. On (b) (6), at 5:04, she experienced the SAE of moderate anemia, and at 12:24 she experienced the SAE of moderate postprocedural hemorrhage. The CRF indicates that both AEs required "other intervention." She was transfused with four units of packed red blood cells. There is no indication that any additional surgery was required. At screening her hemoblobin was 13.3 g/dL and hematocrit 38.9%and on (b) (6) her hemoblobin was 8.1 g/dL (approximately a 40% drop from screening) and hematocrit 23.8. On (b) (6) the subject experienced the concurrent AEs of nausea, vomiting, and malaise. On (b) (6) she experienced concurrent AEs of mild abdominal pain and a moderate migraine headache. On (b) (6) (b) (6), she experienced the concurrent AE of abdominal distension. The subject was discontinued from study drug on (b) (6) due to the SAEs of anemia and postprocedural hemorrhage.

Her past medical history included hepatitis A (nonactive), pelvic pain, and adnexal mass. Perioperative medications administered on (b) (6) for anesthesia included midazolam, Cefazolin, Propofol, sevoflurane, Cisatracurium, and Ondansetron. Other perioperative medications included Fentanyl for prestudy titration and morphine for prestudy titration. Concomitant medications received included Hydrocodone/acetaminophen, Ondansetron, Trimethobanzamide, Cefazolin, Granisetron, Acetaminophen, 4 units packed red blood cells, Acetaminophen with codeine, and Docusate.

Impression
Although postoperative bleeding is likely due to inadequate hemostasis during surgery, the use of ROX-888 may have had a contributory role and played a part in the severity of her bleeding that required multiple transfusions.

Subject 84018 (Study 2005-01/ROX-888)
Subject 84018 is a 46 year old woman with a past medical history of asthma, high cholesterol, hypertension, diabetic neuropathy, diabetes mellitus, cystocele, ovarian lesion, and bilateral tubal ligation. She underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy on (b) (6) (b) (6) She was administered a total of nine doses of ROX-888 and received her last dose (at 48 hours) on (b) (6) at 12:30. On (b) (6), she experienced the SAE of moderate mental status changes lasting from 17:21 to 22:30 that required a visit to the ER. No additional information was provided regarding this SAE. Other adverse events listed on her CRF include blood tinged nasal mucus ((b) (6) 06 at 11:00), nausea ((b) (6)/ 20:40 to (b) (6)/ 10:10), emesis (b) (6) (b) (6)/ 23:00 to (b) (6)/ 10:10) and somnolence (b) (6) According to the CRF the subject was discontinued early from study drug on (b) (6) because her need for analgesia decreased. Review of her concomitant medications reveals that she continued to receive opioids after the 48 hour dose of ROX-888. She received Hydrocodone/acetaminophen 5/500 on (b) (6) at 20:40 and two doses on (b) (6) In addition she had a prn order for Hydrocodone/acetaminophen although it is unclear whether she received any additional Hydrocodone/acetaminophen. While receiving ROX-888 she received three doses of Meperidine

(25 mg IM x 2 doses and 25 mg IV x 1 dose) in addition to her morphine sulfate PCA. One of the Meperidine injections was less than two hours after her first dose of IN ketorolac.

Impression
Insufficient information is provided regarding the SAE of mental status changes to fully assess this event. However, it appears unlikely that IN ketorolac given four days earlier contributed to her mental status changes. IN ketorolac may have contributed to the other adverse events of blood tinged nasal mucus and nausea.

This subject was coded in the CRF as discontinuing study drug due to improvement in pain but continued to have pain sufficient to require opioid analgesics. Also her use of opioids during the study makes it difficult to interpret the efficacy findings.

Subject 85019 (Study 2005-01/ROX-888)
Subject 85019, a 40 year old woman, underwent total abdominal hysterectomy on (b) (6). The CRF indicates that she developed intraoperative bradycardia. She received eight doses of ROX-888 with her last dose (at 42 hours) administered on (b) (6) at 3:30. On (b) (6), she experienced shortness of breath that required admission to the hospital. During this admission she received two units packed red blood cells for anemia, Zythromycin IV for pulmonary infiltrates and Furosemide for shortness of breath. At screening her Hemoglobin was 9.8 g/dL, Hematocrit 32%, platelets 211 and WBC 6.8 and on follow-up after the last dose of study medication on (b) (6) her hemoblobin was 7.4, hematocrit 22.8, platelets 202 x 10^9/L and WBC 8.6 x 10^9/L. No additional details were provided regarding her admission for shortness of breath including her hemoglobin at the time of hospital readmission. The CRF lists this event as resolved on (b) (6)

Her past medical history included hypoactive thyroid, cyst on pancreas, mild anemia, perimenstrual mood disorder, hay fever, symptomatic uterine fibroid, tubal ligation, and insomnia. Peri operative medications administered on (b) (6) for anesthesia included Cefazolin, Midazolam, Propofol, Xylocaine, Rocuronium, sevoflurane, fentanyl, neostigmine), Glycopyrrolate. Other perioperative medications included Glycopyrrolate (at 8:00) for the treatment of bradycardia and morphine (at 9:03, 9:08, and 9: 13) for pre study titration. Concomîtant medications received included Zythromycin, Zolpidem, potassium chloride, Acetaminophen, Levothyroxine, Diphenhydramine, Claritin, Sertraline, red blood cells, Dilaudid, Ondansetron, Hydrocodone/acetaminophen, Propoxyphene/acetaminophen, Furosemide, Ibuprofen, and ferrous sulfate.

Impression
Insufficient details of the subject's readmission to the hospital were provided to determine what caused her shortness of breath. From the limited information available it appears as though her symptoms may have been multifactorial. It is unlikely that her prior use of IN ketorolac contributed to her pulmonary infiltrates or any congestive heart failure if present. However, her shortness of breath may have been partly exacerbated by anemia. She had a 24% drop in hemoglobin from screening to the time of her last dose of study drug. No additional laboratory values were provided after discharge from the hospital. ROX-888 may have been a contributing factor in her postoperative anemia and need for blood transfusion.

Subject 85030 (Study 2005-01/ROX-888)
Subject 85030, a 63 year old woman, underwent sigmoid resection with primary anastomosis, bladder dome resection with primary closure and excision of rectus sheath chronic abdominal wall inflammatory cavity on (b) (6) She received eight doses of ROX-888 with the first dose on (b) (6) at 13:29 and the last dose (at 42 hours) administered on (b) (4) at 6:00. On (b) (6) (b) (6) she experienced the SAE of a severe enterocutaneous fistula that required surgery. This event resolved on (b) (4). On (b) (6), the subject experienced the SAE of severe acute respiratory failure that required intervention. This event resolved on (b) (6), and was considered to be probably not related to the study drug by the investigator. On (b) (6) the subject experienced the AE of moderate anemia (start time 6:45; stop date/time (b) (4):00). On (b) (6), she experienced a concurent AE of moderate renal failure (start time 6:16; stop date (b) (6) In the CRF lab values at screening were: BUN 17 mg/dL, Creatinine 1.0 mg/dL, Hgb 10.4 g/dL, Hct 32% and platelets 387 x 10^9/L. At follow up on (b) (6) the lab values were: BUN 28 mg/dL, creatinine 1.3 mg/dL, Hgb 11.8 g/sL, Hct 35% and platelets 343 x 10^9/L. The patient received one unit of packed red blood cells on (b) (6) She had a positive wound culture (b) (6) (b) (6) No additional laboratory vaules were provided including a CBC prior to her transfusion. On (b) (6), the subject experienced the AE of moderate peritonitis (stop date (b) (6) On (b) (6) she experienced the AEs of severe thrombocytopenia. She received another unit of packed red blood cells on (b) (6) and fresh frozen plasma and platelets. Of note she had been on Warfarin since (b) (6) for atrial fibrillationand and received vitamin K for Warfarin reversal on (b) (6)

As reported in the CRF the subject was discontinued early from the study drug on (b) (6) because her need for analgesia decreased. Following her last dose of study drug on (b) (6) at 6:00 she received morphine 1 mg IV for five doses on the same day.

Her past medical history included chronic atrial fibrillation, hypertension, postoperative tachycardia, diverticulitis, diverticulosis, cholecystectomy (b) (6) appendectomy ((b) (6) open reduction for right hip fracture, head injury (b) (6)), hypothyroidism, chronic urinary tract infections, hysterectomy, proteinuria. Perioperative medications administered on (b) (6) for anesthesia included Cefazolin, Midazolam, Fentanyl, Propofol, Xylocaine, Rocuronium, sevoflurane, gentamicin, Ondansetron, Glycopyrrolate (at 12:05), and prostigmin (at 12: 12). Other perioperative medications included morphine (at 12:29, 12:35, 12:41, and 13:22) for prestudy titration, Lopressor (at 12:31, 12:45, and 12:50) for the treatment of tachycardia, and Dilaudid (12:52, 13:07, and 13: 17) for pre study titration. Concomitant medications received included lisinopril, verapamil, levothyroxine, clonidine, warfarin, digitalis, potassium, Cefazolin, Cardizem, Phenergan, Zosyn, clonidine patch, morphine, Acetaminophen, packed red blood cells, Metoclopramide, gentamicin, Levofloxacin, Docusate, Ceftriaxone, Vasotec, vitamin K, Metronidazole, fresh frozen plasma, platelet transfusion, insulin, total parenteral nutrition, Catapres TTS-3, Lisinopril Furosemide, Fluconazole, and Hydrocodone/acetaminophen.

Impression
The SAEs of colocutaneous fistula and acute respiratory failure do not appear to be related to intranasal ketorolac. However, she did require a transfusion the same day she received her last dose of IN ketorolac. The antiplatlet effect of ketorolac may have contributed to the need for the

transfusion. The severity of the anemia cannot be assessed since no laboratory values were provided postop and prior to the transfusion. The subsequent required trasfusions of RBCs, platlets and fresh frozen plasma were probably due to her anticoagulation with Warfarin and her second surgery but use of IN ketorolac may have exacerbated the anemia.

This patient was coded as discontinuing study drug because her need for analgesia decreased when in fact she continued to have pain requiring parenteral opioids.

Summary of SAEs
The SAEs for the multiple dose Phase 2 and 3 studies are summarized in Table 7.3.2.

Table 7.3.2: Summary of Serious Adverse Events[1]

	ROX-888 N=455	IN Ketorolac 10mg n=43	Placebo n=250	Total n=748
No. of subjects Reporting at least 1 SAE	18 (4.0%)	2 (4.7%)	8 (3.2%)	28 (3.7%)
Bleeding	7 (1.5%)[2,3,4]	1 (2.3%)	1 (0.4%)	9 (1.2%)
Wound healing/ wound infection	4 (0.9%)[2,3,5]	0 (0.0%)	2 (0.8%)	6 (0.8%)
Nausea and vomiting	1 (0.2%)	0 (0.0%)	1 (0.4%)	2 (0.3%)
Ileus/obstruction	3 (0.7%)	0 (0.0%)	2 (0.8%)	5 (0.7%)
Renal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pulmonary emoli	1 (0.2%)	1 (2.3%)	0 (0%)	2 (0.3%)
Altered Mental Status	1 (0.2%)	0 (0%)	0 (0%)	1 (0.1%)
Shortness of Breath	1 (0.2%)	0 (0%)	0 (0%)	1 (0.1%)
Colocutaneous Fistula	1 (0.2%)	0 (0%)	0 (0%)	1 (0.1%)

[1] The table includes SAEs from Studies 2003-01, 2005-01 and 2001-03. No SAEs were reported in Study 2003-05, the single dose study.
[2] Subject 81009 is listed twice in the Table: once under bleeding for pelvic hematoma and once under wound healing due to wound dehiscence. This subject also had the SAE of atrial fibrillation that was not considered to be related to IN ketorolac
[3] Subject 81515 had a wound hematoma and is included in the category on bleeding and not in wound healing
[4] Subject 84013 also had the SAE anemia
[5] Subject 81091 was coded for "wound infection" but had a "chest infection" that was unlikely related to IN ketorolac

The SAEs were analyzed according to the following categories: bleeding, wound healing/wound infection, gastrointestinal and renal

Bleeding: There was a difference in the incidence of SAEs due to bleeding in the IN ketorolac group compared to the placebo group. Using pooled data from the three multiple-dose studies (Study 2003-01, Study 2005-01, and Study 2001-03), a total of 9/748 subjects (1.2 %) experienced a SAE involving bleeding: 1/43 subjects (2.3%) in the 10-mg IN ketorolac group, 7/455 subjects (1.5%) in the ROX-888 group and 1/250 subjects (0.4%) in the placebo group. In the ROX-888 treatment group, a follow-up surgical procedure related to bleeding was required in 6/455 subjects (1.3%) and 4/455 subjects (0.8%) required a blood transfusion. The one subject in the placebo group with a bleeding SAE required a blood transfusion and one subject in the 10 mg group with a bleeding SAE required follow-up surgical treatment. Of the total nine SAEs due to bleeding six resulted in study drug discontinuation, one in the 10 mg group and five in the ROX-888 group.

There was approximately a three-fold higher rate of SAEs due to bleeding in the ROX-888 group compared to the placebo group. A definitive cause of bleeding for each SAE could not be determined in part due to the inherent risk of postoperative bleeding in subjects undergoing major surgical procedures. However, the antiplatlet effect of NSAIDs may be a contributing factor in the higher incidence of postoperative bleeding observed in the ROX-888 treatment group. Even if the bleeding was due to poor surgical hemostasis or the surgical procedure itself, the use of IN ketorolac may have exacerbated the bleeding as measured by the need for blood transfusion or additional surgery.

Since only placebo-controlled data are available for SPRIX and those data clearly show a risk of clinically significant bleeding events compared to placebo, an attempt was made to place the bleeding events observed in the SPRIX development program in context. TORADOL is the identical drug substance and is also formulated for administration via parenteral and oral routes. The reviews for Supplement 004 to NDA 19-698 (Toradol IV) were identified and reviewed. This supplement, submitted in 1994, sought the approval of the injectable formulation via the intravenous route of administration. The approved route of administration was intramuscular.

The risks of bleeding were clearly evident in the medical officer reviews. Dr. Alfred Steinberg, the primary reviewer wrote:

> The overwhelmingly important safety issue with ketorolae has been a predsposition to bleeding. In post-operative patients, such bleeding often has been observed in the areas disrupted by the surgery. In others, gastrointestinal bleeding is most common. However, in an attempt to analyze the safety of IV ketorolac, we are impressed by the lack of complete clarty in presentation of the safety data in the present submission.

Unfortunately, the incidence of clinically significant hemorrhage was not well characterized in these reviews from 1994. This supplement was approved.

Wound healing/wound infection: In the ROX-888 group the following verbatim terms for SAEs were reported once: “wound ooze”, “wound dehiscence”, “wound infection”, and “cellulitis surgical

site". Subject 81009 had a pelvic hematoma requiring additional surgery which may have contributed to the wound dehiscence. Subject 81091 had a chest infection and appears to have been incorrectly coded for a wound infection. In the placebo group the following verbatim terms for SAEs were reported once: "wound ooze" and "postsurgical wound infection". There was no clinically significant difference in the rate of SAEs related to wound infection and wound healing in the ROX-888 group 4/455 subjects (0.9%) compared to 2/250 subjects (0.8%) in the placebo group. There were no differences in the rates of wound infection and wound healing when analyzed separately. The rate for wound infection in the ROX-888 group would have been lower if Subject 81091 with chest infection had been excluded. Althought the rates are similar for wound healing, there was one case of wound dehiscence in the ROX-888 group only. It is difficult to draw any conclusions based on just one case especially since this subject required a repeat surgical procedure.

Gastrointestinal: Gastrointestinal SAEs could be divided into two main categories: nausea and vomiting and obstructive symptoms (ileus/small bowel distention/obstruction). The SAE nausea and vomiting occurred in the ROX-888 group in 1/455 subjects (0.2%) and in the placebo group in 1/250 subjects (0.4%). The one subject with nausea and vomiting in the ROX-888 group was also coded for the SAE of upper abdominal pain. The incidence of obstructive SAE symptoms in the ROX-888 group was 3/455 subjects (0.7%) and in the placebo group 2/250 subjects (0.8%). There was no evidence in the ROX-888 group that IN ketorolac was the likely cause for obstructive symptoms. Subject 83039 had an intestinal bleed but this was most likely due to her surgical procedure. Overall there was no evidence of increased gastrointestinal SAEs in the IN ketorolac group compared to the placebo group.

Renal: There were no renal SAEs in subjects treated with IN ketorolac or placebo.

7.3.3 Dropouts and/or Discontinuations

Dropouts Due to Adverse Events
The number of dropouts due to adverse events was obtained from the adverse event dataset "ADAE" using the term "AESP" to identify subjects that stopped the study due to an AE. A total of 117/828 subjects (14.1%) dropped out of the four Phase 2 and 3 efficacy studies due to 164 adverse events: 5/43 (11.6%) in the 10-mg IN ketorolac group, 80/495 (16.2%) in the ROX-888 group, and 32/290 (11.0%) in the placebo group. The most common adverse event leading to study dropout in the ROX-888 group involved nasal symptoms, 27/495 (5.5%) compared to 7/290 (2.4%) in the placebo group. Discontinuation due to local intolerance was even higher in the ROX-888 group when adverse events of throat irritation and watery eyes were included with nasal adverse events. Nausea and/or vomiting was the reason for dropout in approximately 11/495 (2.2%) of the ROX-888 group and in 9/290 (3.1%) of the placebo group.

Since use of oral NSAIDs can result in renal impairment and bleeding, the CRFs for dropouts due to these adverse events were reviewed in detail and summarized below. The CRFs for adverse events known to occur with IN ketorolac (e.g. nasal irritation) and events clearly not related (e.g. pneumonia) were not reviewed in detail and are not individually summarized. The CRFs for discontinuations due to SAEs are discussed in the section on SAEs and are not included below.

Summary of Dropouts Due to Renal or Bleeding Adverse Events

Subject 81893 (Study 2001-03/ROX-888)

Subject 81893, a 48 year old woman, underwent total abdominal hysterectomy. Her past medical history was significant for anemia, menorrhagia and tubal ligation. ROX-888 was discontinued for the adverse events of bradypnea, hypovolemia and low urine output after receiving two doses of study drug. Vital signs at the time of her first dose were: pulse 56 bpm, respiratory rate 16 and blood pressure 162/94. Vital signs *prior* to her second dose were as follows: pulse 70, respiratory rate 8 and blood pressure 84/50. Screening labs were as follows: BUN 13 mg/dl (4.60 mmol/L) and creatinine 0.7 mg/dl (0.06 mmol/L). Follow-up chemistry labs were as follows: BUN 7 mg/dl (2.60 mmol/L) and creatinine 0.5 mg/dl (0.04 mmol/L). No laboratory values were provided at the time the subject's low urine output was reported. The subject was treated with IV normal saline.

Impression

This subject developed the adverse events of low urine output, bradypnea and hypovolemia after one to two doses of IN ketorolac. No evidence was provided to suggest that IN ketorolac was responsible for her adverse events or that any significant change in renal function occurred. However, interim laboratory results if any (not included in the CRF) may have been transiently abnormal.

Subject 81238 (Study 2003-01/ROX-888)

Subject 81238, a 63 year old man, underwent right total hip replacement on (b) (6). His past medical history was significant for diet controlled diabetes mellitus, gout, depression, osteoarthritis of the hip, asthma and left inguinal hernia repair. He was taking Voltaren SR 75 mg BID prior to admission that was discontinued on (b) (6) He received three doses of ROX-888 with the first dose on (b) (6) and the last dose (at 16 hours) administered on (b) (6) at 6:50. The study was stopped on (b) (6) at 10:20 due to elevated creatinine and BUN, according to a correction made in the CRF on (b) (6). The CRF does not indicate that any intervention was required for these adverse events. The subject was also reported to have dehydration that required "other intervention" but no specifics were provided. All three of these adverse events were reported resolved on (b) (6). Baseline labs on (b) (6) were as follows: BUN 27 mg/dl (9.50 mmol/L) and creatinine 1.2 mg/dl (0.11 mmol/L). Urinalysis showed a few casts, 20 x 10^6 WBCs and trace RBCs. On (b) (6) BUN was 12 mg/dl (4.30 mmol/L) and creatinine was 1.1 mg/dl (0.10 mmol/L). No laboratory values were provided at the time the subject's BUN and creatinine were reported elevated.

Impression

ROX-888 was discontinued on the first postoperative day due to the adverse events of elevated BUN and creatinine. The elevated BUN and creatinine could not be confirmed and the severity of any renal changes could not be assessed since no laboratory results were provided at the time of the purported abnormality. The event was reported to have lasted only one day. Follow-up BUN and creatinine showed no worsening in renal function and there was actual improvement in BUN. Dehydration was also listed as an adverse event and could explain any transient elevation of BUN and creatinine that might have occurred. However, the use of ROX-888 and history of diabetes cannot be completely excluded as contributing factors. The baseline BUN of 27 and creatinine of

1.2 exceeded the normal range but met the eligibility criteria (subjects with creatinine >1.5 were excluded from the study).

Subject 81774 (Study 2003-01/ROX-888)
Subject 81774 was a 46 year old woman with past medical history significant for asthma, DVT, hepatitis, depression and status post hysterectomy who underwent laparotomy and bilateral oopherectomy. ROX-888 was discontinued after one dose due to the adverse events of nasal irritation, facial itchiness, and rash around the nose, all recorded on the CRF as occurring within 15 minutes of receiving study drug. The nasal irritation and facial itching were both reported as moderate in severity and the rash was reported as mild in severity. She received two doses of Phenergan for the rash and itching. No additional details related to these adverse events was provided.

Impression
The facial rash and itching appear to be related to use of IN ketorolac. However, the rash and itching were localized without any apparent evidence of more serious systemic hypersensitivity or anaphylactic reaction.

Subject 81004 (Study 2005-01/ROX-888)
This subject was a 61 year old woman with a past medical history significant for sinusits who underwent laporatomy and bilateral salpingo-oophorectomy on (b) (6). She received four doses of ROX-888 prior to discontinuing study drug due to "Sinusitis". No further details related to the "sinusitis" were provided. Of note on the physical exam of (b) (6) a mild erosion of the left nostril was reported.

Impression
This subject with a history of sinusitis was reported to have discontinued study drug due to sinusitis. It is unlikely that sinusitis could result from use of intranasal ketorolac. However given the presence of a nasal erosion and lack of details in making the diagnosis of sinusitis it is impossible to exclude IN ketorolac as the cause of symptoms that may have been incorrectly attributed to sinusitis based on her history.

Subject 82032 (Study 2005-01/ROX-888)
This subject was a 54 year old man with a past medical history significant for cholecystectomy and colorectal cancer who underwent lower anterior colon resection, total mesorectal excision and diverting ileostomy. Screening labs were as follows: BUN 20 mg/dl and Creatinine 0.9 mg/dl. Urinalysis was negative for protein, glucose, WBCs and RBCs. He received three doses of ROX-888 prior to study drug being discontinued due to "oliguria". No additional details related to this adverse event were provided. Follow-up labs taken after the last dose of study drug showed a BUN of 17 and creatinine of 1.0.

Impression
From the limited information provided there is no evidence of any renal impairment or reason to suspect that ROX-888 resulted in oliguria.

Subject 82051 (Study 2005-01/ROX-888)
Subject 82051 was a 44 year old woman with a past medical history significant for hypertension, bronchitis, uterine fibroids and right hip osteoarthritis who underwent exploratory laparotomy with multiple myomectomies and removal of left ovarian cyst. Screening labs were as follows: Hgb 13.3 g/dl, Hct 40.3%, platelets 185 x 10^9/L, BUN 19 mg/dl and creatinine 0.8 mg/dl. Urinalysis was trace for protein and negative for glucose. There were 2 to 5 WBCs and 5-10 RBCs/hpf. She received five doses of ROX-888 prior to study drug being discontinued for "oliguria". No additional details related to oliguria were provided. She also had the following AEs: hypotension, anemia, blood stained nasal mucus and hypovolemia. She received IV normal saline for her oligura and one unit of packed RBCs for her anemia. Nasal exam on the last day of study drug was reported as showing no clinically significant findings. Follow-up labs taken approximately three days after her last dose of study drug and blood transfusion were significant for the following: Hgb 7.2 g/dl, Hematocrit 22%, platelets 152 x 10^9, BUN 8 mg/dl and creatinine 0.6 mg/dl.

Impression
From the limited information provided there is no evidence of any renal impairment or reason to suspect that ROX-888 resulted in oliguria. Her oliguria may have been related to hypovolemia for which she received IV fluids. Review of the CRF is significant for postoperative anemia with over a 45% drop in hemoglobin requiring a blood transfuision. It is possible that IN ketorolac may have contributed to the severity of her postoperative bleeding and hypovolemia and therefore indirectly exacerbated her oliguria.

Subject 82055 (Study 2005-01/ROX-888)
This was a 54 year old man with past medical history significant for mitral valve prolapse, low back pain, renal calculi, and adenocarcinoma of the prostate who underwent pelvic lymphadenectomy and radical prostatectomy. Screening labs obtained from the CRF were as follows: Hgb 16.6 g/dl, Hct 48.1%, platelets 219 x 10^9/L, BUN 16 mg/dl and creatinine 1.1 mg/dl. Urinalysis was negative for protein, glucose, WBCs and RBCs. He received three doses of ROX-888 prior to study drug being discontinued for an elevated serum creatinine. No additional details related to the elevated creatinine were provided in the CRF. Follow-up labs obtained from the CRF taken the day after his last dose of study drug were significant for the following: Hgb 12.0, Hematocrit 36.2, platelets 192 x 10^9, BUN 14 mg/dl and creatinine 1.1mg/dl. There was a discrepancy between the screening creatinine recorded in the dataset and the CRF. The screening creatinine recorded in the dataset "Laboratory Test Results" for the Screening Visit under the variable for results "LBORRES" was 11 (an apparent error in data entry from the CRF of a creatinine of 1.1). The creatinine recorded in the dataset at the visit "post-dosing follow-up" was 1.1 and consistent with the CRF. It is not entirely clear why the CRF lists the discontinuation due to an increase in creatinine since no increase was recorded on the CRF.

Impression
From the information provided in the CRF there is no evidence of any significant change in renal function. The BUN/creatinine values obtained at follow-up are not significantly different from the screening values. The reason provided for discontinuation from the study, elevated serum creatinine, may be an error or may reflect a transient elevation in creatinine value not provided in the CRF.

Subject 82057 (Study 2005-01/ROX-888)
This was a 56 year old woman with past medical history significant for hypertension, bilateral breast augmentation with subsequent removal, and uterine fibroids who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Screening labs were as follows: Hgb 16.3 g/dl, Hct 46.8%, BUN 15 mg/dl and creatinine 1.1 mg/dl. She received four doses of ROX-888 prior to study drug being discontinued for an elevated serum creatinine. No additional details related to the elevated creatinine were provided in the CRF. Follow-up labs obtained the day after her last dose of study drug were significant for Hgb 12.6 g/dl, Hematocrit 37.5%, BUN 18 mg/dl and creatinine 1.2 mg/dl.

Impression
From the information provided in the CRF there is no evidence of any significant change in renal function. However, a transient elevation not recorded in the CRF may have occurred. The BUN/creatinine values obtained at follow-up are not significantly different from the screening values. Subjects were permitted to enroll in the study with a creatinine of 1.5 mg/dl.

Subject 82060 (Study 2005-01/ROX-888)
This was a 30 year old woman with past medical history significant for obesity, low back pain, fatty infiltration of liver, anemia, right ovarian cyst and dysfunctional uterine bleeding who underwent exploratory laparotomy and right oopherectomy. Screening labs obtained were as follows: Hgb 11.9 g/dl, Hct 37.2%, BUN 8 mg/dl and creatinine 0.5 mg/dl. Urinalysis was unremarkable. She received five doses of ROX-888 prior to study drug being discontinued for the adverse event of oliguria. She received IV normal saline as treatment for her oliguria. Additional adverse events were nausea, vomiting and constipation. No additional details related to the oliguria were provided in the CRF. Follow-up labs obtained the day after her last dose of study drug were significant for the following: Hgb 10.2 g/dl, Hematocrit 31.9%, BUN 8 mg/dl and creatinine 0.3 mg/dl.

Impression
This subject experienced a brief period of oliguria which appears to have responded to IV fluids. From the information provided in the CRF, there is no evidence of any change in renal function or reason to suspect that IN ketorolac caused her oliguria.

Subject 83004 (Study 2005-01/ROX-888)
This was a 55 year old woman with past medical history significant for migraine headache, dysfunctional uterine bleeding, and ovarian cyst who underwent total abdominal hysterectomy and bilateral salpingo-oopherectomy. Screening labs obtained were as follows: Hgb 13 g/dl and Hct 39.2%. She received eight doses of ROX-888 prior to study drug being discontinued for the adverse events of intermittent bleeding form the nose and burning nares. She also had the adverse event of nasal congestion. Follow-up labs obtained the day after her last dose of study drug were significant for Hgb of 10.6 g/dl and hematocrit of 31.5%. At the follow up exam approximately two weeks after the last dose of study drug the subject reported some additional bleeding that was not significant. Nasal exam at that time was reported as showing no significant findings.

Impression

This subject experienced intermittent nasal bleeding as well as other nasal symptoms most likely related to use of IN ketorolac. Of note the nasal exam was unremarkable and the drop in hemoglobin (<20%) was consistent with blood loss from her surgical procedure.

Subject 85025 (Study 2005-01/ROX-888)
This 43 year old woman with past medical history significant for hypertension, anemia and uterine fibroids underwent laparotomy with myomectomy. Screening labs were as follows: Hgb 11.2 g/dl and Hct 33.8%. ROX-888 was discontinued for the adverse events of vaginal bleeding and hypotension reported approximately two hours after her first dose of ROX-888. Follow-up labs obtained the day of her last dose of study drug were significant for Hgb of 9.8 g/dl and hematocrit of 29.5%. The subject received 2 units of packed red blood cells the day prior to surgery but no postoperative transfusion was reported. Screening CBC was obtained the morning of surgery, after her transfusion.

Impression
This subject was discontinued form study drug due to the adverse events of vaginal bleeding and hypotension occurring approximately two hours after receiving IN ketorolac. Insufficient information is provided to determine the exact cause of bleeding but a contributory role from IN ketorolac cannot be excluded. She had approximately a 12.5% drop in hemoglobin for the time of her screening visit to her follow-up exam consistent with blood loss from her surgical procedure.

Subject 85003 (Study 2005-01/ROX-888)
This subject was a 44 year old woman with a past medical history significant for allergies to sulfa, bactrim and ibuprofen as recorded under the "Medical History and Review of Systems" section of the CRF. However, under the exclusion criteria she was not checked off as having an allergic reaction to NSAIDs. She underwent total abdominal hysterectomy and bilateral salpingo-oopherectomy on (b) (6) She received her first dose of ROX-888 at 14:10 on the day of surgery and was reported to have an allergic reaction approximately two hours later at 16:00. No details of the nature of the allergic reaction were provided. The severity was checked off as mild. She received treatment with IV Diphenhydramine 25 mg and the stop date and time for the allergic reaction were reported as (b) (6) at 20:00. The CRF exclusion criteria were corrected to reflect an allergic reaction to NSAIDS on 12 April 2006.

Impression
This subject discontinued study drug due to an unspecified allergic reaction that occurred approximately two hours after receiving her first dose of ROX-888. She had a prior history of allergies to NSAIDs and should not have been enrolled in the study. This allergic reaction in a person with a history of NSAID allergies provides no additional information in assessing the potential for IN ketorolac to cause allergic reactions in subjects without a history of NSAID allergies.

Dropouts due to Adverse Events in Placebo Group
Subject 81826 (Study 2001-03/Placebo)
This was a 19 year old man with past medical history significant for a MVA of unkown date resulting in left forearm fracture, ORIF of fractured mandible, dislocated right elbow with boney

fragments in the elbow joint who underwent ORIF of right radial head fracture. Screening labs were as follows: Hgb 15 g/dl and Hct 45%. Study drug was discontinued for the adverse event of blood stained vomit. No further details or follow-up labs were provided. The patient was lost to follow-up.

Impression
This subject was discontinued form placebo due to the adverse event of blood stained vomit. The severity of bleeding cannot be fully assessed since no postoperative CBC was obtained but review of the CRF does not indicate that a blood transfusion was required.

Subject 81548 (Study 2003-01/Placebo)
Subject 81548 was a 30 year old woman with past medical history significant for hypertension, indigestion, headaches, NIDDM, anemia and menorrhagia who underwent total abdominal hysterectomy. Screening labs were as follows: Hgb 14.6 g/dl and Hct 47%. Placebo was discontinued for the adverse event of postop hemorrhage recorded on the CRF approximately four hours after surgery. The patient received one unit of packed red blood cells. CBC immediately prior to the transfusion was not provided. Follow-up labs obtained after the blood transfusion were significant for Hgb of 10.9 g/dl and hematocrit of 33%.

Impression
This subject on placebo had a postoperative anemia with a 25% drop in hemoglobin (after receiving one unit of packed RBCs).

Subject 81025 (Study 2005-01/Placebo)
This was a 54 year old woman with past medical history significant for hypertension, removal of rib status post trauma, headaches, breast cancer (s/p lumpectomy and chemotherapy), and bilateral oopheorectomy who underwent total abdominal hysterectomy. Screening labs were as follows: Hgb 14.0 g/dl and Hct 41%. She received seven doses of placebo prior to study drug being discontinued for the adverse event of bleeding form the right nostril. Relevant concomitant medications include low molecular weight heparin for DVT prophylaxis. Follow-up labs were significant for Hgb of 10.2 and hematocrit of 30. Nasal exam approximately two weeks after surgery was reported as showing no clinically significant findings.

Impression
This subject experienced right nasal bleeding following seven doses of intranasal placebo. It is possible that placebo treatment and use of low molecular weight heparin may have contributed to nasal irritation and bleeding. There was a 27% drop in hemoglobin at follow-up compared to screening. This was likely due to blood loss from the surgical procedure but there may have been a contributrory role from the Fragmin.

Subject 82039 (Study 2005-01/Placebo)
This was a 58 year old woman with past medical history significant for hypertension and colon cancer with liver metastais who underwent laparoscopic sigmoid colectomy with wedge resection of liver lesion. Study drug was discontinued after four doses due to the adverse event of oliguria.

Screening labs were as follows: BUN 13 mg/dL and creatinine 0.8 mg/dL. Follow-up labs were significant for BUN of 5 mg/dL and creatinine 0.5 mg/dL. She received IV normal saline for her oliguria.

Impression
This subject on placebo experienced oliguria that responded to therapy with IV fluids. There was no evidence of any renal impairment.

Summary of Adverse Events Leading to Discontinuation
Table 7.3.3 summarizes the most common adverse events leading to discontinuation of study drug.

Table 7.3.3: Discontinuations Due to Adverse Events for the 3 Multiple-Dose Postoperative Pain Studies

	ROX-888 N=455	Placebo n=250	IN Ketorolac 10mg n=43
Number of Subjects Discontinued Due to AE	80 (17.6%)	32 (12.8%)	5 (11.6%)
Adverse Event	**ROX-888 N=455**	**Placebo n=250**	**IN Ketorolac 10mg n=43**
Nasal Symptoms[1]	27 (5.9%)[2]	7 (2.8%)	0 (0.0%)
Nausea/Vomiting	12 (2.6%)	9 (3.6%)	0 (0.0%)
Bleeding	7 (1.5%)[3]	2 (0.8%)[5]	1 (2.3%)
Headache	7 (1.5%)	4 (1.6%)	1 (2.3%)
Oliguria/Decreased Urine Output	4 (0.9%)	1 (0.4%)	0 (0.0%)
Increased Creatinine	3 (0.7%)	0 (0.0%)	0 (0.0%)
Hypersensitivity/Rash	2 (0.4%)[4]	0 (0.0%)	0 (0.0%)

[1]Includes nasal congestion, nasal discomfort, rhinalgia and epistaxis
[2]Does not include 3 subjects with throat irritation, 2 subjects with eye symptoms (1 with watery eyes post spray and one with stinging eyes) and 3 subjects with sinus pain
[3]For discontinuations due to bleeding six subjects had SAEs in the ROX-888 group and one subject had an SAE in the IN 10 mg group. Subjects with epistaxis were listed in the category for nasal symptoms
[4] Includes Subject 81774 in Study 2003-01 with rash around nose and Subject 85003 in Study 2005-01 with allergic reaction
[5] Subject 81025 with epistaxis and nasal burning was included in the category nasal symptoms

Other reasons for discontinuations in the ROX-888 group included: throat irritation (3), eye symptoms (2), sinus pain (3), anxiety (1), pneumonia (1), confusion (1), sciatica (1), sore throat (2),

bradycardia (1), and bladder calculus (1). The throat irritation, eye symptoms (watery and stinging eyes) and sinus pain symptoms are possibly related to use of ROX-888. There is no evidence that ROX-888 caused sinusitis but symptoms associated with sinusitis may have been related to ROX-888. In a postsurgical population pneumonia, confusion, sore throat and bradycardia would be expected.

Summary of discontinuations due to adverse events by category
Oliguria: Review of the CRFs suggests that oliguria was most likely related to hypovolemia. There is no significant evidence to suggest that IN ketorolac contributed directly to the oliguria but may have indirectly exacerbated the hypovolemia by increasing bleeding. The one case of oliguria in the placebo group appeared similar to the four cases reported with IN ketorolac.

Bleeding: In the ROX-888 group there were six discontinuations due to bleeding SAEs previously discussed in the section on SAEs and one additional discontinuation due to the adverse event of vaginal bleeding. Subject 83004 discontinued due to the adverse events of bleeding form the nose and nasal discomfort was included in Table 7.3.3 as a discontiuation due to nasal symptoms and not from bleeding. In addition there was one subject that discontinued for the reason of oliguria but had a 45% drop in hemoglobin and required a transfusion. There was one subject in the IN ketorolac 10 mg group that discontinued from the study due to a bleeding serious adverse event. In the placebo group a total of two subjects discontinued due to a bleeding adverse event: Subject 81826 blood stained vomit and Subject 81548 postop hemorrhage. Subject 81548 had a 25% drop in hemoglobin after receiving a unit of packed red blood cells. A third placebo subject had epistaxis but this subject was included in the group with nasal symptoms consistent with the assignment used for ROX-888. Overall the incidence of discontinuation due to bleeding was approximately two fold higher in the ROX-888 group compared to placebo group.

Renal Impairment: Three subjects treated with IN ketorolac were reported to have elevated creatinine but review of the CRFs did not reveal any worsening of renal function at the follow-up visit compared to baseline. There is no evidence that short-term IN ketorolac has an effect on renal function based on the limited number of subject discontinuations due to adverse events.

Hypersensitivity/Allergic Reaction: Of the two subjects that discontinued due to allergic reactions, one had a history of NSAID allergy and the other had a localized rash without any apparent evidence of more serious systemic hypersensitivity or anaphylactic reaction.

7.3.4 Significant Adverse Events

Nasal Adverse Events
Nasal Examinations: A nasal examination was performed in three studies (Study 2005-01, Study 2003-01 and Study 2001-03) but a follow-up nasal exam after subjects were off drug was performed only in Study 2005-01. For Study 2005-01 nasal examinations were performed at the termination visit and 14-day follow-up visit. In Study 2005-01, a total of 312 subjects (103 placebo and 209 ROX-888) underwent a nasal exam at study termination. Since enrollment in this study was restricted to subjects under the age of 65, no subject 65 years of age or older on ROX-888 had a follow-up nasal exam in the entire development program. For Study 2003-01, nasal examinations

were not included in the original protocol but added later at the request of the Division to the termination visit. A total of 60 subjects (19 placebo and 41 ROX-888) had nasal exams including 9 subjects (2 placebo and 7 ROX-888) that were 65 years of age or older. Due to the small number of nasal examinations in elderly subjects submitted in the NDA, the Division requested that the Applicant provide a summary of nasal examinations conducted in patients 65 years of age or older on ROX-888 for Study 2001-03 (Phase 2 study). During this study inspections of the nasal mucosa were conducted pre-dose and at 3, 16, 24, 32, 40 and 48 hours post-dose (final dose of study drug was at hour 40 and final efficacy evaluation was at hour 48). There were 37 subjects (18 placebo, 13 ROX-888 and 6 ketorolac 10 mg) who were age 65 or older. Only 2 subjects, both in the placebo group had an abnormality (erythema) on nasal examination. However, the normal nasal findings after two days of treatment may be misleading since a longer duration of therapy may be required for evidence of nasal injury to appear.

Nasal Exam Results

Study 2003-01 (Termination Visit): There was one 66 year old subject who received nine doses of ROX-888 and had an abnormal nasal exam described as "erosion healing." There were no subjects with erosions in the placebo group. The incidence of abnormal nasal exams in the ROX-888 group was 2.4 % (1/41) and the incidence in subjects 65 or older was 14% (1/7).

Study 2003-01 (14 Day Follow-up Visit): No nasal examinations done.

Study 2005-01

Overall the incidence of abnormal nasal exams was 50% greater in the ROX-888 group compared to the placebo group (Table 7.3.4.1). The greatest difference between groups was in the incidence of erythema and inflammation on intial exam: 3.8% in the ROX-888 group and 1% in the placebo group. For the category of nasal erosion and mucosal injury the incidence was similar in both groups on initial exam. Out of the six subjects with mucosal changes in the ROX-888 group, one of the subjects still had evidence of mucosal injury on follow-up exam. This subject also reported some bleeding. All three subjects with mucosal abnomalities in the placebo group had a normal follow-up exam but two of the subjects reported bleeding. An abnormal exam persisted for one of the eight subjects with erythema in the ROX-888 group. This subject also reported bleeding. Bleeding was also reported in the one placebo subject that had erythema on initial exam.

Of note there were new findings in the follow-up nasal exam in several subjects who had normal initial exams in both the ROX-888 group and placebo group. This suggests that some of the abnormal findings on the initial exam may have been related to causes other than use of the study drug since the development of nasal ulcerations, erythema and bleeding two weeks after stopping study drug is not considered to be related to medication.

The abnormal findings on nasal exam resolved within two weeks in most of the subjects. The incidence of bleeding in subjects with an initial abnormal exam but normal follow-up exam was similar in both groups. Overall the nasal exam findings do not suggest any significant persistent safety finding but the most vulnerable population, subjects 65 years of age or older, who may be at increased risk for mucosal injury were not studied.

Table 7.3.4.1: Subjects with Abnormal Nasal Exams After Last Dose and At 14 Day Follow-up Visit in Study 2005-01				
Clinically Significant Findings	**ROX-888**		**PLACEBO**	
	Exam After Last Dose (N=209)	**Exam at 14 Day F/U (N=188)**	**Exam After Last Dose (N=103)**	**Exam at 14 day F/U (N=94)**
Erosion/Ulceration[1]	81004	Normal	82003	Normal[4]
	81054	81054[4]	82052	Normal
	81064	Normal	83035	Normal[4]
	84015	Normal	Normal	81019[4]
	84021	Normal		
	84025	Normal		
	Normal	84006[4]		
	Normal	81042		
Total Erosion/Ulceration	6 (2.9%)	3 (1.6%)	3 (2.9%)	1 (1.1%)
Erythema[2]	81001	Normal	81003	Normal[4]
	81017	Normal	Normal	81040
	81030	Normal		
	81051	Normal		
	82028	Normal		
	84005	84005[4]		
	84012	Normal		
	86015	No F/U		
	Normal	81011		
Total Erythema	8 (3.8%)	2 (1.1%)	1 (1.0%)	1 (1.1%)
Bleeding[3]	82005	Normal	85006	Normal
	82018	Normal		
	Normal	81066[4]		
Total Bleeding	2 (1.0%)	1 (0.5%)	1 (1.0%)	0 (0%)
Total All Clinically Significant Findings	16 (7.7%)	6 (3.2%)	5 (4.9%)	2 (2.1%)

[1] Erosion/Ulceration includes mucosal injury for subjects 82003 and 82052 and small area healing on prominence of right inferior turbinate mucosa for Subject 81042
[2] Erythema includes inflammation
[3] Bleeding includes dried blood for Subjects 82005, 82018 and 85006 and nosebleeds with a small scab for Subject 81066
[4] Subjective report of bleeding

Dose Response in Study 2005-01
Abnormal nasal exams occurred with as few as two doses of Sprix. In the Sprix group there appeared to be a weak dose response relationship to abnormal nasal exam by my analysis. The Applicant did not find a dose response effect but used a different method for determining the denominator (number of subjects receiving the specified number of doses). For the FDA analysis the denominator was the cumulative number of subjects receiving at least the minimum number of doses in the range (Table 7.3.4.2). The Applicant determined the denominator by the using the number of subjects within each range and excluded subjects who received more doses.

Table 7.3.4.2: Dose Response for Abnormal Nasal Exams After Last Dose in Study 2005-01

No. of Subjects Who Had a Nasal Exam	ROX-888		PLACEBO	
	209		103	
	Applicants Analysis	FDA Analysis	Applicants Analysis	FDA Analysis
No. of Doses 1-4	32	209	8	103
Ulceration or Erosion	1 (3.1%)	1 (0.5%)	0 (0%)	0 (0%)
Erythema or Bleeding	3 (9.4%)	3 (1.4%)	0 (0%)	0 (0%)
No. of Doses 5-8	85	209-32=177	44	103-8=95
Ulceration or Erosion	2 (2.4%)	2 (1.1%)	2 (4.5%)	2 (2.1%)
Erythema or Bleeding	3 (3.5%)	3 (1.7%)	0 (0%)	0 (0%)
No. of Doses 9-12	55	177-85=92	33	95-44=51
Ulceration or Erosion	2 (3.6%)	2 (2.2%)	1 (3.0%)	1 (1.9%)
Erythema or Bleeding	3 (5.5%)	3 (3.2%)	1 (3.0%)	1 (1.9%)
No. of Doses 13-16	34	92-55=37	15	51-33=18
Ulceration or Erosion	1 (2.9%)	1 (2.7%)	0 (0%)	0 (0%)
Erythema or Bleeding	1 (2.9%)	1 (2.7%)	1 (6.7%)	1 (5.6%)
No. of Doses 17-20	3	37-34=3	3	18-15=3
Ulceration or Erosion	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Erythema or Bleeding	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Reference: Adapted from Applicant provided Table 1.2: Frequency Count of Subjects with Specific Symptoms at Their Nasal Examiniation at Termination

Nasal and Cardiovascular Adverse Event Questionnaire

Subjects in Study 2005-01 and a subset of subjects in Study 2003-01 completed a nasal and cardiovascular questionnaire at approximately 14 days after the end of dosing.

Study 2003-01

In Study 2003-01 no cardiovascular or nasal events were reported in the 16 subjects (10 in the ROX-888 group and 6 in the placebo group) that completed the questionnaire. None of the subjects were over the age of 65.

Study 2005-01

A total of 300 subjects completed the nasal and cardiovascular adverse event questionnaire (98 in placebo group and 202 in ROX-888 group). None of the subjects completing the questionnaire were 65 years or older. The Applicant reported that the overall incidence of symptoms related to the nose was 16.8% (34/202) in ROX-888 group and 11.2% (11/98) in the placebo group. There was approximately a two fold higher incidence of nasal bleeding in the ROX-888 group compared to the placebo group, 12.4% and 6.1% respectively.

The overall incidence of cardiovascular symptoms was similar in the ROX-888 group and placebo group, 15.3% (31/202) and 17.3% (17/98) respectively. However, the incidence of irregular heart beat was higher in the ROX-888 group than placebo group, 4% (8/202) and 1% (1/98) respectively. It appears unlikely that the slight increase in arrhythmia was due to ROX-888 since NSAIDS in general are not associated with arrhythmia. There was no significant difference in the incidence of high blood pressure in the ROX-888 group and placebo group, 4.5% (9/202) and 5.1% (5/107) respectively.

Elderly

In the four Phase 2 and 3 studies 51 subjects age 65 or older received ROX-888: 13 in Study 2001-03 (Phase 2 study) and 38 in Study 2003-01. No subjects 65 years or older completed the 14 day follow-up nasal and cardiovascular questionnaire or had a 14 day follow-up nasal exam. Only seven nasal exams were performed in the elderly in Study 2003-01, a five day study. An additional 13 subjects 65 years of age or older had a nasal exam in Study 2001-03, a two day study. Of the twenty nasal exams performed in subjects 65 years of age or older, one subject in Study 2003-01 had an abnormal nasal exam after nine doses of Sprix due to a nasal ulcer. None of the 34 subjects under the age of 65 in Study 2003-01 had an abnormal nasal exam. Results from the limited number of nasal exams in the elderly suggest a possible increase in the risk of nasal mucosal injury. This would be consistent with the apparent age related increase in epistaxis in the Sprix group.

The Applicant provided in tabular form (derived from Table 4 of the ISS) the incidence of cardiac, renal and nasal adverse events based on the following age groups: 18 to < 55 years, 55 to < 65 years, 65 to < 75 years and ≥ 75 years. Review of this information revealed no apparent age related effect of ROX-888 on the incidence of renal or cardiovascular adverse events. The incidence of gastrointestinal adverse events based on age was reviewed in Table 4 of the ISS and no age effect was observed. There appeared to be an age related effect of ROX-888 on the incidence of epistaxis. Subjects on ROX-888 who were 18 to less than 55 years of age had an incidence of epistaxis of 10.8% and subjects 55 to less than 65 years of age had an incidence of 14.9%. For the placebo

group the incidence of epistaxis was 12.5% in the 18 to less than 55 years of age group and 4.3% in the 55 to less than 65 years of age group. For subjects 65 years to less than 75 years of age the incidence was 4.5% in the ROX-888 group and 0% in the placebo group. There also appeared to be an age related increase in nasal discomfort and rhinalgia compared to placebo but the number of subjects involved was very small.

Bleeding Adverse Events

The Division requested that the Applicant provide a comparison between ROX-888 and placebo of several parameters that might indicate bleeding severity e.g., drop in HCT greater than 30% and the number of subjects that required a blood transfusion (Table 7.3.4.3).

Table 7.3.4.3: Bleeding Severity

	Placebo n=250	IN Ketorolac 10mg n=43	ROX-888 n=455	Total n=748
HCT drop > 30%	19 (7.6%)	9 (20.9%)	55 (12.1%)	83 (11.1%)
Blood Transfusion	16 (6.4%)	4 (9.3%)	39 (8.6%)	59 (7.9%)
Anemia AE	37 (14.8%)	12 (27.9%)	80 (17.6%)	129 (17.2%)
Dropped Out of Study Due to Anemia	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)
SAE Related to Bleeding	1 (0.4%)*	1 (2.3%)	7 (1.5%)	9 (1.2%)
HGB < 7 at Follow-up	2 (0.8%)	1 (2.3%)	12 (2.6%)	15 (2.0%)

Adapted form applicant's table contained in letter dated May 20, 2009
* Applicant reports no patients in this category but Subject 81049 in Study 2005-01 on PBO had the SAE of a pelvic hematoma

The anemia appeared more severe in the ROX-888 group compared to placebo group. There was a three fold greater incidence in subjects with hemoglobin less than 7 mg/dl at follow-up in the ROX-888 group compared to placebo group. There was a slight increase in the number of subjects in the ROX-888 group compared to placebo group that required a blood transfusion or had a drop in hematocrit greater than 30% from screening. In the ROX-888 group 12.1% of subjects had a drop in hematocrit greater than 30% compared to 7.6% in the placebo group and 8.6% in the ROX-888 group required a blood transfusion compared to 6.4% in the placebo group. As previously discussed in Section 7.3.2 Nonfatal Serious Adverse Events, there was a three fold increase in the number of serious adverse events due to bleeding in subjects receiving ROX-888.

Standard MedDRA Queries

The Applicant performed Standard MedDRA Queries (SMQs) for severe cutaneous adverse reactions and possible drug related hepatic disorders. For the SMQ of severe cutaneous adverse reaction Subject 86002 on ROX-888 was reported to have a ruptured blister on the abdomen graded as severe. All of the other skin related SMQs were graded as mild or moderate and were localized conditions i.e. mouth ulcer, blister on buttock or sacrum etc. The study was not stopped for any adverse event related to a SMQ for severe cutaneous adverse reactions. There did not appear to be a severe cutaneous adverse reactions related to the use of intranasal ketorolac.

There were 17 subjects who had a SMQ of possible drug related hepatic disorders: 11/455 (2.4%) in the ROX-888 group and 6/250 (2.4%) in the placebo group (Table 7.3.4.4). None of the subjects stopped the study due to a SMQ for possible drug related hepatic disorders. Subject 83003, a 49 year old woman, on ROX-888 following a hysterectomy had the greatest increase in LFTs. Baseline LFTs were normal but follow-up AST was 275 and ALT 438. Bilirubin remained within the normal range. She stopped the study due to burning nares after three doses of ROX-888. No follow-up labs were submitted but her 14-day follow-up visit did not hot report any health-related problems since leaving the hospital except for erythema around the incision. ROX-888 cannot be excluded as a cause of her elevated transaminases since there is no other apparent cause. She received several doses of Hydrocodone/acetaminophen but her elevated transaminases preceded her receiving Hydrocodone/acetaminophen. Three subjects in the ROX-888 group had an increase in bilirubin to 1.1 mg/dL. No subject met the criteria for Hy's Law.

Table 7.3.4.4: Possible Drug Related Hepatic Disorders SMQ						
Subject	AST, U/L		ALT, U/L		Total Bili, mg/dl	
	Base	F/U	Base	F/U	Base	F/U
Study 2003-01						
ROX 81004	21	104	24	104	0.7	1.1
ROX 81094	46	65	78	125	0.5	0.5
ROX 81097	46	175	55	157	0.4	0.6
ROX 81173	34	141	52	170	0.5	1.1
ROX 81194	27	33	26	32	0.6	0.5
ROX 81250	26	100	25	111	0.4	0.4
ROX 81320	28	87	38	108	0.6	0.3
ROX 81523	20	24	24	120	0.4	0.3
ROX 81768	34	241	30	245	0.5	1.1
PBO 81027	18	118	14	96	0.7	0.8
PBO 81249	20	19	24	20	0.2	0.3
PBO 81796	17	64	22	111	0.6	0.8
Study 2005-01						
ROX 83003	18	275	15	438	0.2	0.7
ROX 81067	17	132	30	272	0.5	0.5
PBO 81008	19	55	17	72	1.1	0.6
PBO 81012	20	27	14	203	0.4	0.5
PBO 82074	17	151	18	159	0.3	0.9

Normal ranges for: AST 0-35, ALT 0-35 and Total Bilirubin 5.1-17 µmol/L (0.3-1.0 mg/dl)
Table derived from Listing 3 and Listing 6 of the ISS, Volume 22, Module 5

<u>Summary</u>
Nasal adverse events: The incidence of abnormal nasal exams was 50% greater in the ROX-888 group compared to the placebo group. Abnormal nasal exam occurred with as few as two doses and there appeared to be a small dose response effect. Only one of the six subjects with an ulceration/erosion in the ROX-888 group was not healed at the follow-up exam. The incidence of epistaxis, nasal discomfort and rhinalgia appeared increased in the elderly but due to the small numbers the clinical significance is unclear. The incidence of nasal mucosal injury may be greater in the elderly but the findings were based on a single abnormal nasal exam due to the limited number of nasal exams in elderly performed by the Applicant.

Cardiovascular, severe cutaneous reactions and gastrointestinal adverse events: Overall, there was no significant increase in cardiovascular, severe cutaneous reactions, or gastrointestinal adverse events in the ROX-888 group compared to placebo.

Bleeding: Bleeding appeared more severe in the ROX-888 group compared to placebo group as measured by: SAEs due to bleeding, hemoglobin less than seven at follow-up and need for blood transfusion.

Possible Drug Related Hepatic Disorders SMQ: The incidence of abnormal SMQs was similar in both groups but the highest elevations in transaminases were noted in the ROX-888 group. NSAIDs can cause an elevation in transaminases and this was observed with the common adverse events (Section 7.4).

7.3.5 Submission Specific Primary Safety Concerns

All safety issues are discussed in other sections.

7.4 Supportive Safety Results

Common Adverse Events

In the two Phase 3 pivotal studies 95.7% (594/621) of subjects reported an adverse event: 94.9% (392/413) in the ROX-888 group and 97.1% (202/208) in the placebo group. Adverse events occurring with a greater incidence in the ROX-888 group compared to placebo are summarized in Table 7.4.1.

Table 7.4.1: Common Adverse Events (AEs) reported in ≥ 2% of patients on ROX-888 and greater in ROX-888 than placebo for the 2 Phase 3 Multiple-Dose Studies[1]

	ROX-888	Placebo
Number of Subjects	413	208
Number of Subjects Reporting any Adverse Events	392 (94.9%)	202 (97.1%)
Nasal/Local Symptoms [2]	171 (41%)	40 (19%)
Vomiting	107 (25.9%)	53 (25.5%)
Headache	94 (22.8%)	44 (21.2%)
Anemia	69 (16.7%)	23 (11.1%)
Hypotension	39 (9.4%)	14 (6.7%)
Wound secretion	29 (7.0%)	13 (6.3%)
Edema peripheral	19 (4.6%)	7 (3.4%)
Oliguria	13 (3.1%)	2 (1.0%)
Rash	10 (2.4%)	1 (0.5%)
ALT and/or AST increased[3]	9 (2.2%)	3 (1.4%)
Bradycardia	9 (2.2%)	1 (0.5%)
Urine output decreased	9 (2.2%)	1 (0.55)

[1] Studies 2003-01 and 2005-01
[2] Includes preferred terms epistaxis, nasal discomfort, rhinalgia, nasal mucosal disorder, nasal disorder, rhinitis, rhinorrhea, nasal ulcer, sneezing, nasal dryness, nasal septum disorder, lacrimation increased, throat irritation and pharyngeal pain (from ADAE dataset)
[3] Derived from ADAE dataset using preferred terms alanine aminotransferase increased and aspartate aminotransferase increased
Adapted from Applicant's Table 1.17 in the ISS

For subjects receiving at least five doses, the rates of adverse events appeared similar for ROX-888 and placebo groups. An exception was for nasal symptoms which were more frequent in the ROX-888 group. The incidence of adverse events increased with the number of doses administered for both ROX-888 and placebo. The overall pattern of adverse events did not change significantly except for an increased number of nasal symptoms with increasing doses of ROX-888.

7.4.2 Laboratory Findings

Analyses focused on outliers or shifts from normal to abnormal

BUN/Creatinine
Only one subject in the ISS shift table assigned to the placebo group experienced an increase in serum creatinine values from normal to high defined as serum creatinine >1.5 mg/dL. Subject 81187 assigned to placebo treatment had a baseline creatinine of 110 µmol/L (1.2 mg/dL) and follow-up creatinine of 140 µmol/L (1.6 mg/dL). Subject 81275 assigned to ROX-888 was originally reported to have had a change from normal at baseline to high during the study due to an error. The applicant

has determined that the elevated creatinine value of 6200 µmol/L (70 mg/dL) was due to a transcription error and should have been 110 µmol/L (1.2 mg/dL). Thus this patient's creatinine throughout the study was normal.

To identify any significant change in renal function occurring within the normal range, an additional analysis was completed. The incidence of subjects with an increase in creatinine from baseline of > 0.2 mg/dL AND creatinine > 1.0 mg/dL was as follows: 1.6% (7/438) in the ROX-888 group, 2.3% (1/43) in the 10 mg group and 2.2% (5/232) in the placebo group.

AST/ALT/Total Bilirubin
The number of subjects that experienced an increase in LFTs from normal to high as reported in the ISS shift table was as follows: *AST* – placebo 32/209 (15.3%), ROX-888 58/403 (14.4%), and 10 mg 7/40 (17.5%), *ALT* – placebo 35/194 (18%), ROX-888 47/332 (14.1%) and 10 mg 4/36 (11.1%), *total bilirubin* – placebo 12/167 (7.2%), ROX-888 16/332 (4.8%) and 10 mg 0/34 (0%). The total number of subjects for each parameter for the treatment group includes subjects who had that parameter assessed at baseline and follow-up and for whom the baseline assessment was normal. The normal values used for AST and ALT were 35 U/L and for total bilirubin 17 µmol/L (1.0 mg/dL).

Summary
BUN/Creatinine
There is no laboratory evidence in the safety dataset that ROX-888 results in impaired renal function. No subject treated with intranasal ketorolac had a shift in creatinine from normal to abnormal. Additional analyses of subjects with creatinine >1.0 mg/dL at follow-up AND an increase from baseline of > 0.2 mg/dL showed no effect from intranasal ketorolac.

LFTs
There were more adverse events due to elevated AST and ALT in the ROX-888 group compared to placebo group. In general the elevations were mild and not considered to be clinically significant. Subject 83003 had markedly increased ALT and AST and is discussed in Section 7.3.4. No laboratory follow-up was obtained for this subject but the clinical follow-up does not suggest symptoms related to liver impairment. NSAIDs are known to result in elevated transaminases and the risk is described in the approved ketorolac label.

7.4.3 Vital Signs

Vital signs were checked at screening, prior to the first dose, every eight hours after the first dose (up to 48 hours) and at follow-up visit for Studies 2001-03, 2003-01 and 2005-01.

At the FDA's request the Applicant provided summary statistics (mean, median and range) for vital signs (SBP, DBP and HR) for Studies 2001-03, 2003-01 and 2005-01 combined. These statistics were reviewed. There did not appear to be a clinically meaningful difference in groups for any vital sign changes.

7.4.4 Electrocardiograms (ECGs)

Overview of ECG testing in the development program, including brief review of preclinical results
The Applicant reports that there were no clinically relevant changes in ECGs recorded at screening and at the termination visit in Phase 1 studies.

7.4.5 Special Safety Studies/Clinical trials

Study 2002-02 conducted with radiolabeled drug demonstrates that after intranasal administration the drug appears to remain mainly in the nasal cavity with a negligible percentage in the lungs (<0.5%). Lung function tests did not show evidence of bronchospasm in any of the subjects studied.

7.4.6 Immunogenicity

Since this is a small molecule product there are no immunogenicity issues.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Findings

Study 2001-01 compared the safety, tolerability, and PK parameters of single intranasal doses of 20 mg, 30 mg and 40 mg of ketorolac. More nasal adverse events were noted with the 40 mg dose. One subject following intranasal administration of 40 mg of ketorolac was withdrawn from the study due to the development of a nasal ulceration. The nasal ulceration persisted for over one month but resolved by the time of her appointment with an ENT specialist approximately seven weeks after receiving study drug.

The Applicant reports that in general on application of study drug mild nasal irritation, nasal burning/stinging or occasionally burning/stinging at the back of the throat (sometimes associated with an unpleasant taste) was reported with duration from a few seconds to one hour after administration; with most reports less than 20 minutes in duration.

In Study 2001-01 nasal adverse events were dose related. One subject receiving 42 mg developed a nasal ulceration that persisted for over one month. Abnormal nasal exams also appeared to be related to the number of doses administered in Study 2005-01.

7.5.2 Time Dependency for Adverse Findings

Due to the short duration of the studies (≤ 5 days) it is difficult to assess time dependency for adverse findings. However, there appeared to be a slight relation to the number of doses administered and the presence of an abnormal nasal exam in Study 2005-01 (Table 7.3.4.2).

7.5.3 Drug-Demographic Interactions

Elderly
There was no apparent age related effect of Sprix on the incidence of renal, gastrointestinal or cardiovascular adverse events. There appeared to be an age related effect of Sprix on the incidence of nasal mucosal injury and epistaxis (See Section 7.3.4 Significant Adverse Events for additional details).

The Cmax and AUC in elderly (≥ 65 years of age) compared to nonelderly appears to be slightly higher by approximately 10% and 23%, respectively (Study 2007-02). The clinical pharmacologist did not feel that the magnitude of increase in exposure in the elderly directly warranted dose adjustment. However, since elderly patients are expected to suffer from more frequent GI tract AEs the Applicant proposed to reduce the dose to 15mg Q6h-8 hours. The Applicant's proposal is appropriate and consistent with the dosing recommendation for use of IM ketorolac in the elderly.

7.5.4 Drug Disease Interactions

In Study 2007-03, there was no evidence of effect of subjects with allergic rhinitis on the absorption of intransal ketorolac.

Drug-Drug Interactions

There was no evidence of effect of intranasal oxymetazoline or intranasal fluticasone propionate on the absorption of ROX-888 in healthy volunteers or subjects with allergic rhinitis in Studies 2007-03, 2006-03 and 2006-04

7.6 Additional Safety Evaluations

All safety evaluations are discussed in other sections.

7.6.1 Human Carcinogenicity

Carcinogenicity studies are not relevant since the product is intended for short-term use (≤ 5 days).

7.6.2 Human Reproduction and Pregnancy Data

No formal clinical trials in humans have been conducted assessing the effects of intranasal ketorolac on reproduction, pregnancy, or lactation.

7.6.3 Pediatrics and Assessment of Effects on Growth

The requirement for pediatric studies was deferred. The Applicant conducted one single-dose PK study (Study 2006-02) in 20 children that had undergone general surgery. Children were between the ages of 12 to 17 years and dosed with 15 mg and 30 mg of intranasal ketorolac. According to the

FDA pharmacologist, the AUC of ketorolac appeared comparable or slightly higher in children compared to adults.

One SAE of severe vomiting was reported starting on the morning after the day of dosing in Subject 3. This subject was a 17 year old male subject who underwent an osteoid osteoma excision and encountered seven episodes of severe intensity vomiting starting the morning after dosing. The SAE resolved later on the same day and was not considered by the Applicant to be related to study treatment. Nasal adverse events were the most common adverse event to occur. There was no apparent significant safety risk identified in this single-dose study.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The NSAID class of drugs is not associated with a drug abuse potential.

7.7 Additional Submissions / Safety Issues

All safety issues are discussed in other sections.

8 Postmarket Experience

This formulation is currently not approved anywhere in the world and, therefore, there is no postmarketing information available for intranasal ketorolac. Refer to Section 2.3 for a discussion of ketorolac and NSAID safety issues.

9 Appendices

9.1 Literature Review/References

Not applicable

9.2 Labeling Recommendations

The following are the major changes recommended for the applicant's proposed labeling.

BOXED WARNING
1. The risk of bleeding should be included in the boxed warning. There was an increase in the number of serious adverse events due to bleeding in subjects using intranasal ketorolac. There was approximately a three fold higher incidence of SAEs due to bleeding in the ROX-888 group compared to placebo group. The approved label for ketorolac (Roche 1/2009) contains the following Black Box Warning that should be added to the proposed label:

Risk of Bleeding

- Ketorolac tromethamine inhibits platelet function and is, therefore, CONTRAINDICATED in patients with suspected or confirmed cerebrovascular bleeding, patients with hemorrhagic diathesis, incomplete hemostasis, and those at high risk of bleeding (see WARNINGS and PRECAUTIONS).
- Ketorolac tromethamine is CONTRAINDICATED as prophylactic analgesic before any major surgery, and is CONTRAINDICATED intraoperatively when hemostasis is critical because of the increased risk of bleeding.

In addition the label should indicate that the severity of bleeding at times required blood transfusion and/or additional surgery.

2. The following risks found in the approved label for IV/IM ketorolac should also be added to the proposed Black Box Warning:

- Hypersensitivity
- Labor, Delivery and Nursing
- Concomitant Use with NSAIDs

3. The standard Black Box Warning for cardiovascular and gastrointestinal risks for all approved NSAIDs should be included. The standard text for gastrointestinal risk in approved NSAIDs should replace the Applicant's proposed language.

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS).
- (Name of NSAID) is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).

HIGHLIGHTS OF PRESCRIBING INFORMATION

The Applicant's proposed Drug Interactions section states that concomitant use with anticoagulants may increase the risk of serious GI bleeding. Increased risk of postoperative bleeding should also be added to this statement.

INDICATIONS

1. The proposed indication should be changed from "moderate to severe pain" to "moderately severe pain." This change would be consistent with the approved label for other ketorolac products and the demonstrated efficacy of the product. The indication should also be for "(b) (4) pain."

2. The indication should be restricted to use in an inpatient setting. There is insufficient safety and efficacy data to support use in an outpatient setting. The risk of renal impairment is likely to be greater in the outpatient setting due to volume depletion in subjects most likely to use the product i.e. poor oral intake.

(b) (4)

6 Adverse Reactions
The table of adverse events should group nasal symptoms together. Adverse events listed separately for the dental extraction pain study should not be included in the label since it is a single dose study.

6.4 Information from Postmarketing Studies with IM/IV Ketorolac
Remove the information from the study comparing three parenteral NSAIDs (ketorolac, diclofenac and ketoprofen) since no placebo was included in the study. Although, there may not be an increased risk of adverse events with ketorolac compared to other NSAIDs, the safety data submitted with this NDA indicates that there is an increased risk with ketorolac compared to placebo.

8.5 Pediatric Use
The applicant has included PK data for pediatric patients but safety and efficacy have not been established. This information should be deleted from the label.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held for this product.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	KETOROLAC TROMETHAMINE NASAL SPRAY
NDA 22382	ORIG 1	ROXRO PHARMA INC	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/

ROBERT A LEVIN
08/20/2009

ROBERT B SHIBUYA
08/20/2009
I concur with Dr. Levin's review.

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-382 **Applicant:** ROXRO PHARMA **Stamp Date:** Dec 5, 2008

Drug Name: SPRIX (PROPOSED) **NDA Type:** 505(b)(2)

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	✓			Paper 5 Modules
2.	On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	✓			
3.	Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	✓			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?			✓	
5.	Are all documents submitted in English, or are English translations provided when necessary?	✓			
6.	On its face, is the clinical section of the application legible so that substantive review can begin?	✓			
LABELING					
7.	Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57 (or 21 CFR Subpart C for OTC products), current divisional and Center policies, and the design of the development package?	✓			Initial submission did not contain version that could be edited. Word version submitted
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	✓			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	✓			Module 5 Vol 19-22
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	✓			Module 5 Vol 19
11.	Has the applicant submitted a benefit-risk analysis for the product?	✓			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	✓			RLD TORADOL (NDA 19-645 19-678)
DOSE					
13.	If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: 2001-03 Study Title: 2003-05 single dose, determined Sample Size: dosing at least every 6 hrs Arms: similar PK of approved Location in submission: Module 5	✓			compared 10 mg, 30 mg and PBO Not an NME IM route
EFFICACY					
14.	On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 2003-01 Pivotal Study #2 2005-01 Indication: post-op pain	✓			Primary endpoint SPID 6

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	✓			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	✓			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	✓			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	✓			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			✓	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	✓			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[2]) been exposed at the dose (or dose range) believed to be efficacious?			✓	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	✓			
23.	Has the sponsor submitted the coding dictionary[3] used for mapping investigator verbatim terms to preferred terms?	✓			
24.	Has the sponsor adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	✓			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		✓		Narratives for SAEs but not adverse dropouts
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?	✓			Nasal evaluation
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*,			✓	

[2] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[3] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	NA	Comment
	label comprehension, self selection and/or actual use)?			✓	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	✓			Peds deferral request Module 1 Vol 1
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			✓	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	✓			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	✓			Safety datasets adequate Additional efficacy requested
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?		✓		Additional Datasets requested
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		✓		"
34.	Are all datasets to support the critical safety analyses available and complete?	✓			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		✓		Requested by Division
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	✓			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			✓	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	✓			Form 3454
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	✓			
CONCLUSION					
40.	From a clinical perspective, is this application fileable? If not, please state why.	✓			

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer — Date: 2/13/09

Clinical Team Leader — Date: 2/17/09

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

/s/

Robert A. Levin
2/18/2009 10:34:58 AM
MEDICAL OFFICER

Robert Shibuya
2/18/2009 01:30:00 PM
MEDICAL OFFICER