CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20811

Trade Name: ACULAR PF

Generic Name: KETOROLAC TROMETHAMINE

Sponsor: HOFFMAN-LAROCHE

Approval Date: NOVEMBER 3, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 20811

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter			X	
Approvable Letter	X			
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20811

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-811

NOV - 3 1997

Hoffmann-LaRoche Inc.
Attention: Lynn DeVenezia-Tobias
Program Manager, Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. DeVenezia-Tobias:

Please refer to your new drug application dated July 26, 1996, received July 29, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Acular® PF (ketorolac tromethamine ophthalmic solution), 0.5% Preservative-Free. We also refer to our letters dated January 28 and September 18, 1997.

We acknowledge receipt of your submissions dated September 30 and October 7, 1997.

This new drug application provides for Acular PF for use in the reduction of ocular pain and photophobia following incisional refractive surgery.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated October 7, 1997 with the revisions identified below. Accordingly, the application is approved effective on the date of this letter. As discussed by telephone on October 10, 1997, between Elizabeth Bancroft of Allergan and Joanne Holmes and Lissante LoBianco of this Division, the following revisions will be made:

1. The second sentence of the third paragraph of the Clinical Pharmacology section will be revised to read: "Significant differences favored Acular® PF for the treatment of ocular pain and photophobia."

2. The zip code for Allergan will be corrected to 92612 in the package insert.

These revisions are terms of the NDA approval. Marketing the product before making these revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. **For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-811. Approval of this submission of FPL by FDA is not required before the labeling is used.**

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Lissante C. LoBianco, Regulatory Health Project Manager, at (301) 827-2090.

Sincerely,

WAC 11/3/97

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
NDA 20-811
HFD-550/Div. files
HFD-550/CSO/L.LoBianco (with labeling)
HFD-550/MO/Bull (with labeling)
HFD-725/Patrician
HFD-880/Wang
HFD-550/Weir
HFD-830/Bhavnagri
HFD-550/Dep Dir/Chambers (with labeling)
HFD-550/Clin Rev/Holmes (with labeling)
HFD-002/ORM
HFD-105/Office Director
HFD-101/L.Carter
HFD-830/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) -
HFI-20/Press Office (with labeling)

Drafted by: LoBianco/October 14, 1997/20811.ap

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20811

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 18 1997

NDA 20-811

Hoffman-LaRoche, Inc.
Attention: Lynn DeVenezia-Tobias
Program Manager, Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. DeVenezia-Tobias:

Please refer to your new drug application dated July 26, 1996, received July 29, 1996, submitted under section 505 (b) of the Federal Food, Drug and Cosmetic Act for Acular® (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-free, Sterile. We refer to our letter dated January 28, 1997.

We acknowledge receipt of your submissions dated February 4, 7, and 12, March 20, April 10, July 11, and August 15 and 29, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit revised draft labeling consistent with the attached draft labeling and including a revised tradename. Additionally, please submit container and carton labels consistent with attached labeling.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw this application.

Under 21 CFR 314.102(d) of the new drug regulations you may request an informal or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact LCDR D'Annie Gunter, Project Manager, at (301) 827-2090.

Sincerely,

WAC 9/18/97

Wiley A. Chambers, M.D.
Deputy Division Director
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20811

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 20-811

NDA #20-811 AKA 19-700/SE1-010
M.O. Review #1

Submission: 12/12/96
Review completed: 8/26/97

Drug name:	Acular
Generic name:	Non preserved ketorolac tromethamine 0.5%. ophthalmic solution
Chemical name:	(±)-5-benzoyl-2, 3-dihydro-1H pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)
Inactive ingredients:	edetate disodium 0.1%; octoxynol 40; sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4; and purified water.
Preservative:	none
Applicant:	Roche Pharmaceuticals 340 Kingsland Street Nutley, NY 07110-1199 (201) 812-2040
Contact:	Elizabeth Bancroft Allergan Inc. (714) 246-4391
Pharmacologic Category:	Non-steroidal anti-inflammatory drug
Proposed Indication(s):	Ocular Pain following incisional refractive surgery
Dosage Form(s):	Solution
Route(s) of Administration:	Topical ophthalmic
Related Drugs:	Voltaren ophthalmic solution

Related Applications: **NDA 19-700**

NDA 19-700 was approved on November 9, 1992 for the indication of relief of ocular itching due to seasonal allergic conjunctivitis. Several clinical supplements have been submitted and are here summarized:

- S-003: Provided for an extension of the dosing period beyond one week of therapy
- S-004: Draft labeling to reflect the change in dosing
- S-005: Additional fill size of 10 mL

List of INDs and NDAs

2 Table of Contents

3 **Material Reviewed** Volumes 20.1-20.14, 20-23-20-32, plus amendments

4 **Chemistry/Manufacturing Controls- See Chemistry Review**

5 Animal Pharmacology/Toxicology - No new Pharm/Tox issues

6 **Clinical Background**

The rationale for using NSAIDs in the treatment of pain following radial keratotomy is based on the inhibition of the release of prostaglandins initiated by the mechanical trauma associated with the surgical procedure. Prostaglandins are different from other chemical mediators in that they increase the sensitivity of pain receptors to other painful stimuli. Prostaglandins, however, have not been demonstrated to exert pain by themselves (Ferreira et al, 1973). Prostaglandins increase cyclic AMP and free calcium levels at the nociceptor membrane resulting in a lowered threshold of activity. This results in the transmission of increased pain to the CNS (Capetola et al, 1983). Inhibitors of prostaglandin synthesis, such as NSAIDs, are peripheral-acting analgesics and attenuate the state of increased pain, or hyperalgesia, produced by prostaglandins. In addition, the analgesic activity of these peripherally acting drugs is independent of their anti-inflammatory activity (Capetola et al, 1983).

Ketorolac has demonstrated analgesic efficacy for the systemic treatment of various types of postoperative pain. A review of this subject by Naidu and associates (1994) shows that oral ketorolac has been used successfully to reduce moderate-to-severe postpartum uterine pain; postoperative oral-surgery pain; pain after orthopedic surgery, abdominal surgery, and gynecologic surgery; and acute musculoskeletal pain.

The sponsor's present application considers an ophthalmic formulation of ketorolac for the treatment of postsurgical pain following radial keratotomy. The early ketorolac solution studies were conducted by Syntex Inc. which has now become a part of Hoffmann-LaRoche Inc. The studies reported here (KETO-105-8718 and KETO-106-8718) were conducted by Allergan as part of a licensing agreement with Syntex/Hoffmann-LaRoche.

6.6 Proposed Directions for Use

For the reduction of ocular pain and symptoms of discomfort following incisional refractive surgery, instill one drop of Acular ophthalmic solution into the operated eye four times daily until there is no ocular pain or up to 3 days after incisional refractive surgery.

7 Description of Clinical Data Sources

The sponsor has submitted two clinical studies, KETO-105-8718 and KETO-106-8718

Controlled Clinical Studies

Study No.	Investigators	Study Design	Treatment	Dose	Duration	Number of Subjects	Mean Age in Years (Min-Max)	Sex (M/F)	Race* (W/B/Or/H/Oth)
KETO-105-8344	Casebeer Durrie Grene Price Yee	randomized multicenter, double-masked, parallel-group	nonpreserved ketorolac tromethamine 0.5% vehicle of nonpreserved ketorolac tromethamine 0.5%	one drop, q.i.d.; until no ocular pain or 3 days	1 week with safety follow-up at: 1 month, 3 months, 6 months, 1 year	170	39.4 (24 - 61)	(78/92)	(159/4/0/6/1)
KETO-106-8344	Abel Assil Brint Buckley Hays Hettinger Imperia Lindstrom Macy Thompson Volk	randomized multicenter, double-masked, parallel-group	nonpreserved ketorolac tromethamine 0.5% vehicle of nonpreserved ketorolac tromethamine 0.5%	one drop, q.i.d.; until no ocular pain or 3 days	1 week with safety follow-up at: 1 month, 3 months, 6 months, 1 year	170	37.7 (18-59)	(68/102)	(154/13/6/6)

- W=White, B=Black, Or=Oriental, H=Hispanic, Oth=Other.

8.1.1 Reviewer's Trial # 1 **Sponsor's protocol #** KETO-105-8718

Indication : For the Treatment of Pain Following Incisional Refractive Surgery

Study Title: THE ANALGESIC EFFICACY AND SAFETY OF KETOROLAC NONPRESERVED OPHTHALMIC SOLUTION IN SUBJECTS UNDERGOING RADIAL KERATOTOMY

Study Dates: August 1994 to July 1995 (through day 7/Visit 4)

Study Treatment: ketorolac nonpreserved ophthalmic solution
Treatment Duration: until no ocular pain or 3 days
Analysis: 7-day efficacy and safety

8.1.1.1 Objective/Rationale
To evaluate the analgesic efficacy and safety of non-preserved, topical ketorolac 0.5% compared with vehicle when used following radial keratotomy.

8.1.1.2 Design
This study was a multicenter, double-masked, randomized, parallel-group, vehicle-controlled comparison. Subjects were randomly assigned to receive either non-preserved ketorolac tromethamine 0.5% or vehicle in the operative eye(s) four times daily for the first 24 hours following radial keratotomy (RK) and four times a day for up to three days after RK. Dosing duration was not to exceed three days after surgery.

Study Medications
Nonpreserved ketorolac tromethamine 0.5% ophthalmic solution (Allergan formulation no. 8718X) contains: ketorolac tromethamine 0.5%, sodium chloride, hydrochloric acid and/or sodium hydroxide for pH adjustment, and purified water. Supplied in unit-dose containers.

Vehicle of nonpreserved ketorolac ophthalmic solution (Allergan formulation no. 8717X) contains: sodium chloride, tromethamine, hydrochloric acid and/or sodium hydroxide for pH adjustment, and purified water. Supplied in unit-dose containers.

Four foil packages, each containing four unit-dose vials of masked medication, were dispensed to each patient.

Procedural solutions and medications consisted of:

- REFRESH PLUS™ lubricant ophthalmic solution (Allergan formulation no.8197X) contains: carboxymethylcellulose sodium 0.5%, calcium chloride, magnesium chloride, potassium chloride, purified water, sodium chloride, and sodium lactate. Supplied in sterile, preservative-free, disposable, single-use containers of 0.01 fluid ounces.
- PILOCAR® 1.0% sterile ophthalmic solution (Allergan formulation no. 8684X) contains: pilocarpine hydrochloride 10 mg/mL, in an isotonic, buffered solution of boric acid, potassium chloride, sodium carbonate and purified water, preserved with benzalkonium chloride. Supplied in 1 mL dropperette®.
- Tetracaine HCl 0.5% sterile ophthalmic solution (Allergan formulation no. 8683X) contains: tetracaine hydrochloride, chlorobutanol anhydrous, sodium chloride and purified water. Supplied in 1 mL dropperette®.
- OCUFLOX® ophthalmic solution (Allergan formulation no. 7651X) contains: 0.3% ofloxacin, sodium chloride, purified water, preserved with benzalkonium chloride. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH. Supplied in 5 mL plastic dropper bottles.

Escape medication consisted of:

- Acetaminophen (generic TYLENOL®, tablet contains: acetaminophen 325 mg. Supplied in 10 bubble packets of 2 tablets each (total of 20 tablets).

8.1.1.3 Protocol

Amendments: One amendment was made to the protocol [A-1(August 2, 1994)] which is summarized below.

Amendment	Description of Protocol Change
A-1	New co-investigators were added. Cycloplegics were removed from the list of permitted medications. After day 3, a patient was no longer required to return daily to the investigator's office until the patient recorded no ocular pain in their diary.

8.1.1.3.1 Population

One hundred fifty (150) evaluable subjects scheduled to undergo unilateral or bilateral RK surgery for the correction of myopia were proposed to be enrolled into the study at multiple centers.

Patients who were scheduled for unilateral or concurrent bilateral radial keratotomy surgery were screened for entry in the study.

Inclusion Criteria

The following were requirements for patient inclusion into the study:

- Male or female 21 years of age or older
- Signature on the Informed Consent Form and the Subject's Bill of Rights (if applicable)
- Scheduled for unilateral or concurrent bilateral RK surgery requiring a minimum of four radial incisions in the cornea
- Likely to complete the entire course of the study and to follow instructions.

Exclusion Criteria

The following were criteria for exclusion from participating in the study:

Medical Exclusion Criteria

- Any uncontrolled systemic disease (i.e., hypertension, diabetes) or the presence of any significant illness that could be expected to interfere with the study or that would be likely to influence corneal wound healing [connective tissue disease (i.e., rheumatoid arthritis, systemic lupus, atopy)]
- Need for immunosuppressant or systemic anti-inflammatory agents (i.e., corticosteroids, NSAIDs)
- Female patient who was pregnant or nursing, or planning a pregnancy during the study, or thought she might have been pregnant at the start of the study
- Known hypersensitivity, including the complete or partial syndromes of asthma, urticaria, nasal polyps and angioedema, to ketorolac, flurbiprofen, aspirin or any other nonsteroidal anti-inflammatory drug
- Bleeding disorder and/or require anticoagulant therapy
- Known hypersensitivity to acetaminophen, tetracaine, ofloxacin, pilocarpine, benzalkonium chloride, chlorobutanol or any other components of the study or procedural medications
- Any surgical procedure within a week preceding the scheduled RK
- Use of any medications (e.g., diazepam or lorazepam) or any drugs (e.g., alcohol), in close proximity to the scheduled RK surgery, with lingering effects that may influence the patient's perception of pain and interfere with the outcome of this study.

Ophthalmic Exclusion Criteria (for study eye)

- Myopia due to cataract
- Clinically significant, active ocular inflammation, corneal disorder or abnormality
- History of herpetic keratitis, anterior segment surgery or trauma which could affect corneal sensitivity (e.g., cataract surgery, limbal corneal incision)
- Previously undergone RK in either eye
- Use of any other ocular medication(s) during seven days after surgery except those specified by the study protocol and those that have been provided by the sponsor

- Use of topical ocular corticosteroids/corticosteroid combination medications during the 12-month study period
- Use of bandage contact lens(es) concomitant with the use of masked pain medication after RK surgery
- Patching of the operated eye(s)
- Requirement for an RK enhancement procedure before visit 4 (day 7) or after visit 7 (6 months after RK).

General Exclusion Criteria

- Concurrent involvement in any other clinical trial involving an investigational drug/device or participation in a clinical trial within the last 30 days

Washout Period: any systemic or ophthalmic corticosteroids, or NSAIDS, or any other prohibited medication must be discontinued 48 hours prior to surgery.

Concomitant Medication/Prohibited Medications

The medications listed below were prohibited during the 48-hour washout period prior to surgery and for 7 days after RK (visit 4). Administration of a prohibited medication in an emergency situation was done with the safety of the study participant as the prime consideration.

- Systemic corticosteroids, corticosteroid combinations, or NSAIDs
- Any topical ocular medications, except the masked study medication, OCUFLOX®, and fluorescein stain
- Any escape analgesic other than the acetaminophen provided by the study sponsor

The use of topical ocular corticosteroids or corticosteroid combinations were prohibited for up to twelve months after RK (visit 8):

Allowed Medications

Preoperative/ Intraoperative	•	tetracaine
	•	pilocarpine
	•	REFRESH PLUS™
	•	OCUFLOX®
Postoperative	•	OCUFLOX®
	•	acetaminophen
	•	REFRESH PLUS™

Randomization
After giving written informed consent, qualified patients within each investigator's population were assigned equally to masked treatment groups (ketorolac or its vehicle) sequentially, corresponding to a randomization schedule generated by the Sponsor and using a block of four design.

Withdrawal Criteria
Patients could voluntarily withdraw from the study at any time they chose. Any patient who had an unacceptable response to treatment was removed from the study. Any patient who could not complete the study for other reasons unrelated to the use of the study medication (e.g., failure to comply with the visit schedule) was removed from the study.

8.1.1.3.2 Endpoints

Efficacy Measures
The primary efficacy variables were:
- pain intensity
- pain relief

Secondary efficacy measures included:
- use of escape medication (acetaminophen)
- symptoms of general discomfort (quality of sleep, headache, nausea, level of fatigue)
- symptoms of ocular discomfort (foreign body sensation, photophobia, burning/stinging, tearing, itching)

Other measures included:
- quality of life measures (reading newspaper or magazine, telling time from a wristwatch, watching television, recognizing people across a room, seeing traffic signs and signals, seeing steps, spending time in a well-lighted room, spending time outside in daylight).

Differences between the ketorolac and vehicle groups of ≥ 1.0 unit were considered clinically significant findings indicating efficacy. The study was sized to provide adequate statistical power to detect such differences.

Reviewer's Comments: *For a 7 point scale, a clinically significant difference should be at least 1.5-2 units.*

Pain Intensity

On the day of surgery, pain intensity was recorded in patient diaries at 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after receiving the first dose of masked medication after surgery. Subsequently, pain intensity was recorded prior to instillation of masked medication four times daily. This process continued until masked medication was stopped. Pain intensity was evaluated using a 7-point ordinal scale:

0	No pain at all
1	Very mild pain: awareness of pain sensation, but there is no discomfort
2	Mild pain: occasional pain with slight discomfort
3	Moderate pain: frequent pain with some discomfort, but does not interfere with daily activity and/or sleep
4	Severe pain: continuous pain with enough discomfort that sometimes interferes with daily activity and/or sleep
5	Very severe pain: continuous pain with significant discomfort that often interferes with daily activity and/or sleep
6	Extremely severe pain: continuous pain with overwhelming discomfort that completely interferes with daily activity and/or sleep

Pain Relief

On the day of surgery, pain relief was recorded in patient diaries at 30 minutes, 1 hour, 2 hours, 3 hours, and 4 hours after receiving the first dose of masked medication after surgery. Subsequently, pain relief was recorded prior to instillation of masked medication four times daily. This process continued until masked medication was stopped. Pain relief was evaluated using a 7-point ordinal scale:

0	No relief (0%)
1	Little relief (10%)
2	Some relief (30%)
3	Moderate relief (50%)
4	Good deal of relief (70%)
5	Great deal of relief (90%)
6	Complete relief (100%) and "I was not having any pain"

Secondary Efficacy Variables

Use of Escape Medication

Patients recorded the date and time of the first use of escape medication (acetaminophen) in their diaries. The date and number of acetaminophen tablets used were recorded on the patients' case report forms.

Symptoms of General Discomfort

In an office interview, the quality of sleep was evaluated by questionnaire at the preoperative baseline visit (visit 2, day 0) when patients were asked to assess their average, normal sleep time. Postoperatively, (days 1-6), patients were asked if they were awakened by pain, how many hours had they slept since the last visit, if they had trouble falling asleep since the last visit, and if they had used additional pain medication to help fall asleep.

The level of fatigue was graded according to the following 3-point scale:

Rested	0
Tired	1
Very fatigued	2

Headache and nausea were evaluated at all visits and graded according to the following 5-point scale:

None	0
Trace	1
Mild	2
Moderate	3
Severe	4

Symptoms of Ocular Discomfort

Foreign body sensation, photophobia, burning/stinging, tearing and itching were evaluated for each surgically-treated eye at all visits and graded using the following 5-point scale:

None	0
Trace	1
Mild	2
Moderate	3
Severe	4

Quality of life variables (reading newspaper or magazine, telling time from a wristwatch, watching television, recognizing people across a room, seeing traffic signs and signals, seeing steps, spending time in a well-lighted room, spending time outside in daylight) were evaluated for uncorrected vision at baseline (visit 2--day 0), at visits 4-8, and by patients in their diaries. Variables were scored using the following 4-point scale:

Without any difficulty	0
With some difficulty	1
With much difficulty	2
Unable to do	3

Safety Measures

Throughout the study, patients were monitored for adverse events; wound healing progression; visual acuity, refraction, and keratometry changes; and biomicroscopic findings.

Adverse Events

Any adverse event occurring during the study was recorded by the investigator, graded for severity (mild, moderate, or severe), and assessed for relationship to the study treatment (none, unlikely, possible, probable, definite, unknown). In the case of a serious adverse event, investigators were instructed to notify the Sponsor immediately and provide to the Sponsor a complete written case history.

A serious adverse event was defined as an experience that was fatal or life-threatening, permanently disabling, required hospitalization or prolongation of an existing hospitalization, or was a congenital anomaly, cancer, or overdose.

Safety Variables

Wound Healing Progression

An assessment of wound healing was made by the investigator at each return visit after surgery to assess whether healing was progressing normally or if there were any complications.

Visual Acuity

Visual acuity (corrected and uncorrected) was measured at visit 1, and visits 4-8 using a 96% contrast, Regan letter-acuity chart.

Refraction

Manifest refraction was performed at visit 1 and visits 4-8 and cycloplegic refraction was performed at visit 1(day -45 to -3) and visits 6-8. Manifest refraction was reported through day 7 in this report, and both manifest and cycloplegic refraction will be evaluated in the one-year safety report.

Keratometry

Keratometry was performed at visit 1 (day -45 to -3) and visits 6-8 and will be evaluated in the one-year safety report.

Biomicroscopy

Slit-lamp biomicroscopy (without pupil dilation) was performed at all study visits except for the day of surgery (day 0).

Schedule of Visits, Measurements, and Dosing

The study consisted of eight scheduled visits. The schedule of office visits and the study variables evaluated at each visit are presented below.

Visit	Day	Hx	Vf-1	Vf-2	Bio	RK	Sx	Sl	F	P	Rx	EM	A/W
1	-45 to -3	X	X[ß]	X	X								
2	0						X	X	X	X			X
	Surgery					X					X*		
	30 Min[¶]									X		X	
	60 Min[¶]									X		X	
	2 Hours									X		X	
	3 Hours								X	X	X†	X	
	4 Hours						X	X		X		X	X
3	Day 1				X		X	X	X	X	X†	X	X
Interim[¥]	Day 2				X		X	X	X	X	X†	X	X
Interim[¥]	Day 3				X		X	X	X	X	X†	X	X
Interim[∞]	Day 4-6				X		X		X				X
4	Day 7		X[ß]		X		X		X				X
5	Day 28-32		X[ß]		X		X		X				X
6	Day 86-94		X[ß]	X	X		X		X				X
7	Day 176-184		X[ß]	X	X		X		X				X
8	Day 354-374		X[ß]	X	X		X		X				X

* Immediately after RK surgery

¶ Pain query was done at the investigator's office

¥ Patients must return for daily visits until the patient records "No pain at all" for pain intensity in their diary and the masked medication has been stopped

† Masked medication was instilled 4 times daily for the first 24 hours after surgery and 4 times daily thereafter until patients record "No pain at all" for pain intensity (as verified by the investigator or study coordinator). Dosing duration did not exceed 3 days after RK surgery

∞ Optional interim visits

ß Uncorrected and Corrected Visual Acuity

Key to Abbreviations

Hx= History including Iris Color, Pupil Size and Informed Consent
Vf-1= Visual Function including Visual Acuity (using Regan charts), Manifest Refraction
Vf-2= Cycloplegic Refraction and Keratometry
Bio= Biomicroscopy
RK= Radial Keratotomy
Sx= Symptoms of Ocular Discomfort
Sl= Quality of Sleep
F= Functional/Activity Assessment (Quality of Life)
P= Pain Intensity and Pain Relief Evaluation (at Hour 0, presence of pre-existing pain only)
Rx= Dispensing and Use of Masked Study Medication
EM= Escape Medication
A/W= Assessment of adverse events, wound healing, and ocular complications

8.1.1.3.3 Statistical considerations

The sponsor's key efficacy variable used to calculate power was pain intensity at day 1. Pain relief was also considered by the sponsor as an important variable and the study was sized to detect treatment differences for pain relief which required a larger sample size due to a larger estimated variation in pain relief than in pain intensity.

The power approximations were based on the two -sample t-test with a type I error of 0.05 and the difference among treatment (1.0 units of severity) which is considered by the sponsor to be clinically significant. There was a pre-study estimate that 74 subjects per treatment would be necessary to detect as significant a difference of 1.0 units or greater on the seven point (0-6) severity scale. This estimate had estimated standard deviations of 1.55 and 2.16 for Day-1 pain intensity and pain relief respectively.

APPEARS THIS WAY
ON ORIGINAL

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ON ORIGINAL

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

Investigator List and Study Summary by Site

Investigator and Address	Patient Disposition	# of Adverse Events	# of Patients with Adverse Events
	KETO-105-8718		
J. Charles Casebeer, MD 15100 North 78th Way Suite 100 Scottsdale, AZ 85260 (602) 483-9077	Enrolled: 21 Completed Day 7: 17 Discontinued: 0 Terminated LOE: 4 Terminated AE: 0	2	1
Daniel S. Durrie, MD 4321 Washington Street Medical Plaza 3 Suite 6000 Kansas City, MO 64111 (816) 931-4733	Enrolled: 5 Completed Day 7: 5 Discontinued: 0 Terminated LOE: 0 Terminated AE: 0	0	0
R. Bruce Grene, MD 8020 E. Central Suite 200 Witchita, KS 67206 (316) 636-2010	Enrolled: 77 Completed Day 7: 72 Discontinued: 1 Terminated LOE: 4 Terminated AE: 0	23	22
Francis W. Price, Jr., MD 9002 N. Meridian Street Suite 207 Indianapolis IN 46260 (317) 844-5530	Enrolled: 9 Completed Day 7: 6 Discontinued: 1 Terminated LOE: 2 Terminated AE: 0	1	1
Richard Yee, MD Department of Ophthalmology University of Texas at Houston 6411 Fannin Street Houston, TX 77030 (713) 704-7123	Enrolled: 58 Completed Day 7: 54 Discontinued: 1 Terminated LOE: 3 Terminated AE: 0	19	13

Summary of All Subjects Evaluability and Exit Status

Visit	Disposition	Reason	Ketorolac N (%)	Vehicle N (%)	Total N (%)
Total	Patients Enrolled	Enrolled	86	84	170
	Completed Day 7	Completed	84 (97.7%)	71 (84.5%)	155 (91.2%)
	Terminated	Lack of Efficacy	1 (1.2%)	12 (14.3%)	13 (7.6%)
		Adverse Event	0 (0%)	0 (0.0%)	0 (0.0%)
	Discontinued	Administrative Reason	1 (1.2%)	1 (1.2%)	2 (1.2%)
Visit 2	Terminated	Lack of Efficacy	1 (1.2%)	3 (3.6%)	4 (2.4%)
Visit 3	Terminated	Lack of Efficacy	0 (0.0%)	9 (10.7%)	9 (5.3%)
	Discontinued	Administrative Reason	1 (1.2%)	1 (1.2%)	2 (1.2%)

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Patient Demographics/Relevant Entry Data

Variable		Ketorolac	Vehicle	Total	p-Value
Age (Years)	N	86	84	170	0.038
	Mean	38.2	40.6	39.4	
	Min	24	25	24	
	Max	61	60	61	
Sex	Male	33 (38.4%)	45 (53.6%)	78 (45.9%)	0.047
	Female	53 (61.6%)	39 (46.4%)	92 (54.1%)	
Race	Caucasian	80 (93.0%)	79 (94.0%)	159 (93.5%)	
	Black	3 (3.5%)	1 (1.2%)	4 (2.4%)	
	Hispanic	3 (3.5%)	3 (3.6%)	6 (3.5%)	
	Asian	0 (0.0%)	1 (1.2%)	1 (0.6%)	
	Caucasian	80 (93.0%)	79 (94.0%)	159 (93.5%)	0.786
	Non-Caucasian	6 (7.0%)	5 (6.0%)	11 (6.5%)	
Iris Color	Blue	31 (36.5%)	33 (39.8%)	64 (38.1%)	
	Brown	30 (35.3%)	26 (31.3%)	56 (33.3%)	
	Green	6 (7.1%)	8 (9.6%)	14 (8.3%)	
	Hazel	18 (21.2%)	14 (16.9%)	32 (19.0%)	
	Gray	0 (0.0%)	2 (2.4%)	2 (1.2%)	
	Missing Data	1	1	2	
	Light*	55 (64.7%)	57 (68.7%)	112 (66.7%)	0.626
	Dark	30 (35.3%)	26 (31.3%)	56 (33.3%)	
	Missing Data	1	1	2	
Ophthalmic History	Contact lens wear	75 (87.2%)	67 (79.8%)	142 (83.5%)	0.191
Study Eye Unilateral vs Bilateral	Unilateral	37 (43%)	35 (41.7%)	72 (42.4%)	0.858
	Bilateral	49 (57.0%)	49 (58.3%)	98 (57.6%)	
Attempted Correction (diopters)	N	86	83	169	0.574
	Mean	-3.3	-3.5	-3.4	
	Min	-7	-8	-8	
	Max	-1	-1	-1	
Operative Complications		7 (8.2%)	6 (7.1%)	13 (7.7%)	0.790

* Light: blue, green, hazel or grey vs. Dark: brown or black.

Concomitant Medication/Prohibited Medications

Five patients used corticosteroid nasal inhalants concurrently during the study. Four of these patients were treated with ketorolac (#337, #341, #445, #450) and one with vehicle (#409). These were not considered to be protocol violations.

Twenty-three ketorolac-treated patients and 22 vehicle-treated patients took prohibited medications after discontinuing masked medication but during the first 7 days following surgery. Patient #402 in the vehicle group who underwent bilateral surgery had only three incisions in the OS eye, but had four in the OD eye.

Prohibited Medications Used While taking Masked Medication

Treatment	Patient	Medication	Start Date	Comment
Ketorolac	322	Tylenol	10/5/94	Pt used for headache. Discontinued due to failure to follow instructions at Visit 3.01 (10/6/94). Masked medication last used on 10/6/94
Vehicle	104	Percodan	10/20/94	Pt used for pain. Masked medication last used on 10/22/94.
Vehicle	111	Percodan Dalmane	11/30/94 11/30/94	Pt used for pain. Terminated due to lack of efficacy at Visit 2 (11/30/94). Masked medication last used at Surgery (11/30/94).
Vehicle	115	Darvocet Dalmane	12/14/94 12/14/94	Pt used for pain. Terminated due to lack of efficacy at Visit 3 (12/15/94). Masked medication last used on 12/14/94.
Vehicle	116	Percodan	12/16/94	Pt used for pain. Terminated due to lack of efficacy at Visit 3.01 (12/17/94). Masked medication last used on 12/16/94.
Vehicle	118	Percodan Advil	1/13/95 1/13/95	Pt used for pain. Terminated due to lack of efficacy at Visit 2 (1/13/95). Masked medication last used at Surgery (1/13/95).
Vehicle	306	Vicodin	9/6/94	Pt used for pain. Terminated due to lack of efficacy at Visit 3 (9/7/94). Masked medication last used on 9/7/94.
Vehicle	316	Fiorinal w/ codeine	9/26/94	Pt used for pain. Terminated due to lack of efficacy at Visit 3 (9/27/94). Masked medication last used on 9/27/94.
Vehicle	323	Ibuprofen	10/11/94	Pt used for pain. Terminated due to lack of efficacy at Visit 3 (10/12/94). Masked medication last used on 10/12/94.
Vehicle	432	Aspirin	Current	Pt took aspirin prior to and during the study.
Vehicle	435	Bayer aspirin	12/3/94	Pt used for headache. Masked medication last used on 12/4/94.
Vehicle	436	Ibuprofen	12/8/94	Pt used for eye pain. Masked medication last used on 12/9/94.
Vehicle	444	Tylenol #3	12/8/94	Pt used for eye pain. Masked medication last used on 12/10/94.
Vehicle	448	Lortab Tylenol #3	1/12/95 1/12/95	Pt used for headache. Masked medication last used on 1/15/95.
Vehicle	449	Alka Seltzer Cold	1/13/95	Pt used for runny nose, watery eyes. Masked medication last used on 1/16/95.
Vehicle	452	Ibuprofen	1/21/95	Pt used for pain. Masked medication last used on 1/23/95.
Vehicle	455	Cellufresh	2/1/95	Pt used for ocular comfort. Terminated due to lack of efficacy at Visit 3.01 (2/3/95). Masked medication last used on 2/2/95.
Vehicle	463	Extra-Strength Tylenol	2/10/95	Pt used for pain. Terminated due to lack of efficacy at Visit 3 (2/11/95). Masked medication last used on 2/11/95.

Prohibited Concurrent Medications Before Taking Masked Medications

Treatment	Patient	Medication	Start Date	Comment
Ketorolac	418	Sine-Off	Current	Unknown if pt discontinued 48 hrs prior to surgery. Pt did discontinue for 7 days after surgery.
Ketorolac	421	Aspirin	Current	Unknown if pt discontinued 48 hrs prior to surgery. Pt did discontinue for 7 days after surgery.
Ketorolac	467	Aleve	Current	Pt instructed not to use 24 hrs prior to surgery and for 7 days post-op.
Ketorolac	501	Aspirin Rev-eyes	Current Visit 2	Pt took aspirin at 6 AM of surgery, but will not take any more until pain portion is complete. Used post-operatively.
Vehicle	429	Aspirin	Current	Unknown if pt discontinued 48 hrs prior to surgery. Pt did discontinue for 7 days after surgery.
Vehicle	466	Tylenol EC	Current	Pt told to discontinue 24 hrs prior to surgery and not for 7 days post-op.
Vehicle	468	Excedrin	Current	Pt told to discontinue 24 hrs prior to surgery and for 7 days post-op.
Vehicle	469	Excedrin	Current	Pt told to discontinue 24 hrs prior to surgery and for 7 days post-op.

Protocol Violations in Treatment Regimen

Treatment	Patient	Medication	Treatment Regimen Violation
Ketorolac	101	Masked Ocuflox	Pt instilled TID between Day 2 and Day 3. Pt instilled TID between Day 1 and Day 3.
Ketorolac	320	Masked	Pt instilled once on 10/10/94, which was after discontinuing the drops per protocol on 10/6/94.
Ketorolac	322	Masked Ocuflox	Pt instilled 1-2 drops QID between Day 0 and Day 1. Pt instilled 3-4 drops QID between Day 0 and Day 1.
Ketorolac	332	Ocuflox	Pt instilled 1-2 drops TID between Day 0 and Day 1.
Ketorolac	337	Masked Ocuflox	Pt instilled 2 extra drops at 3:00 AM on Day 1. Pt instilled 1 extra drop at 3:00 AM on Day 1.
Ketorolac	338	Masked Ocuflox	Pt instilled drops TID between Day 1 and Day 2.
Ketorolac	351	Masked Ocuflox	Pt instilled 2 drops QID between Day 0 and Day 1.
Ketorolac	358	Masked	Pt instilled once on 3/4/95 and twice on 3/5/95, which was after discontinuing the drops per protocol on 2/28/95.
Ketorolac	404	Masked Ocuflox	Pt instilled drops BID between Day 0 and Day 1.
Ketorolac	420	Masked Ocuflox	Pt instilled drops TID between Day 2 and Day 3.
Ketorolac	439	Ocuflox	Pt instilled drops 6 times a day between Day 1 and Day 2.
Ketorolac	448	Masked Ocuflox	Pt instilled drops BID between Day 0 and Day 1; missed bedtime dose on Day 0.
Vehicle	455	Masked	Pt did not instill drops on 2/3/95; wants to be removed from study.
Vehicle	470	Masked	Pt instilled drops TID between Day 1 and Day 2. Pt did not instill drops after Day 2.
Vehicle	201	Masked Ocuflox	Pt instilled drops at Hour 4 on Day 0 in OS only.
Vehicle	333	Masked	Pt instilled TID between Day 2 and Day 3.
Vehicle	419	Masked Ocuflox	Pt instilled drops 2 times between Day 0 and Day 1; missed bedtime dose on Day 0.
Vehicle	423	Masked Ocuflox	Pt instilled drops 5 times between Day 0 and Day 1.
Vehicle	426	Masked	Pt instilled 1 drop immediately post-op on Day 0. Pt did not instill masked medication between Day 0 and Day 1.
Vehicle	436	Masked Ocuflox	Pt instilled drops BID between Day 0 and Day 1; missed bedtime dose on Day 0.
Vehicle	442	Masked	Pt instilled QID between Day 3 and Day 7.

Prohibited Medications Used After Discontinuing Masked Medication But During the First 7 Days Following Surgery

Treatment	Patient	Medication	Start Date	Comment
Ketorolac	103	Aspirin	10/24/94	Pt used for gum pain.
Ketorolac	105	Tylenol	11/1/94	Pt used for allergies.
Ketorolac	107	Tylenol	11/8/94	Pt used for headache.
Ketorolac	207	Refresh PM	11/16/94	Pt used for irritation.
Ketorolac	318	Tetracaine 0.05%	10/2/94	Pt used for pain, unable to open eye.
Ketorolac	322	Polytrim Tylenol	10/7/94 10/7/94	Pt used for allergy to Ocuflox. Pt used for burning/irritation.
Ketorolac	325	Aspirin Tylenol	12/4/94 12/4/94	Pt used for scratched eye.
Ketorolac	328	Extra-Strength Tylenol	10/23/94	Pt used for headache.
Ketorolac	336	Walgreen Non-Aspirin	11/19/94	Pt used for pain OS.
Ketorolac	337	Tylenol Max	11/20/94	Pt used for headache.
Ketorolac	343	Tylenol	11/25/94	Pt used for headache.
Ketorolac	347	Ibuprofen	12/10/94	Pt used for headache.
Ketorolac	348	Tylenol Cold and Flu	12/25/94	Pt used for cold.
Ketorolac	352	Motrin Tylenol	1/23/95 1/24/95	Pt used for headache.
Ketorolac	359	Tylenol	3/1/95	Pt used for eye pain.
Ketorolac	424	Voltaren 0.1%	11/21/94	Pt used for ocular discomfort.
Ketorolac	428	Tylenol	12/6/94	Pt used for ocular pain.
Ketorolac	433	Flarex 0.1%	12/6/94	Pt used for ocular discomfort.

Reviewer's Comment: *The above table has one subject having access post-op to a steroid for ocular discomfort and one other to Tetracaine.*

8.1.1.4.2 Efficacy endpoint outcomes

The primary efficacy variables were: pain intensity and pain relief

Pain Intensity

Interaction p-value

Time Period	Statistics	Ketorolac	Vehicle	p-value	By Site	By Sex	By Age
30 minutes	N	81	82	0.019	0.084	0.564	0.059
	Mean	0.8	1.3				
	Min						
	Max						
1 hour	N	82	79	0.001	0.294	0.031	0.228
	Mean	1.3	2.2				
	Min						
	Max						
2 hours	N	77	78	0.001	0.587	0.049	0.653
	Mean	1.6	3.1				
	Min						
	Max						
3 hours	N	78	72	0.001	0.309	0.092	0.767
	Mean	1.7	3.3				
	Min						
	Max						
4 hours	N	70	69	0.001	0.813	0.077	0.451
	Mean	1.3	3.3				
	Min						
	Max						
7-12 hours	N	72	70	0.001	0.552	0.592	0.799
	Mean	1.5	3.0				
	Min						
	Max						

13-18 hours	N	54	46	0.047	0.346	0.226	0.445
	Mean	1.8	2.5				
	Min						
	Max						
19-24 hours	N	78	74	0.009	0.905	0.933	0.855
	Mean	1.6	2.2				
	Min						
	Max						
25-30 hours	N	65	69	0.007	0.470	0.594	0.213
	Mean	1.4	2.0				
	Min						
	Max						
31-36 hours	N	59	68	0.001	0.331	0.991	0.050
	Mean	1.0	1.9				
	Min						
	Max						
37-42 hours	N	47	41	0.006	0.256	0.856	0.939
	Mean	0.6	1.5				
	Min						
	Max						
43-48 hours	N	60	66	0.010	0.096	0.769	0.455
	Mean	0.7	1.2				
	Min						
	Max						

Reviewer's Comment: *A significant difference of 2 units was present only at the 4 hour timepoint. For time points after 12 hours, the difference in the mean value for pain intensity was consistently less than one unit. Corrected for multiple comparisons, a significant p-value would be less than 0.004.*

Incidence of Subjects Reporting No Pain at Each Timepoint

Time Period	Ketorolac Overall = 86 N/Total*	Vehicle Overall = 84 N/Total*	p-Value
30 minutes	37/81 (45.7%)	28/82 (34.1%)	0.133
1 hour	31/82 (37.8%)	14/79 (17.7%)	0.005
2 hours	25/77 (32.8%)	6/78 (7.7%)	0.001
3 hours	25/78 (32.1%)	5/72 (6.9%)	0.001
4 hours	29/70 (41.4%)	6/69 (8.7%)	0.001
7-12 hours	29/72 (40.3%)	5/70 (7.1%)	0.001
13-18 hours	19/54 (35.2%)	6/46 (13%)	0.001
19-24 hours	27/78 (34.6%)	11/74 (14.9%)	0.005
25-30 hours	28/65 (43.1%)	13/69 (18.8%)	0.002
31-36 hours	31/59 (52.5%)	15/68 (22.1%)	0.001
37-42 hours	31/47 (66.0%)	18/41 (43.9%)	0.038
43-48 hours	40/60 (66.7%)	30/66 (45.5%)	0.017
49-54 hours	44/55 (80%)	36/60 (60%)	0.020
55-60 hours	47/55 (85.5%)	35/55 (63.6%)	0.009
61-66 hours	48/52 (92.3%)	35/45 (77.8%)	0.079
67-72 hours	53/55 (96.4%)	40/54 (74.1%)	0.001
>72 hours	52/53 (98.1%)	42/52 (80.8%)	0.004

Reviewer's Comment: *The percentages of patients reporting no pain is greater at all timepoints for ketorolac.*

Pain Relief

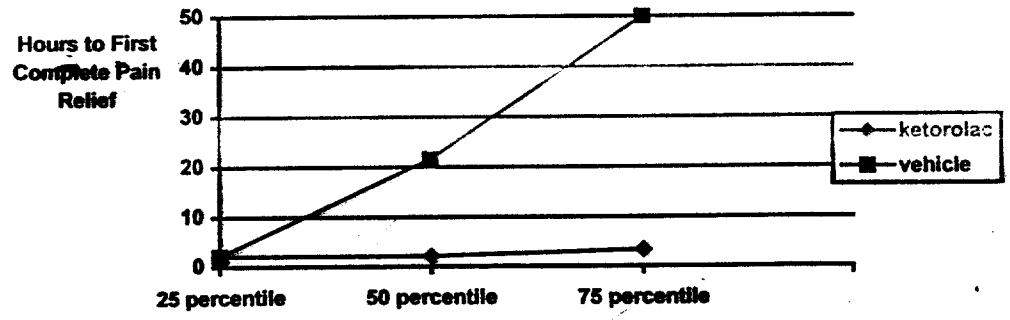
Pain Relief: Incidence Complete

Time Period	Ketorolac Overall=86 N/Total[b] (%)	Vehicle Overall=84 N/Total (%)	P-value[c]
30 min	73/80 (91.3%)	68/82 (82.9%)	0.115
1 hr	65/82 (79.3%)	61/80 (76.3%)	0.644
2 hrs	**58/74 (78.4%)**	**35/78 (44.9%)**	**0.001**
3 hrs	**56/78 (71.8%)**	**25/72 (34.7%)**	**0.001**
4 hrs	**34/69 (49.3%)**	**14/69 (20.3%)**	**0.001**
7-12 hrs	**36/73 (49.3%)**	**11/69 (15.9%)**	**0.001**
13-18 hrs	**17/50 (34.0%)**	**10/44 (22.7%)**	**0.228**
19-24 hrs	**30/72 (41.7%)**	**13/73 (17.8%)**	**0.002**
25-30 hrs	**33/68 (48.5%)**	**15/68 (22.1%)**	**0.001**
31-36 hrs	**34/61 (55.7%)**	**16/68 (23.5%)**	**0.001**
37-42 hrs	**32/45 (71.1%)**	**15/37 (40.5%)**	**0.005**
43-48 hrs	**36/58 (62.1%)**	**25/61 (41.0%)**	**0.021**
49-54 hrs	**41/54 (75.9%)**	**30/55 (54.5%)**	**0.019**
55-60 hrs	**44/52 (84.6%)**	**32/49 (65.3%)**	**0.025**
61-66 hrs	**45/48 (93.8%)**	**30/37 (81.1%)**	**0.095**
67-72 hrs	**50/52 (96.2%)**	**38/50 (76.0%)**	**0.004**
>72 hrs	49/50 (98.0%)	39/48 (81.3%)	0.007

Time (Hour) to First Complete Pain Relief[a]: Kaplan-Meier Survival Estimates

	Ketorolac	Vehicle
Total	**84**	**82**
Mean	**13.8**	**28.1**
S.E.M	**2.5**	**3.1**
25 percentile	**2.1**	**2.1**
50 percentile (Median)	**2.1**	**21.6**
75 percentile	**3.4**	**50.0**
Censored[c]	**9**	**20**

0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. Scores from the first 1.5 hours were ignored due to the effect of anesthetic.
Censored patients are those with pain relief data who never recorded scores for complete or no pain.



Reviewer's Comment: *There is consistently greater complete pain relief at all timepoints for the ketorolac treatment group.*

Secondary efficacy measures:

Use of escape medication (acetaminophen) First Acetaminophen Escape Medication Use:

Hour Interval	Ketorolac (overall=86)	Vehicle (overall=84)
30 min	2 (2.3%)	3 (3.6%)
1 hr	2 (2.3%)	9 (10.8%)
2 hrs	4 (4.7%)	11 (13.3%)
3 hrs	3 (3.5%)	10 (12.0%)
4 hrs	1 (1.2%)	15 (18.1%)
6-12 hrs	5 (5.8%)	5 (6.0%)
13-18 hrs	4 (4.7%)	3 (3.6%)
19-24 hrs	0 (0.0%)	1 (1.2%)
25-30 hrs	1 (1.2%)	1 (1.2%)
31-36 hrs	0 (0.0%)	1 (1.2%)
37-42 hrs	0 (0.0%)	0 (0.0%)
43-48 hrs	1 (1.2%)	0 (0.0%)
49-54 hrs	0 (0.0%)	1 (1.2%)
55-60 hrs	0 (0.0%)	0 (0.0%)
61-66 hrs	0 (0.0%)	0 (0.0%)
67-72 hrs	0 (0.0%)	1 (1.2%)
>72 hrs	0 (0.0%)	0 (0.0%)
Not Taken	63 (73.3%)	22 (26.5%)

Reviewer's Comment: ***There were minor differences in the sponsor's data that did not impact the outcomes but should be noted:***

1) ***Three Ketorolac patients (#404, 451, 453) who did not take acetaminophen are not included in the survival analysis because no censoring time (diary observation time) was recorded.***
2) ***Two ketorolac patients (#209, 356) and one vehicle patient (#118) who did take acetaminophen are not included in tables 16-19, because the number of capsules taken were not recorded.***
3) ***One Ketorolac patient (#434) is included in the sponsor analyses as having taken acetaminophen, but is counted as not taking acetaminophen because time of first use was not recorded.***
4) ***One vehicle patient (#208) recorded a pre-surgery time for taking acetaminophen and is not included***

Time to First Acetaminophen Use: Survival Analysis Point Estimates

Statistics	Ketorolac	Vehicle	P-value[a]
Total	83	83	0.001
Mean	33.7	21.9	
S.E.M	1.9	3.1	
25 percentile	16.8	2.3	
50 percentile (Median)	N/E[b]	4.5	
75 percentile	N/E[b]	50.1	
Censored[c]	60	22	

[a] Estimated by Kaplan-Meier method.
[b] Not estimable. The median is not estimable because over half of the ketorolac patients never took acetaminophen.
[c] Censored patients are those with diary data who never recorded use of acetaminophen.

Reviewer's Comment: *There is significantly less use of escape medication for the ketorolac treatment group compared to vehicle.*

Symptoms of general discomfort (quality of sleep)

Awakened by Pain: Incidence

Study Day	Ketorolac Overall=86 N/Total (%)	Vehicle Overall=84 N/Total (%)	P-value
4 hr-post	2/81 (2.5%)	6/77 (7.8%)	0.157
Day 1	15/84 (17.9%)	28/81 (34.6%)	0.013
Day 2	2/27 (7.4%)	11/41 (26.8%)	0.064
Day 3	1/11 (9.1%)	3/14 (21.4%)	0.604

Subjects Reporting Taking Additional Pain Medication to Fall Asleep: Incidence

Study Day	Ketorolac Overall=86 N/Total[a] (%)	Vehicle Overall=84 N/Total (%)	P-value[b]
4 hr-post	7/81 (8.6%)	19/77 (24.7%)	0.006
Day 1	13/84 (15.5%)	36/81 (44.4%)	0.001
Day 2	4/27 (14.8%)	14/41 (34.1%)	0.156
Day 3	0/11 (0.0%)	3/14 (21.4%)	0.230

Symptoms of ocular discomfort (foreign body sensation, photophobia, burning/stinging, tearing, itching)

Foreign Body Sensation: Incidence Moderate or Greater

Study Day	Ketorolac Overall=86 N/Total (%)	Vehicle Overall=84 N/Total (%)	P-value
Pre-op	0/85 (0.0%)	0/84 (0.0%)	>0.999
4 hr-post	18/82 (22.0%)	41/77 (53.2%)	0.001
Day 1	25/85 (29.4%)	33/81 (40.7%)	0.126
Day 2	5/33 (15.2%)	10/52 (19.2%)	0.631
Day 3	3/15 (20.0%)	3/24 (12.5%)	0.658
Day 4	2/5 (40.0%)	1/2 (50.0%)	N/A
Day 5	0/3 (0.0%)	0/1 (0.0%)	N/A
Day 6	0/1 (0.0%)	2/4 (50.0%)	N/A
Day 7	8/82 (9.8%)	5/80 (6.3%)	0.398

Photophobia: Incidence Moderate or Greater (Subjects with moderate or greater scores at pre-op were not included at subsequent timepoints.)

Study Day	Ketorolac Overall=86 N/Total (%)	Vehicle Overall=84 N/Total (%)	P-value
Pre-op	0/85 (0.0%)	6/84 (7.1%)	0.014
4 hr-post	16/82 (19.5%)	41/72 (56.9%)	0.001
Day 1	18/85 (21.2%)	39/76 (51.3%)	0.001
Day 2	4/33 (12.1%)	22/50 (44.0%)	0.003
Day 3	2/15 (13.3%)	9/23 (39.1%)	0.145
Day 4	3/5 (60.0%)	2/2 (100.0%)	N/A
Day 5	0/3 (0.0%)	0/1 (0.0%)	N/A
Day 6	0/1 (0.0%)	4/4 (100.0%)	N/A
Day 7	25/82 (30.5%)	20/75 (26.7%)	0.563

Burning/Stinging: Incidence Moderate or Greater

Study Day	Ketorolac Overall=86 N/Total (%)	Vehicle Overall=84 N/Total (%)	P-value
Pre-op	0/85 (0.0%)	0/84 (0.0%)	>0.999
4 hr-post	7/82 (8.5%)	33/77 (42.9%)	0.001
Day 1	11/85 (12.9%)	24/81 (29.6%)	0.008
Day 2	2/33 (6.1%)	7/52 (13.5%)	0.472
Day 3	2/15 (13.3%)	2/24 (8.3%)	0.631
Day 4	2/5 (40.0%)	0/2 (0.0%)	N/A
Day 5	0/3 (0.0%)	0/1 (0.0%)	N/A
Day 6	0/1 (0.0%)	2/4 (50.0%)	N/A
Day 7	8/82 (9.8%)	5/80 (6.3%)	0.412

Tearing: Incidence Moderate or Greater

Study Day	Ketorolac Overall=86 N/Total (%)	Vehicle Overall=84 N/Total (%)	P-value
Pre-op	0/85 (0.0%)	0/84 (0.0%)	>0.999
4 hr-post	18/82 (22.0%)	51/77 (66.2%)	0.001
Day 1	30/85 (35.3%)	35/81 (43.2%)	0.296
Day 2	1/33 (3.0%)	11/52 (21.2%)	0.024
Day 3	2/15 (13.3%)	2/24 (8.3%)	0.631
Day 4	2/5 (40.0%)	1/2 (50.0%)	N/A
Day 5	0/3 (0.0%)	0/1 (0.0%)	N/A
Day 6	0/1 (0.0%)	3/4 (75.0%)	N/A
Day 7	8/82 (9.8%)	5/80 (6.3%)	0.395

In summary, statistically significant differences between the treatment groups in the incidence of moderate or greater symptoms of ocular discomfort, all favoring nonpreserved ketorolac, were found in the first 4 hours postop for all symptoms except for that of itching, as is shown in the following table:

	4-Hours Postop	Day 1	Day 2
Symptoms of Ocular Discomfort			
	P-values		
Foreign Body Sensation	≤0.001	0.126	0.631
Photophobia	≤0.001	≤0.001	0.003
Burning/stinging	≤0.001	0.008	0.472
Tearing	≤0.001	0.296	0.024
Itching	0.108	0.715	0.151

Quality of life measures

For the quality of life variables, it was somewhat less difficult for ketorolac-treated patients than for vehicle-treated patients to read a newspaper or magazine, to watch television, to see steps, to spend time in a well-lighted room, and to spend time outside in daylight at the early timepoints in the first day after surgery. The statistical analysis was highly variable with very few reaching significance.

8.1.1.4.3 Safety outcomes

Safety Variables

Wound Healing Progression

An assessment of wound healing was made by the investigator at each return visit after surgery to assess whether healing was progressing normally or if there were any complications. The investigators were asked to assess whether wound healing progressed as expected. When the data were analyzed, there were no statistically significant differences between the treatment groups in wound healing through day 7. Wound healing progressed as expected in similar numbers of patients in each of the treatment groups through day 7.

Wound Healing and Complications

Study Day: 1

Variable	Ketorolac (overall=85) N/total (%)	Vehicle (overall=82) N/total (%)	p-value
Healing as expected	72 (84.7%)	71 (86.6%)	.73
Gaping of incisions	0 (0.0%)	1 (1.2%)	.49
Exudate from incisions	0 (0.0%)	0 (0.0%)	.99
Raised epithelial ridges	1 (1.2%)	3 (3.7%)	.36
Thin epithelium covering	5 (5.9%)	4 (4.9%)	.99
Epithelial cysts	0 (0.0%)	0 (0.0%)	.99
Persistent epithelial plugs	0 (0.0%)	0 (0.0%)	.99
Other epithelial cell changes	2 (2.4%)	3 (3.7%)	.67
Bowman's membrane changes	0 (0.0%)	0 (0.0%)	.99
Stromal changes	4 (4.7%)	0 (0.0%)	.12
Endothelial changes	0 (0.0%)	1 (1.2%)	.50
Other	2 (2.4%)	0 (0.0%)	.50

Wound Healing and Complications

Study Day: 7

Variable	Ketorolac (overall=84) N/total (%)	Vehicle (overall=80) N/total (%)	P-value
Healing as expected	72 (85.7%)	74 (92.5%)	.17
Gaping of incisions	3 (3.6%)	4 (5.0%)	.72
Exudate from incisions	0 (0.0%)	0 (0.0%)	.99
Raised epithelial ridges	0 (0.0%)	0 (0.0%)	.99
Thin epithelium covering	0 (0.0%)	1 (1.3%)	.49
Epithelial cysts	0 (0.0%)	0 (0.0%)	.99
Persistent epithelial plugs	0 (0.0%)	0 (0.0%)	.99
Other epithelial cell changes	7 (8.3%)	1 (1.3%)	.06
Bowman's membrane changes	0 (0.0%)	0 (0.0%)	.99
Stromal changes	2 (2.4%)	0 (0.0%)	.50
Endothelial changes	0 (0.0%)	0 (0.0%)	.99
Other	0 (0.0%)	0 (0.0%)	.99

Wound healing did not progress as expected on day 7 in 18 patients (12 ketorolac, 6 vehicle); 17 of these patients were from one site (#1240, Investigator Bruce Grene). Reasons for wound healing not progressing as expected in the ketorolac-treated patients included stromal changes of edema (2), wound gaping (3), and other epithelial cell changes (7). Why this incidence clustered so prominently at one site is not apparent from the review though this may reflect more stringent reporting of any perceptible changes in the exam by this investigator that might be related to healing.

These "other epithelial cell changes" were specified as superficial punctate keratitis over the incision graded as trace (5) or mild (1). The best-corrected visual acuity in 10 of these 12 patients was better than or equal to 20/20 (Snellen; 8.00 Regan) by day 7 . The remaining two patients (#462 and #467) had visual acuity better than 20/20 on day 30 (data beyond day 7 will be included in the 12-month report). For the six vehicle-treated patients whose wound healing was less than expected on day 7, all of their best-corrected visual acuity scores were better than 20/20 on day 7.

Reviewer's Comment: *There is strongly suggestive evidence here that wound healing was delayed in the ketorolac group and under-reporting is suspected by some of the investigators.*

Additionally, corrected visual acuity was reviewed by the sponsor for patients who had less than expected progression in wound healing at day 7. When the corrected visual acuity of these 18 patients was evaluated, all achieved visual acuity equal to or better than 20/20 (Snellen).

Visual Acuity/Refraction/Biomicroscopy

Visual acuity (corrected and uncorrected) was measured at visit 1, and visits 4-8 using a 96% contrast, Regan, letter-acuity chart. There were no significant differences between ketorolac and vehicle regarding visual acuity and manifest refraction. Cycloplegic refraction and keratometry results will be reported at the end of the one-year study. The only differences between the groups in biomicroscopic variables graded as mild or greater were for lid erythema and lid edema, both of which favored ketorolac.

Keratometry

Keratometry was performed at visit 1 (day -45 to -3) and visits 6-8 and will be evaluated in the one-year safety report.

Biomicroscopy

Slit-lamp biomicroscopy (without pupil dilation) was performed at all study visits except for the day of surgery (day 0).

Adverse Events: Overall Incidence of Patients with Any Adverse Event[a]

		Ketorolac (overall=86) N(%)	Vehicle (overall=84) N(%)	Total (overall=170) N(%)
	Ocular	19 (22.1%)	13 (15.5%)	32 (18.6%)
	Systemic	3 (3.5%)	4 (4.8%)	7 (4.1%)
Ocular	Blepharitis	2 (2.3%)	1 (1.2%)	3 (1.8%)
	Blepharospasm	0 (0.0%)	1 (1.2%)	1 (0.6%)
	Edema Eyelid	1 (1.2%)	1 (1.2%)	2 (1.2%)
	Conjunctivitis allergic	2 (2.3%)	2 (2.4%)	4 (2.4%)
	Hyperemia Conjunctival	1 (1.2%)	0 (0.0%)	1 (0.6%)
	Infection	0 (0.0%)	1 (1.2%)	1 (0.6%)
	Corneal Infiltrates	1 (1.2%)	0 (0.0%)	1 (0.6%)
	Edema Corneal	9 (10.5%)	3 (3.6%)	12 (7.1%)
	Keratitis (NOS)	1 (1.2%)	1 (1.2%)	2 (1.2%)
	Eye Trauma	2 (2.3%)	2 (2.4%)	4 (2.4%)
	Foreign Body Sensation	1 (1.2%)	0 (0.0%)	1 (0.6%)
	Pain Eye	1 (1.2%)	1 (1.2%)	2 (1.2%)
	Photophobia	1 (1.2%)	2 (2.4%)	3 (1.8%)
Systemic	Pain	0 (0.0%)	1 (1.2%)	1 (0.6%)
	Nausea	2 (2.3%)	0 (0.0%)	2 (1.2%)
	Hypertonia	0 (0.0%)	1 (1.2%)	1 (0.6%)
	Infection	1 (1.2%)	0 (0.0%)	1 (0.6%)
	Pain Ear	0 (0.0%)	1 (1.2%)	1 (0.6%)
	Browache	0 (0.0%)	1 (1.2%)	1 (0.6%)
	Edema Face	0 (0.0%)	1 (1.2%)	1 (0.6%)

[a] Note that patients with multiple adverse events appear more than once in this table, once for each relevant reaction term.

8.1.1.5 Reviewer's Conclusions Regarding Efficacy Data.

The objective of this study was to evaluate the ocular safety and efficacy of ketorolac compared with its vehicle in reducing postsurgical ocular pain in patients after radial keratotomy surgery. The results of this study demonstrate a statistically significant reduction in the intensity of pain experienced by ketorolac patients following RK surgery at all timepoints as well as greater pain relief than vehicle in the peri-operative period. Statistically significant differences were far more persistent at timepoints out to 72 hours for the primary efficacy variables than were clinically significant differences.

Several other indicators of the pain-relieving efficacy of ketorolac in the setting of radial keratotomy were demonstrated. Fewer ketorolac-treated patients than vehicle-treated patients used the escape medication, acetaminophen. Seventeen patients took additional protocol-prohibited pain medications in the vehicle group compared with only one patient in the ketorolac group. Also, significantly fewer patients were terminated from the study due to lack of efficacy (intolerable pain) in the ketorolac group (1/86 or 1.2%) than in the vehicle group (12/84 or 14.3%).

There was suggestive evidence in the study that wound healing was delayed in the ketorolac group.

8.1.2.: Reviewer's Trial #2 **Sponsor's Trial: KETO-106-8718**

Study Title: THE ANALGESIC EFFICACY AND ONE YEAR SAFETY FOLLOW-UP OF KETOROLAC NONPRESERVED OPHTHALMIC SOLUTION IN SUBJECTS UNDERGOING RADIAL KERATOTOMY

Indication : Ocular pain after radial keratotomy
Treatment Duration: until no ocular pain or 3 days

STUDY DATES May 1995 to May 1996 (through day 7 [visit 4])

OBJECTIVE

To evaluate the analgesic efficacy and safety of nonpreserved topical ketorolac tromethamine 0.5% compared with vehicle when used following radial keratotomy (RK).

DESIGN

The study design was of a multicenter, double-masked, randomized, parallel comparison of 1 week duration, with follow-up at 1 month, 3 months, 6 months, and 1 year. The protocol was essentially the same as that in the previous study and will not be reproduced again here.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

DISPOSITION BY INVESTIGATOR: There were eleven U.S. sites for this study.

Name and Address	Investigator Identification Number	No. Patients Enrolled, Treatment Group	Patient Numbers
Marc L. Abel, DO Tulsa, OK 74133	2390	38 Ketorolac: 19 Vehicle: 19	701-738
Kerry K. Assil, MD Santa Monica, CA 90404	2438	12 Ketorolac: 6 Vehicle: 6	A01-A12
Stephen F. Brint, MD New Orleans, LA 70127	1289	39 Ketorolac: 19 Vehicle: 20	301-306 308-340*
Britt A. Buckley, MD Colorado Springs, CO 80907	2437	12 Ketorolac: 6 Vehicle: 6	501-512
James C. Hays, MD Atlanta, GA 30327	1773*	8 Ketorolac: 4 Vehicle: 4	401-408
Michael E. Hettinger, MD Overland Park, KS 66204	2391*	8 Ketorolac: 4 Vehicle: 4	801-808
Paul S. Imperia, MD Medford, OR 97504	2510*	9 Ketorolac: 4 Vehicle: 5	B01-B09
Richard L. Lindstrom, MD Minneapolis, MN 55404	0360*	1 Ketorolac: 0 Vehicle: 1	101
Jonathan I. Macy, MD Los Angeles, CA 90048	0304	18 Ketorolac: 9 Vehicle: 9	201-211, 213-218 222
Vance M. Thompson, MD Sioux Falls, SD 57105	2224	20 Ketorolac: 10 Vehicle: 10	601-620
Stephan C. Volk, MD Richmond, VA 23226	2509*	5 Ketorolac: 2 Vehicle: 3	C01-C05

* Patient #307 was skipped because a change in the operative plan during surgery made the patient ineligible for the study. The numbered study medications were opened, but not used.

*Because of small sample sizes, data from five study sites (1773, 2391, 2510, 0360, and 2509) were pooled for by-investigator tables and for any investigator-by-treatment interaction tests.

Patient Demographics: Age, Sex, Race and Iris Color

Variable		Ketorolac	Vehicle	Total	P-value[a]
Age (Years)	N	83	87	170	0.28
	Mean	37.0	38.4	37.7	
	S.E.M.	1.01	0.86	0.66	
	Min	18	22	18	
	Max	59	58	59	
Gender	Male	35 (42.2%)	33 (37.9%)	68 (40.0%)	0.57
	Female	48 (57.8%)	54 (62.1%)	102 (60.0%)	
Race	Caucasian	76 (91.6%)	78 (89.7%)	154 (90.6%)	
	Black	1 (1.2%)	0 (0.0%)	1 (0.6%)	
	Oriental	0 (0.0%)	3 (3.4%)	3 (1.8%)	
	Hispanic	2 (2.4%)	4 (4.6%)	6 (3.5%)	
	Other[c]	4 (4.8%)	2 (2.3%)	6 (3.5%)	
	Caucasian	76 (91.6%)	78 (89.7%)	154 (90.6%)	0.80
	Non-caucasian	7 (8.4%)	9 (10.3%)	16 (9.4%)	
Iris Color	Blue	29 (34.9%)	24 (27.6%)	53 (31.2%)	
	Brown	23 (27.7%)	37 (42.5%)	60 (35.3%)	
	Green	10 (12.0%)	16 (18.4%)	26 (15.3%)	
	Black	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Hazel	21 (25.3%)	10 (11.5%)	31 (18.2%)	
	Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	Light	60 (72.3%)	50 (57.5%)	110 (64.7%)	0.04
	Dark	23 (27.7%)	37 (42.5%)	60 (35.3%)	

Treatment-by-site interaction was not significant (p>0.10). Sex, race (caucasian vs. non-caucasian), and iris color (light: blue, green or hazel vs. dark: brown or black) were analyzed by chi-square or Fisher's exact test.
[a] P-value were calculated for between-treatment comparisons. Age was analyzed by the Kruskal-Wallis
[c] The race other category included one Indonesian, one native American, one American Indian and three Persians.

Ophthalmic Prestudy History

Contact Lens Wear	69 (83.1%)	73 (83.9%)	142 (83.5%)	0.89

Operative Report

Study Eye (Unilateral vs. Bilateral)				
Unilateral	47 (56.6%)	49 (56.3%)	96 (56.5%)	0.97
Bilateral	36 (43.4%)	38 (43.7%)	74 (43.5%)	
Complications	1 (1.2%)	4 (4.6%)	5 (2.9%)	0.37

Attempted Correction

	Ketorolac	Vehicle	Total	P-value[a]
Number of Incisions [b] N	83	87	170	0.98
Mean	7.0	6.9	6.9	
S.E.M.[c]	0.21	0.22	0.15	
Min				
Max				
Attempted Correction N	83	87	170	0.47
Mean	-3.3	-3.1	-3.2	
S.E.M.[c]	0.16	0.16	0.11	
Min				
Max				

Patient Disposition

Visit	Disposition	Reason	Ketorolac N (%)	Vehicle N (%)	Total N (%)
Total	Patients Enrolled		83 (100.0%)	87 (100.0%)	170 (100.0%)
	Completed Day 7	Completed	77 (92.8%)	77 (88.5%)	154 (90.6%)
	Terminated	Lack of Efficacy	2 (2.4%)	8 (9.2%)	10 (5.9%)
		Adverse Events	3 (3.6%)	2 (2.3%)	5 (2.9%)
	Discontinued	Administrative Reason	1 (1.2%)	0 (0.0%)	1 (0.6%)
Visit 2	Terminated	Lack of Efficacy	0 (0.0%)	5 (5.7%)	5 (2.9%)
		Adverse Events	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visit 3	Terminated	Lack of Efficacy	2 (2.4%)	3 (3.4%)	5 (2.9%)
		Adverse Events	3 (3.6%)	2 (2.3%)	5 (2.9%)
	Discontinued	Administrative Reason	1 (1.2%)	0 (0.0%)	1 (0.6%)

Patients Discontinued or Terminated from the Study

	Treatment	Patient ID	Visit[a]	Exit Reason	Comment	Reaction Term
Terminated	Ketorolac	204	3.00	Lack of Efficacy	EFFCY	
		702	3.01	Adverse Event	ADVEVT	CORNEAL INFILTRATES
		711	3.00	Adverse Event	ADVEVT	CORNEAL INFILTRATES
		736	3.00	Lack of Efficacy	EFFCY	
		A09	3.01	Adverse Event	ADVEVT	ALLERGIC RXN TO STUDY MEDS ASSOCIATED WITH DELAY WOUND HEALING
	Vehicle	209	2.00	Lack of Efficacy	EFFCY	INTOLERABLE PAIN
		213	2.00	Lack of Efficacy	EFFCY	SEVERE PAIN
		401	3.00	Adverse Event	ADVEVT	SUBJECT HAD CONJUNCTIVITIS POSSIBLE ALLERGIC REACTION MED
		512	3.00	Lack of Efficacy	EFFCY	LIDS & EYE WAS SWOLLEN & IN SEVERE PAIN
		704	2.00	Lack of Efficacy	EFFCY	PT PRESCRIBED TYLENOL #3 & ACULAR DUE TO INTOLERABLE PAIN
		709	2.00	Lack of Efficacy	EFFCY	RX'D ACULAR Q1H; OCUFLOX Q1H
		722	3.00	Lack of Efficacy	EFFCY	UNABLE TO TOLERATE DISCOMFORT
		738	3.00	Lack of Efficacy	EFFCY	WAS RX'D TYLENOL #3 FOR PAIN
		A06	2.00	Lack of Efficacy	EFFCY	EXITED DUE TO INTOLERABLE PAIN
		B08	3.00	Adverse Event	ADVEVT	SEVERE BURNING SENSATION BURNING/STINGING IN EYE UPON INSTILLING OCUFLOX + STUDY EYE DROPS
Discontinued	Ketorolac	705	3.00	Non-compliance	NONCOMP	

[a] Visits 3 and 3.01 are pooled by the sponsor as visit 3.

Protocol Deviations

Eight patients (4 each, ketorolac and vehicle-treated) from two sites did not receive pilocarpine 1% as part of the preoperative medication, and the surgical eye of one patient (vehicle group) from a third clinical site was irrigated with balanced salt solution. All of these actions were deviations from the protocol, but the patients are included in the intent-to-treat analysis.

Prohibited Concurrent Medications Before Taking Masked Medications

Treatment	Patient	Medication	Start Date	Comment
Ketorolac	208	Klonopin	1/1/94 (on-going)	Pt. took med. for anxiety/sleep aid. Can not confirm washout prior to surgery or use during 7-day post-op period.
Ketorolac	705	Serax	unknown start (on-going)	Routinely taken for sleep. Can not confirm washout prior to surgery or use during 7-day post-op period.
Vehicle	613	non-aspirin allergy/sinus	unknown start (on-going)	Can not confirm washout prior to surgery or use during 7-day post-op period.

Violations of Study Treatment Regimen

There were 2 patients in the ketorolac group and the 9 patients in the vehicle group who took masked medications at variance with the protocol specified regimen: one drop, q.i.d., on days 0 - 3. No data were excluded from the analysis due to these minor violations.

Patients Using Prohibited Medications

Six patients in the vehicle group and one patient in the ketorolac group took additional prohibited medications while taking masked medication.

Prohibited Medications Used While Taking Masked Medication

Treatment	Patient	Medication	Start Date	Comment
Ketorolac	204	Hydrocodone 500 mg.	11/13/95	Pt used for pain, OS. Masked medication last used on 11/14/95
Vehicle	321	Darvocet-N Vicodin	10/11/95	Pt used for pain, OU. Masked medication last used on 10/13/95
Vehicle	324	Vicodin	10/25/95	Pt used for pain, OU. Masked medication last used 10/27/95
Vehicle	707	Tylenol #3 Acular	11/2/95	Pt used for pain, OS. Masked medication last used on 11/3/95
Vehicle	715	Tylenol ES	11/16/95	Pt used to help sleep. Masked medication last used on 11/17/95
Vehicle	722	Tylenol #3	1/11/96	Pt used for pain, OD. Masked medication last used 1/12/96
Vehicle	738	Tylenol #3	4/29/96	Pt used for pain, OS. Masked medication last used on 4/30/96

Twenty-one ketorolac-treated patients and 16 vehicle-treated patients took prohibited medications after discontinuing masked medication but during the first 7 days following surgery.

Efficacy Measures - same as Study #1

Pain Intensity[a]: Mean Score

Time Period		Ketorolac	Vehicle	P-value[b]	Interaction P-value[c] By Site	By Sex	By Age	By Iris Color
1 Hour	N	78	81	0.093	0.685	0.455	0.954	0.583
Mean		1.3	1.8					
Min								
Max								
3 Hours	N	75	73	<0.001	0.282	0.892	0.556	0.191
Mean		2.0	3.2					
Min								
Max								
4 Hours	N	72	70	<0.001	0.182	0.798	0.523	0.106
Mean		1.7	3.1					
Min								
Max								
7-12 Hours	N	72	74	<0.001	0.275	0.816	0.762	0.213
Mean		1.7	2.7					
Min								
Max								
13-18 Hours	N	49	33	0.616	0.040	0.990	0.172	0.140
Mean		1.8	1.6					
Min								
Max								
19-24 Hours	N	80	77	0.093	0.057	0.913	0.448	0.911
Mean		1.4	1.7					
Min								
Max								
25-30 Hours	N	73	74	0.033	0.057	0.949	0.637	0.819
Mean		0.8	1.3					
Min								
Max								
31-36 Hours	N	68	69	0.033	0.249	0.298	0.567	0.508
Mean		0.6	1.1					
Min								
Max								
37-42 Hours	N	60	47	0.611	0.188	0.445	0.203	0.727
Mean		0.4	0.5					
Min								
Max								
43-48 Hours	N	72	72	0.190	0.407	0.999	0.906	0.508
Mean		0.3	0.5					
Min								
Max								

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[b] P-value for between-treatment comparisons analyzed by Kruskal-Wallis tests.
[c] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Pain Intensity[a]: Mean Score

Time Period		Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age	By Iris Color
49-54 Hours	N	64	69	0.004	0.590	0.978	0.839	0.677
Mean		0.1	0.4					
Min								
Max								
55-60 Hours	N	63	65	0.064	0.681	0.912	0.504	0.485
Mean		0.0	0.3					
Min								
Max								
61-66 Hours	N	62	58	0.145	0.716	0.210	0.210	0.450
Mean		0.0	0.1					
Min								
Max								
67-72 Hours	N	64	68	0.098	0.744	0.967	0.742	0.587
Mean		0.0	0.2					
Min								
Max								
>72 Hours	N	67	63	0.963	0.379	0.320	0.965	0.393
Mean		0.0	0.0					
Min								
Max								

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[c] P-value for between-treatment comparisons analyzed by Kruskal-Wallis tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Reviewer's Comment: *The means for pain intensity, though numerically less at all timepoints for ketorolac, evidence clinical significance was not demonstrated and statistically significant differences occurred only within the first 12 hours.*

Pain Intensity[a]: Incidence No Pain

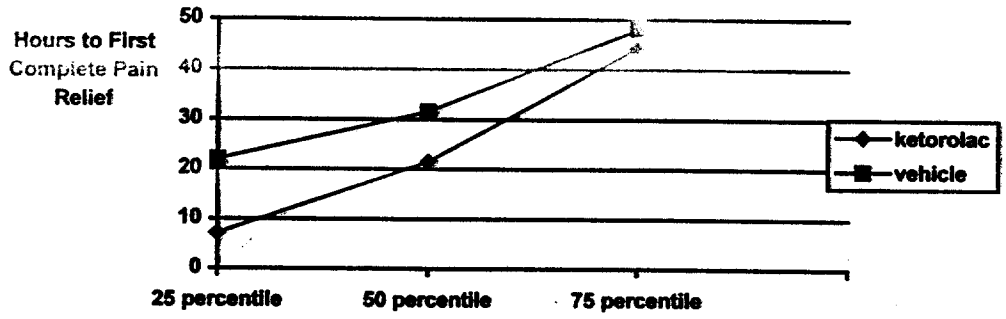
Time Period	Ketorolac Overall=83 N/Total[b] (%)	Vehicle Overall=87 N/Total[b] (%)	P-value[c]
1 Hour	19/78 (24.4%)	18/81 (22.2%)	0.750
3 Hours	9/75 (12.0%)	5/73 (6.8%)	0.284
4 Hours	16/72 (22.2%)	6/70 (8.6%)	0.025
7-12 Hour	14/72 (19.4%)	8/74 (10.8%)	0.145
13-18 Hours	13/49 (26.5%)	11/33 (33.3%)	0.507
19-24 Hours	31/80 (38.8%)	24/77 (31.2%)	0.320
25-30 Hours	40/73 (54.8%)	33/74 (44.6%)	0.216
31-36 Hours	44/68 (64.7%)	33/69 (47.8%)	0.046
37-42 Hours	45/60 (75.0%)	34/47 (72.3%)	0.756
43-48 Hours	60/72 (83.3%)	54/72 (75.0%)	0.218
49-54 Hours	61/64 (95.3%)	54/69 (78.3%)	0.004
55-60 Hours	60/63 (95.2%)	56/65 (86.2%)	0.078
61-66 Hours	61/62 (98.4%)	54/58 (93.1%)	0.148
67-72 Hours	62/64 (96.9%)	61/68 (89.7%)	0.102
>72 Hours	65/67 (97.0%)	61/63 (96.8%)	>0.999

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[b] Non-missing total at each time period.
[c] P-value for between-treatment comparisons analyzed by Chi-square or Fisher's exact tests.

Time (Hour) to First No Pain Intensity[a]: Survival Analysis Point Estimates

Statistics	Ketorolac	Vehicle	P-value[b]
Total	83	85	0.004
Mean	26.0	35.2	
S.E.M.	2.2	2.3	
25% percentile	7.1	22.0	
50% percentile (Median)	21.5	31.6	
75% percentile	44.2	47.9	
Censored[c]	15	21	

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. Scores from the first 1.5 hours were ignored due to the effect of anesthetic.
[b] Estimated by Kaplan-Meier method.
[c] Censored patients are those with pain data who never record a score of no pain.



Reviewer's Comment: *The time to first" no pain" is less impressive in this study than in Study 105. The incidence of patients reporting no pain is however greater at all timepoints for ketorolac.*

Pain Relief[a]: Mean Score

Time Period		Ketorolac	Vehicle	P-value[b]	Interaction P-value[c] By Site	By Sex	By Age	By Iris Color
1 Hour	N	76	81	0.901	0.496	0.485	0.186	0.081
Mean		5.4	5.3					
Min								
Max								
3 Hours	N	75	71	<0.001	0.725	0.504	0.784	0.953
Mean		4.7	3.0					
Min								
Max								
4 Hours	N	69	68	<0.001	0.516	0.371	0.800	0.532
Mean		3.9	2.1					
Min								
Max								
7-12 Hours	N	70	71	<0.001	0.444	0.936	0.279	0.724
Mean		4.1	2.3					
Min								
Max								
13-18 Hours	N	44	29	0.404	0.177	0.660	0.336	0.466
Mean		3.9	3.5					
Min								
Max								
19-24 Hours	N	70	67	0.069	0.117	0.508	0.478	0.866
Mean		3.9	3.2					
Min								
Max								
25-30 Hours	N	63	68	0.018	0.551	0.706	0.200	0.659
Mean		4.6	3.7					
Min								
Max								
31-36 Hours	N	58	63	0.001	0.291	0.766	0.470	0.462
Mean		5.2	3.9					
Min								
Max								
37-42 Hours	N	50	40	0.201	0.531	0.923	0.531	0.506
Mean		5.3	4.8					
Min								
Max								
43-48 Hours	N	59	61	0.065	0.637	0.844	0.747	0.393
Mean		5.5	4.7					
Min								
Max								

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] P-value for between-treatment comparisons analyzed by Kruskal-Wallis tests.
[c] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Pain Relief[a]: Mean Score

Time Period		Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age	By Iris Color
49-54 Hours	N	49	58	0.006	0.490	0.076	0.576	0.868
	Mean	5.9	5.2					
	Min							
	Max							
55-60 Hours	N	47	54	0.013	0.904	0.545	0.682	0.783
	Mean	6.0	5.3					
	Min							
	Max							
61-66 Hours	N	47	46	0.077	0.837	0.272	0.397	0.260
	Mean	6.0	5.8					
	Min							
	Max							
67-72 Hours	N	48	55	0.042	0.623	0.881	0.285	0.789
	Mean	6.0	5.5					
	Min							
	Max							
>72 Hours	N	51	51	0.989	0.186	0.200	0.401	0.420
	Mean	6.0	5.9					
	Min							
	Max							

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Kruskal-Wallis tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Reviewer's Comment: *There is a statistically significant difference between the treatment groups in half of timepoints out to 36 hours. A clinically significant difference however is not present.*

Pain Relief[a]: Incidence Complete

Time Period	Ketorolac Overall=83 N/Total[b] (%)	Vehicle Overall=87 N/Total[b] (%)	P-value[c]
1 Hour	58/76 (76.3%)	63/81 (77.8%)	0.828
3 Hours	43/75 (57.3%)	24/71 (33.8%)	0.004
4 Hours	20/69 (29.0%)	8/68 (11.8%)	0.012
7-12 Hours	24/70 (34.3%)	9/71 (12.7%)	0.002
13-18 Hours	14/44 (31.8%)	8/29 (27.6%)	0.700
19-24 Hours	24/70 (34.3%)	16/67 (23.9%)	0.181
25-30 Hours	33/63 (52.4%)	25/68 (36.8%)	0.072
31-36 Hours	39/58 (67.2%)	27/63 (42.9%)	0.007
37-42 Hours	38/50 (76.0%)	26/40 (65.0%)	0.253
43-48 Hours	46/59 (78.0%)	40/61 (65.6%)	0.132
49-54 Hours	47/49 (95.9%)	45/58 (77.6%)	0.007
55-60 Hours	46/47 (97.9%)	45/54 (83.3%)	0.015
61-66 Hours	47/47 (100.0%)	43/46 (93.5%)	0.075
67-72 Hours	47/48 (97.9%)	48/55 (87.3%)	0.044
>72 Hours	50/51 (98.0%)	50/51 (98.0%)	>0.999

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] Non-missing total at each time period.
[c] P-value for between-treatment comparisons analyzed by Chi-square or Fisher's exact tests.

Reviewer's Comment: *There were only a few statistically significant time points in this study for comparisons of the incidence of complete pain relief of the treatment groups.*

APPEARS THIS WAY
ON ORIGINAL

Time (Hour) to First Complete Pain Relief[a]: Survival Analysis Point Estimates

Statistics	Ketorolac	Vehicle	P-value[b]
Total	**83**	**85**	**0.015**
Mean	**35.5**	**44.0**	
S.E.M.	2.6	2.7	
25% percentile	19.8	24.9	
50% percentile (Median)	31.4	44.6	
75% percentile	**47.8**	**68.1**	
Censored[c]	**16**	**24**	

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Complete: complete or no pain. Scores from the first 1.5 hours were ignored due to the effect of anesthetic.
[b] Estimated by Kaplan-Meier method.
[c] Censored patients are those with pain data who never record a score of no pain.

First Acetaminophen Escape Medication Use: Incidence at Each Hour[a]

	Ketorolac Overall=83	Vehicle Overall=87
Time Period	N (%)	N (%)
30 Minutes	0 (0.0%)	4 (4.6%)
1 Hour	5 (6.0%)	9 (10.3%)
2 Hours	1 (1.2%)	14 (16.1%)
3 Hours	3 (3.6%)	11 (12.6%)
4 Hours	8 (9.6%)	15 (17.2%)
7-12 Hour	6 (7.2%)	4 (4.6%)
13-18 Hours	3 (3.6%)	3 (3.4%)
19-24 Hours	2 (2.4%)	2 (2.3%)
25-30 Hours	2 (2.4%)	2 (2.3%)
31-36 Hour	0 (0.0%)	1 (1.1%)
37-42 Hours	0 (0.0%)	1 (1.1%)
43-48 Hours	0 (0.0%)	0 (0.0%)
49-54 Hours	0 (0.0%)	0 (0.0%)
55-60 Hour	0 (0.0%)	0 (0.0%)
61-66 Hours	0 (0.0%)	0 (0.0%)
67-72 Hours	0 (0.0%)	0 (0.0%)
>72 Hours	0 (0.0%)	0 (0.0%)
Not Taken	53 (63.9%)	21 (24.1%)

[a] There are inconsequential differences among tables 14-19 that have been left as is:
1) One Ketorolac patient (#204) did not record the time of first acetaminophen use and is not counted on tables 15.
2) One vehicle patient (#731) who did take acetaminophen is missclassified in tables 16-19 because the number of capsules taken were not recorded.

Reviewer's Comment: *After the first 12 hours, the incidence of the use of acetaminophen for pain relief was essentially equal in the treatment groups.*

Patients Awakened by Pain, Incidence

	Ketorolac Overall=83		Vehicle Overall=87		
Time Period	N/Total[a]	(%)	N/Total[a]	(%)	P-value[b]
4-hour Post	5/81	(6.2%)	6/84	(7.1%)	0.352
Day 1	19/83	(22.9%)	21/87	(24.1%)	0.848
Day 2	0/45	(0.0%)	4/52	(7.7%)	0.121
Day 3	0/11	(0.0%)	2/23	(8.7%)	>0.999

[a] Non-missing total at each time period.
[b] P-value for between-treatment comparisons analyzed by chi-square or Fisher's exact tests.

Required Topical Anesthetic to Open the Surgical Eye, Incidence

Time Period	Ketorolac Overall=83 N/Total[a]	(%)	Vehicle Overall=87 N/Total[a]	(%)	P-value[b]
Day 1	2/83	(2.4%)	12/87	(13.8%)	0.007
Day 2	0/45	(0.0%)	1/52	(1.9%)	>0.999
Day 3	0/11	(0.0%)	0/23	(0.0%)	>0.999

[a] Non-missing total at each time period.
[b] P-value for between-treatment comparisons analyzed by chi-square or Fisher's exact tests.

Reviewer's Comment: *There was a significant difference for this secondary efficacy measure only on Day 1.*

Foreign Body Sensation: Incidence Moderate or Greater

Time Period	Ketorolac Overall=83 N/Total[b]	(%)	Vehicle Overall=87 N/Total[b]	(%)	P-value[c]
Pre-op	0/83	(0.0%)	0/87	(0.0%)	>0.999
4-hour Post	20/81	(24.7%)	43/84	(51.2%)	<0.001
Day 1	16/83	(19.3%)	21/87	(24.1%)	0.443
Day 2	0/46	(0.0%)	6/52	(11.5%)	0.028
Day 3	0/11	(0.0%)	3/23	(13.0%)	0.535
Day 4	1/3	(33.3%)	0/2	(0.0%)	N/A
Day 5	2/6	(33.3%)	0/7	(0.0%)	N/A
Day 6	2/5	(40.0%)	0/2	(0.0%)	N/A
Day 7	6/81	(7.4%)	2/84	(2.4%)	0.163

[a] 0-4 Scale for None, Trace, Mild, Moderate, Severe.
[b] Non-missing total at each time period.
[c] P-value for between-treatment comparisons analyzed by chi-square or Fisher's exact tests.

Photophobia: Incidence Moderate or Greater

Time Period	Ketorolac Overall=83 N/Total[b]	(%)	Vehicle Overall=87 N/Total[b]	(%)	P-value[c]
Pre-op	2/83	(2.4%)	2/87	(2.3%)	>0.999
4-hour Post	28/81	(34.6%)	54/84	(64.3%)	<0.001
Day 1	25/83	(30.1%)	44/87	(50.6%)	0.007
Day 2	8/46	(17.4%)	18/52	(34.6%)	0.054
Day 3	3/11	(27.3%)	8/23	(34.8%)	>0.999
Day 4	1/3	(33.3%)	2/2	(100.0%)	N/A
Day 5	6/6	(100.0%)	3/7	(42.9%)	N/A
Day 6	5/5	(100.0%)	0/2	(0.0%)	N/A
Day 7	31/81	(38.3%)	26/84	(31.0%)	0.323

[a] 0-4 Scale for None, Trace, Mild, Moderate, Severe.
[b] Non-missing total at each time period.
[c] P-value for between-treatment comparisons analyzed by chi-square or Fisher's exact tests.

Burning/Stinging: Incidence Moderate or Greater

Time Period	Ketorolac Overall=83 N/Total[b] (%)	Vehicle Overall=87 N/Total[b] (%)	P-value[c]
Pre-op	0/83 (0.0%)	0/87 (0.0%)	>0.999
4-hour Post	17/81 (21.0%)	41/84 (48.8%)	<0.001
Day 1	12/83 (14.5%)	18/87 (20.7%)	0.287
Day 2	1/46 (2.2%)	3/52 (5.8%)	0.620
Day 3	0/11 (0.0%)	1/23 (4.3%)	>0.999
Day 4	1/3 (33.3%)	0/2 (0.0%)	N/A
Day 5	3/6 (50.0%)	0/7 (0.0%)	N/A
Day 6	1/5 (20.0%)	0/2 (0.0%)	N/A
Day 7	10/81 (12.3%)	4/84 (4.8%)	0.098

[a] 0-4 Scale for None, Trace, Mild, Moderate, Severe.
[b] Non-missing total at each time period.
[c] P-value for between-treatment comparisons analyzed by chi-square or Fisher's exact tests.

Tearing: Incidence Moderate or Greater

Time Period	Ketorolac Overall=83 N/Total[b] (%)	Vehicle Overall=87 N/Total[b] (%)	P-value[c]
Pre-op	0/83 (0.0%)	0/87 (0.0%)	>0.999
4-hour Post	27/81 (33.3%)	60/84 (71.4%)	<0.001
Day 1	17/83 (20.5%)	33/87 (37.9%)	0.013
Day 2	2/46 (4.3%)	5/51 (9.8%)	0.440
Day 3	1/11 (9.1%)	4/23 (17.4%)	>0.999
Day 4	0/3 (0.0%)	0/2 (0.0%)	N/A
Day 5	2/6 (33.3%)	1/7 (14.3%)	N/A
Day 6	4/5 (80.0%)	0/2 (0.0%)	N/A
Day 7	6/81 (7.4%)	4/84 (4.8%)	0.530

[a] 0-4 Scale for None, Trace, Mild, Moderate, Severe.
[b] Non-missing total at each time period.
[c] P-value for between-treatment comparisons analyzed by chi-square or Fisher's exact tests.

Reviewer's Comment: *For the preceding study parameters of foreign body sensation, photophobia, burning/stinging, and tearing the incidence was less in the early post-operative period for ketorolac.*

Safety Measures

Safety measures evaluated by the sponsor included adverse events, wound healing progression, visual acuity (Regan; corrected and uncorrected), refraction (manifest and cycloplegic), biomicroscopy (without pupil dilation), endothelial cell density

Adverse Events :

There were three patients in the ketorolac group and two patients in the vehicle group were terminated due to adverse events.

Patients with Any Adverse Event[a]

Category	Body System	Ketorolac (overall=83) N(%)	Vehicle (overall=87) N(%)	Total (overall=170) N(%)
Overall	Any	22 (26.5%)	14 (16.1%)	36 (21.2%)
	Ocular	20 (24.1%)	11 (12.6%)	31 (18.1%)
	Systemic	3 (3.6%)	3 (3.4%)	6 (3.5%)
Ocular	Eye Lid Edema	1 (1.2%)	1 (1.1%)	2 (1.2%)
	Conjunctivitis Allergic	1 (1.2%)	1 (1.1%)	2 (1.2%)
	Corneal Infiltrate	2 (2.4%)	0 (0.0%)	2 (1.2%)
	Keratitis	1 (1.2%)	1 (1.1%)	2 (1.2%)
	Keratoconjunctivitis Allergic	1 (1.2%)	0 (0.0%)	1 (0.6%)
	Eye Dryness	0 (0.0%)	1 (1.1%)	1 (0.6%)
	Eye Trauma	2 (2.4%)	0 (0.0%)	2 (1.2%)
	Pruritis Eye	0 (0.0%)	1 (1.1%)	1 (0.6%)
	Inflammation Eye	10 (12.0%)	4 (4.6%	14 (8.2%)
	Burning Sensation in Eye	0 (0.0%)	1 (1.1%)	1 (0.6%)
	Iritis	3 (3.6%)	1 (1.1%)	4 (2.4%)
Systemic	Sinus Headache	0 (0.0%)	1 (1.1%)	1 (0.6%)
	Neck Pain	0 (0.0%)	1 (1.1%)	1 (0.6%)
	Syncope	1 (1.2%)	0 (0.0%)	1 (0.6%)
	Dyspepsia	0 (0.0%)	1 (1.1%)	1 (0.6%)
	Rash	1 (1.2%)	0 (0.0%)	1 (0.6%)
	Urinary Tract Infection	1 (1.2%)	0 (0.0%)	1 (0.6%)

[a] Patients with multiple adverse events appear more than once in this table, once for each relevant reaction term.
[b] P-value for between-treatment comparisons by chi-square or Fisher's exact tests.

Overall, during the study, 26.5% (22/83) of the patients treated with ketorolac and 16.1% (14/87) of the patients treated with vehicle experienced adverse events. Of note is that one site reported 41.6% [15/36] of the total adverse events. There were three adverse events in the ketorolac group and five in the vehicle group which were considered related to treatment.

Wound healing progression

Wound Healing and Complications

Study Day: 1

Variable	Ketorolac (overall=83) N/total (%)	Vehicle (overall=87) N/total (%)	P-value
Healing as expected	75 (90.4%)	81 (93.1%)	0.52
Gaping of incisions	1 (1.2%)	1 (1.1%)	0.99
Exudate from incisions	0 (0.0%)	0 (0.0%)	0.99
Raised epithelial ridges	0 (0.0%)	2 (2.3%)	0.50
Thin epithelium covering	4 (4.8%)	4 (4.6%)	0.99
Epithelial cysts	0 (0.0%)	0 (0.0%)	0.99
Persistent epithelial plugs	0 (0.0%)	0 (0.0%)	0.99
Other epithelial cell changes	1 (1.2%)	1 (1.1%)	0.99
Bowman's membrane changes	0 (0.0%)	0 (0.0%)	0.99
Stromal changes	3 (3.6%)	1 (1.1%)	0.36
Endothelial changes	0 (0.0%)	0 (0.0%)	0.99
Other[c]	1 (1.2%)	0 (0.0%)	0.49

Study Day: 7

Variable	Ketorolac (overall=82) N/total (%)	Vehicle (overall=84) N/total (%)	P-value
Healing as expected	75 (91.5%)	82 (97.6%)	0.10
Gaping of incisions	0 (0.0%)	0 (0.0%)	0.99
Exudate from incisions	0 (0.0%)	0 (0.0%)	0.99
Raised epithelial ridges	1 (1.2%)	0 (0.0%)	0.49
Thin epithelium covering	3 (3.7%)	0 (0.0%)	0.12
Epithelial cysts	0 (0.0%)	0 (0.0%)	0.99
Persistent epithelial plugs	0 (0.0%)	0 (0.0%)	0.99
Other epithelial cell changes	4 (4.9%)	1 (1.2%)	0.21
Bowman's membrane changes	0 (0.0%)	0 (0.0%)	0.99
Stromal changes	2 (2.4%)	0 (0.0%)	0.24
Endothelial changes	0 (0.0%)	0 (0.0%)	0.99
Other[c]	0 (0.0%)	2 (2.4%)	0.50

In this study, investigators were asked whether wound healing progressed as expected. When the data for days 1 to 7 were analyzed, there were no significant differences between the treatment groups in wound healing except on day 2, where vehicle-treated patients were favored (p=0.024).

Reviewer's Comment: *At day 7, a larger percentage of patients in the vehicle group have "healed as expected" than in the ketorolac group.*

Visual Acuity (best corrected)

Visual Acuity[a]: Best Corrected: Mean Score

Study Day	Statistics[b]	Ketorolac	Vehicle	P-value [b]
Pre-op	N	83	87	0.60
	Mean	8.3	8.5	
	Min			
	Max			
Day 7	N	76	78	0.76
	Mean	8.9	8.8	
	Min		5	
	Max			

[a] 0-11 Scale for 20/126, 20/100, 20/80, 20/63, 20/50, 20/40, 20/32, 20/25, 20/20, 20/16, 20/13 and 20/10.
[b] P-value for between-treatment comparisons analyzed by the Wilcoxon-Mann-Whitney rank sum test.

Additionally, corrected visual acuity was reviewed for eight patients who had less than expected wound healing at day 7. When the corrected visual acuity of these patients was examined, all achieved visual acuity equal to or better than 20/20 (Snellen).

Biomicroscopy (without pupil dilation)

The incidence of differences between the study groups in biomicroscopic variables graded as mild or greater were for lid erythema, lid edema, and conjunctival erythema, all of which favoring ketorolac.

9 Overview of Efficacy

Two controlled clinical studies (KETO-105-8718 and KETO-106-8718) were submitted in this supplement evaluate the ocular safety and efficacy of nonpreserved ketorolac solution compared with its vehicle in reducing ocular pain in patients who had undergone radial keratotomy surgery.

Both studies were randomized, multicenter, double-masked, parallel-group clinical trials. Patients were randomized to receive nonpreserved ketorolac (50%) or vehicle (50%) in blocks of four.

A total of 340 patients participated in the two studies with 170 patients participating in KETO-105-8718 and 170 in KETO-106-8718. As had been previously agreed with the Agency, data submitted evaluated the first 7 days of these studies; a subsequent report will evaluate follow-up, year-long safety data.

Of the 340 patients enrolled in both studies, 309 (90.9%) completed the studies, 23 (6.8%) were terminated from the studies due to lack of efficacy and 5 (1.5%) due to adverse events. Three patients (0.9%) were discontinued due to administrative reasons.

Patient ages ranged from 18 to 61 years of age with a mean of 38.6 years with patients significantly older (approximately 2 years) in the vehicle-treated group ($p=0.038$). Slightly more women participated in the studies than men (57.1% [194/340] vs 42.9% [146/340]). The large majority of the study population was Caucasian (92.1%, 313/340).

The study had patients receive one drop of either nonpreserved ketorolac solution or vehicle, four times daily, starting immediately after RK surgery and continuing until patients either had no ocular pain or reached 3 days after surgery.

The primary efficacy variables, pain intensity and pain relief, were evaluated in the first few hours after surgery and during the following 3 days or until no pain was perceived. Secondary variables included use of escape medication (acetaminophen), symptoms of general discomfort (quality of sleep, headache, nausea, level of fatigue), and symptoms of ocular discomfort (difficulty in opening the surgical eye without anesthesia, foreign body sensation, photophobia, burning/stinging, tearing, itching).

The sponsor also evaluated quality of life measures (reading a newspaper or magazine, telling time from a wristwatch, watching television, recognizing people across a room, seeing traffic signs and signals, seeing steps, spending time in a well-lighted room, spending time outside in daylight). These measures were only minimally helpful in assessing the clinical efficacy for these studies.

The statistical analysis performed for both studies was an intent-to-treat analysis. Differences between the ketorolac and vehicle groups of ≥ 2.0 unit represented clinically significant findings indicating efficacy and were adequately sized to provide statistical power to detect such differences.

Pain Intensity[a]: Mean Scores KETO-105-8718 and KETO-106-8718

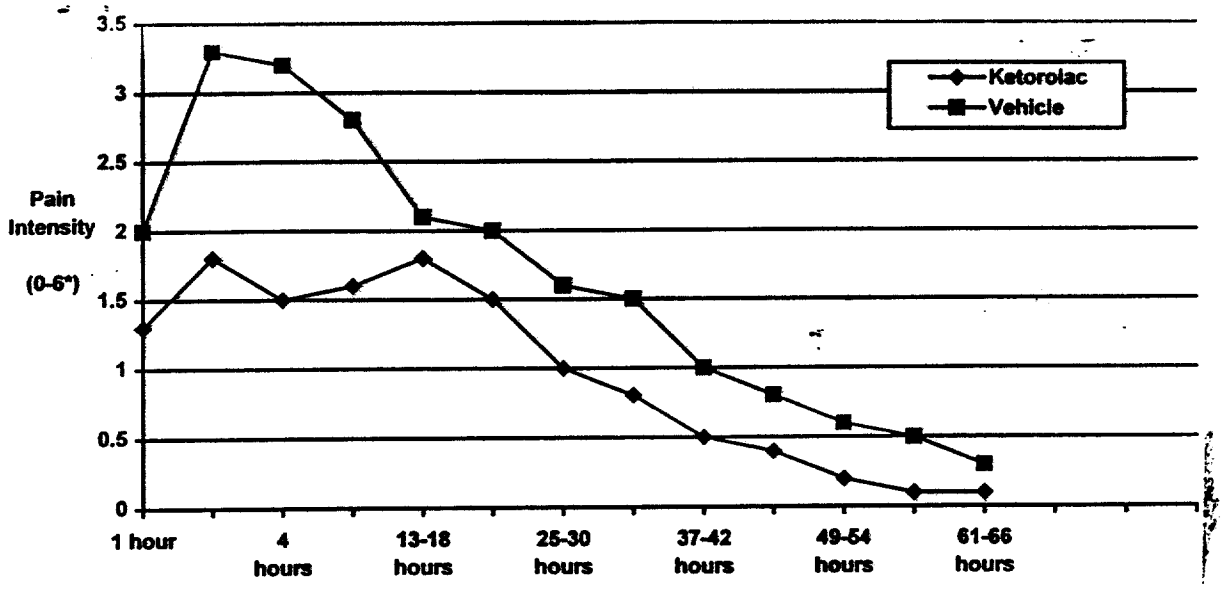
Pain intensity scores were lower in the ketorolac-treated group than in the vehicle-treated group for the 72-hour period evaluated.

				Interaction P-value[d]			
Time Period	Ketorolac	Vehicle	P-value[c]	By Site	By Sex	By Age	By Iris Color
30 Minutes	81	82	0.019	0.084	0.564	0.059	0.572
Mean	0.8	1.3					
1 Hour	160	160	<0.001	0.555	0.208	0.515	0.828
Mean	1.3	2.0					
2 Hours	77	78	<0.001	0.587	0.049	0.653	0.334
Mean	1.6	3.1					
3 Hours	153	145	<0.001	0.256	0.266	0.605	0.628
Mean	1.8	3.3					
4 Hours	142	139	<0.001	0.283	0.172	0.855	0.563
Mean	1.5	3.2					
7-12 Hours	144	144	<0.001	0.332	0.597	0.884	0.451
Mean	1.6	2.8					
13-18 Hours	103	79	0.182	0.037	0.130	0.964	0.304
Mean	1.8	2.1					
19-24 Hours	158	151	0.003	0.206	0.894	0.576	0.870
Mean	1.5	2.0					
25-30 Hours	138	143	<0.001	0.195	0.422	0.397	0.453
Mean	1.0	1.6					
31-36 Hours	127	137	<0.001	0.203	0.771	0.236	0.853
Mean	0.8	1.5					
37-42 Hours	107	88	0.017	0.083	0.930	0.389	0.017
Mean	0.5	1.0					
43-48 Hours	132	138	0.005	0.135	0.504	0.633	0.531
Mean	0.4	0.8					

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[b] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[c] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Reviewer's Comment: *Though statistically significant at most timepoints, a clinically meaningful difference for pain intensity is present only up to 4 hours post operatively.*

Pain Intensity Following Radial Keratectomy



*(0-6) Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.

Reviewer's Comment: *The effect on pain intensity by the active agent is greatest in the first 12 hours following the procedure.*

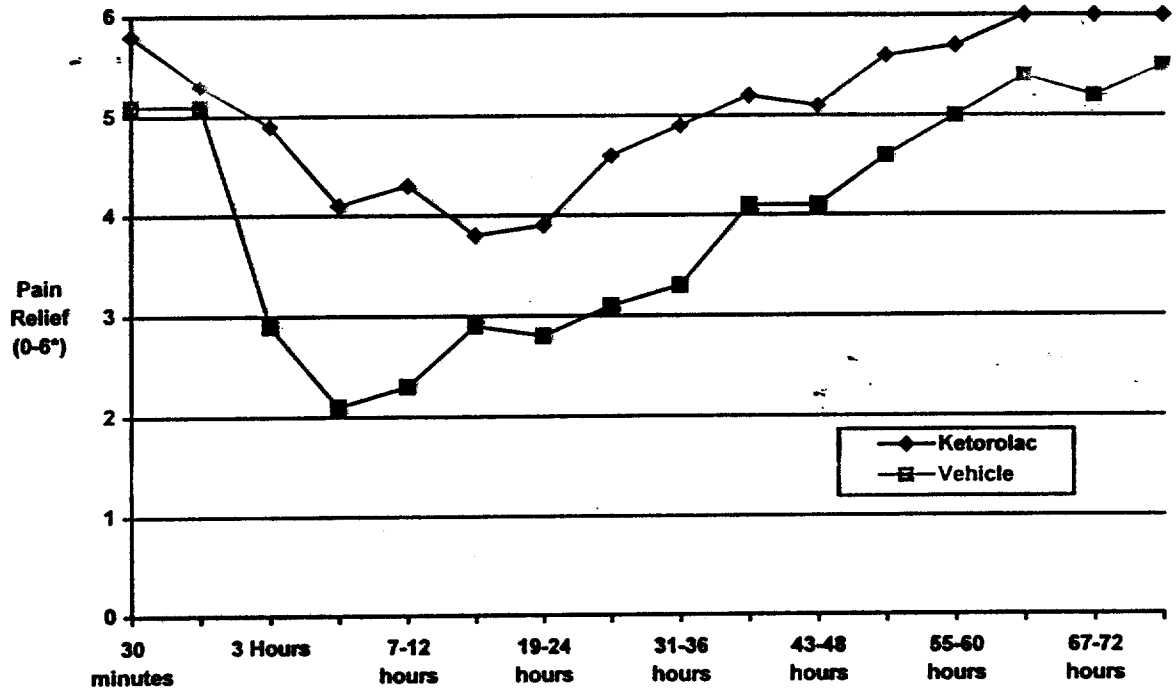
Pain Relief: Mean Score KETO-105-8718 and KETO-106-8718

Pain relief was greater in the ketorolac-treated group than in the vehicle-treated group for the entire 72-hour period evaluated. This difference was both clinically (mean difference ≥ 2 units) and statistically significant at all time periods from 3 to 12 hours. The difference was statistically significant at most time periods from hours 2 to 72.

Time Period	Ketorolac		Vehicle		P-value[c]	Interaction P-value[d] By Site	By Sex	By Age	By Iris Color
30 Minutes	80		82		0.077	<0.001	0.211	0.710	0.554
Mean		5.8		5.1					
1 Hour	158		161		0.618	0.022	0.494	0.838	0.648
Mean		5.3		5.1					
2 Hours	74		78		<0.001	0.178	0.533	0.032	0.839
Mean		5.2		3.4					
3 Hours	153		143		<0.001	0.602	0.714	0.211	0.716
Mean		4.9		2.9					
4 Hours	138		137		<0.001	0.835	0.638	0.908	0.906
Mean		4.1		2.1					
7-12 Hours	143		140		<0.001	0.721	0.467	0.334	0.965
Mean		4.3		2.3					
13-18 Hours	94		73		0.013	0.215	0.319	0.538	0.397
Mean		3.8		2.9					
19-24 Hours	142		140		<0.001	0.053	0.901	0.427	0.713
Mean		3.9		2.8					
25-30 Hours	131		136		<0.001	0.033	0.821	0.367	0.469
Mean		4.6		3.1					
31-36 Hours	119		131		<0.001	0.104	0.740	0.507	0.654
Mean		4.9		3.3					
37-42 Hour	95		77		0.001	0.110	0.104	0.236	0.224
Mean		5.2		4.1					
43-48 Hours	117		122		0.001	0.704	0.152	0.617	0.132
Mean		5.1		4.1					
49-54 Hours	103		113		<0.001	0.754	0.002	0.619	0.460
Mean		5.6		4.6					
55-60 Hours	99		103		0.002	0.537	0.126	0.303	0.673
Mean		5.7		5.0					
61-66 Hours	95		83		0.019	0.595	0.320	0.086	0.207
Mean		6.0		5.4					
67-72 Hours	100		105		<0.001	0.555	0.108	0.947	0.235
Mean		6.0		5.2					
>72 Hours	101		99		0.014	0.450	0.012	0.311	0.011
Mean		6.0		5.5					

0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[c] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Pain Relief Following Radial Keratectomy



* 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward

Reviewer's Comment: *A clinically meaningful difference of two units is present from the 3 through 12 hour period post-operatively. A statistically significant difference is present at most timepoints. Though pain relief is always greater at the timepoints studied for ketorolac, there is a noticeable leveling of effect at the later timepoints relative to the vehicle.*

Terminations Due to Lack of Efficacy

	Ketorolac Group	Vehicle Group	
KETO-105-8718	1/86 (1.2%)	12/84 (14.3%)	
KETO-106-8718	2/83 (2.4%)	8/87 (9.2%)	
Total	3/169 (1.8%)	20/171 (11.7%)	($p \leq 0.001$).

Fewer patients were terminated due to lack of efficacy due to intolerable pain in the ketorolac group. More patients in the ketorolac group (73.3%, 63/86 [KETO-105-8718]; 62.7%, 52/83 [KETO-106-8718]) than in the vehicle group (26.5%. 22/83 [KETO-105-8718]; 24.1%, 21/87 [KETO-106-8718]) never had to use acetaminophen as an escape medication during the study.

Symptoms of Ocular Discomfort

	Study Number	4-Hours Postop	Day 1	Day 2
		P-values		
Foreign Body Sensation	KETO-105	≤0.001	0.126	0.631
	KETO-106	≤0.001	0.443	0.028
Photophobia	KETO-105	≤0.001	≤0.001	0.003
	KETO-106	≤0.001	0.007	0.054
Burning/stinging	KETO-105	≤0.001	0.008	0.472
	KETO-106	≤0.001	0.287	0.620
Tearing	KETO-105	≤0.001	0.296	0.024
	KETO-106	≤0.001	0.013	0.440

Reviewer's Comment: *There is a statistically significant effect in both studies only for photophobia in the first two days post operatively.*

10 Overview of Safety

The submitted studies evidenced a tendency toward slower healing in the eyes treated with ketorolac than those treated with vehicle.

Wound Healing and Complications (Day 1)
KETO-105-8718 and KETO-106-8718

Variable	Ketorolac (overall=168) N/total[a] (%)	Vehicle (overall=169) N/total (%)	P-value
Healing as expected	147 (87.5%)	152 (89.9%)	0.48
Gaping of incisions	1 (0.6%)	2 (1.2%)	>0.99
Exudate from incisions	0 (0.0%)	0 (0.0%)	>0.99
Raised epithelial ridges	1 (0.6%)	5 (3.0%)	0.22
Thin epithelium covering	9 (5.4%)	8 (4.7%)	0.79
Epithelial cysts	0 (0.0%)	0 (0.0%)	>0.99
Persistent epithelial plugs	0 (0.0%)	0 (0.0%)	>0.99
Other epithelial cell changes	3 (1.8%)	4 (2.4%)	>0.99
Bowman's membrane changes	0 (0.0%)	0 (0.0%)	>0.99
Stromal changes	7 (4.2%)	1 (0.6%)	0.04
Endothelial changes	0 (0.0%)	1 (0.6%)	>0.99
Other	3 (1.8%)	0 (0.0%)	0.12

(Day 7)

Variable	(overall=166) N/total (%)	(overall=164) N/total (%)	P-value
Healing as expected	147 (88.6%)	156 (95.1%)	0.03
Gaping of incisions	3 (1.8%)	4 (2.4%)	0.72
Exudate from incisions	0 (0.0%)	0 (0.0%)	>0.99
Raised epithelial ridges	1 (0.6%)	0 (0.0%)	>0.99
Thin epithelium covering	3 (1.8%)	1 (0.6%)	0.62
Epithelial cysts	0 (0.0%)	0 (0.0%)	>0.99
Persistent epithelial plugs	0 (0.0%)	0 (0.0%)	>0.99
Other epithelial cell changes	11 (6.6%)	2 (1.2%)	0.02
Bowman's membrane changes	0 (0.0%)	0 (0.0%)	>0.99
Stromal changes	4 (2.4%)	0 (0.0%)	0.12
Endothelial changes	0 (0.0%)	0 (0.0%)	0.99
Other	0 (0.0%)	2 (1.2%)	0.25

[a] Non-missing total.

Visual Acuity[a]: Uncorrected: Mean Score

KETO-105-8718 and KETO-106-8718

Study Day		Ketorolac	Vehicle	P-value [c]	Interaction P-value[d] Site	Sex	Age	Iris-Color
Pre-op	N	168	170	0.701	0.522	0.010	0.067	0.800
	Mean	0.7	0.8					
	S.E.M.	0.13	0.14					
	Min	0	0					
	Max	7	9					
Day 7	N	162	159	0.479	0.787	0.307	0.266	0.214
	Mean	7.3	7.1					
	S.E.M.	0.17	0.18					
	Min	0	0					
	Max	10	10					

[a] 0-11 Scale for 20/126, 20/100, 20/80, 20/63, 20/50, 20/40, 20/32, 20/25, 20/20, 20/16, 20/13 and 20/10.
[b] S.E.M. - standard error of mean.
[c] P-value for between-treatment comparisons analyzed by the Wilcoxon-Mann-Whitney rank sum test.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F tests, modeling response as a function of subgroup, treatment, and interaction.

Reviewer's Comments: *The preceding data evidence no significant difference in visual acuity between study groups at pre-op and at Day 7.*

APPEARS THIS WAY
ON ORIGINAL

ADR Incidence Tables

Patients with Any Adverse Event (KETO-105-8718 and KETO-106-8718)

		Ketorolac (overall=169)	Vehicle (overall=171)
Ocular	Total	39 (23.1%)	24 (14.0%)
Systemic	Total	6 (3.6%)	7 (4.1%)
Ocular	Inflammation Eye	10 (5.9%)	4 (2.3%)
	Edema Corneal	9 (5.3%)	3 (1.8%)
	Conjunctivitis allergic	4 (2.2%)	3 (1.8%)
	Eye Trauma	4 (2.4%)	2 (1.2%)
	Iritis	3 (1.8%)	1 (0.6%)
	Corneal Infiltrate	3 (1.8%)	0 (0.0%)
	Blepharitis	2 (1.2%)	1 (0.6%)
	Keratitis	2 (1.2%)	2 (1.2%)
	Edema Eyelid	2 (1.2%)	2 (1.2%)
	Hyperemia Conjunctival	1 (0.6%)	0 (0.0%)
	Photophobia	1 (0.6%)	2 (1.2%)
	Pain Eye	1 (0.6%)	1 (0.6%)
	Foreign Body Sensation	1 (0.6%)	0 (0.0%)
	Eye Dryness	0 (0.0%)	1 (0.6%)
	Burning Sensation in Eye	0 (0.0%)	1 (0.6%)
	Infection	0 (0.0%)	1 (0.6%)
	Pruritis Eye	0 (0.0%)	1 (0.6%)
	Blepharospasm	0 (0.0%)	1 (0.6%)
Systemic	Browache	0 (0.0%)	1 (0.6%)
	Edema Face	0 (0.0%)	1 (0.6%)
	Sinus Headache	0 (0.0%)	1 (0.6%)
	Neck Pain	0 (0.0%)	1 (0.6%)
	Syncope	1 (0.6%)	0 (0.0%)
	Digestive Pain	0 (0.0%)	1 (0.6%)
	Dyspepsia	0 (0.0%)	1 (0.6%)
	Nausea	2 (1.2%)	0 (0.0%)
	Hypertonia	0 (0.0%)	1 (0.6%)
	Infection	1 (0.6%)	0 (0.0%)
	Rash	1 (0.6%)	0 (0.0%)
	Pain Ear	0 (0.0%)	1 (0.6%)
	Urinary Tract Infection	1 (0.6%)	0 (0.0%)

[a] Patients with multiple adverse events appear more than once in this table, once for each relevant reaction term.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20811

CHEMISTRY REVIEW(S)

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-811

REVIEW # 1 **DATE REVIEWED:** 1/16/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	7/26/96	7/29/96	9/16/96
AMENDMENT			

NAME & ADDRESS OF APPLICANT:
Syntex (USA) Inc.
PO Box 10850
Palo Alto, CA 94303

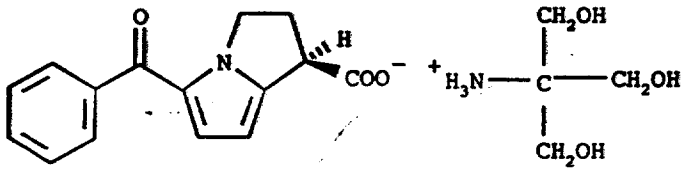
DRUG PRODUCT NAME
Proprietary: Acular® 0.5% Sterile Ophthalmic Solution,
Established: Ketorolac 0.5% Sterile Ophthalmic Solution,
Code Name/#:
Chem.Type/Ther.Class:

PHARMACOL. CATEGORY: Antiinflammatory
DOSAGE FORM: Sterile Ophthalmic Solution
STRENGTHS: 0.5%
ROUTE OF ADMINISTRATION: in to the eye
DISPENSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Chemical Name:
(+)-5-benzoyl-2,3 dihydro lH-pyrrolizine-l-carboncylic acid, 2-amino-2 hydroxymethyl- 1,3-propanediol

5.4 Structural Formula:



Molecular Formula
$C_{19}H_{24}N_2O_6$,

Molecular weight:
376.41

Physical Description:
A white to pale yellow powder.

SUPPORTING DOCUMENTS:

NDA #19-700,

RELATED DOCUMENTS

USP Dictionary (1996) pg. 387, Merck Index (12th ed.) 5319.

REMARKS:

The drug substance will be manufactured by Roche Pharmaceuticals-Syntex Ireland. The drug product will be manufactured by Allergan Pharmaceuticals plant in Waco, Texas, under licence from Syntex (USA), which is a subsidiary of Roche Pharmaceuticals. As a result, the documents are from these various sources.

This NDA came in initially as a supplement to the approved NDA # 19-700. For administrative reasons this supplement was made into an NDA and given a new number (NDA # 20811). Therefore, the formulation in this NDA only differs from that of the an Approved NDA (NDA 19-700) in that this formulation does not contain the preservative benzalkonium chloride. This change was made to allow the use of the product by persons sensitive to benzalkonium chloride. A FONSI (and EA) has been submitted, because the applicant does not envision any additional use of the drug product, and hence no increase in the level of production of the drug substance (see attachment). An EER and a microbiological consult has also been requested.

CONCLUSIONS & RECOMMENDATIONS:

There are no major CMC issues, but some minor deficiencies need to be addressed. The NDA is approvable.

Hasmukh B. Patel
Hasmukh Patel Ph. D., Team Leader
1-27-97

Vispi P. Bhavnagri
Vispi P. Bhavnagri Ph. D. / Review Chemist
Jan. 27, '97.

JUL 2 1997

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-811

REVIEW # 2 DATE REVIEWED: 1/16/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	3/20/97	3/21/97	4/7/97
AMENDMENT			

NAME & ADDRESS OF APPLICANT:
Syntex (USA) Inc.
PO Box 10850
Palo Alto, CA 94303

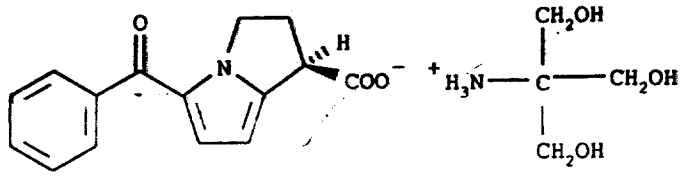
DRUG PRODUCT NAME
Proprietary: Acular® 0.5% Sterile Ophthalmic Solution, Preservative Free
Established: Ketorolac 0.5% Sterile Ophthalmic Solution, Preservative Free
Code Name/#:
Chem.Type/Ther.Class:

PHARMACOL. CATEGORY: Antiinflammatory
DOSAGE FORM: Sterile Ophthalmic Solution
STRENGTHS: 0.5%
ROUTE OF ADMINISTRATION: in to the eye
DISPOSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Chemical Name:
(+)-5-benzoyl-2,3 dihydro lH-pyrrolizine-l-carboncylic acid, 2-amino-2 hydroxymethyl- 1 ,3-propanediol

5.4 Structural Formula:



Molecular Formula
$C_{19}H_{24}N_2O_6$

Molecular weight:
376.41

Physical Description:
A white to pale yellow powder

SUPPORTING DOCUMENTS:

NDA #19-700,

RELATED DOCUMENTS

USP Dictionary (1996) pg. 387, Merck Index (12th ed.) 5319.

REMARKS:

The drug product will be manufactured by Allergan's Pharmaceuticals plant in Waco, Texas, under licence from Syntex (USA), which is a subsidiary of Roche Pharmaceuticals. As a result, the documents are from these various sources.

This NDA came in initially as a supplement to the approved NDA # 19-700. For administrative reasons this supplement was made into an NDA and given a new number (NDA # 20811). Therefore, the formulation in this NDA only differs from that of the approved NDA (NDA 19-700) in that this formulation does not contain the preservative benzalkonium chloride. This change was made to allow the use of the product by persons sensitive to benzalkonium chloride.

A number of deficiencies were found and have been addressed in this submission as an amendment.

A FONSI (and EA) has been prepared and is awaiting Nancy Sager's concurrence.

The company requested a name change from Acular® 0.5% Sterile Ophthalmic Solution, P F to Acular® 0.5% Sterile Ophthalmic Solution, Preservative Free. The nomenclature committee has found this acceptable (see attachment).

A microbiological consult has also been requested.

CONCLUSIONS & RECOMMENDATIONS:

All the deficiencies have been addressed satisfactorily. The NDA is approvable, pending satisfactory completion of the following (1) acceptable microbiological review and (2) acceptable sign-off of the FONSI by Nancy Sager.

Hasmukh B. Patel

Hasmukh Patel Ph. D., Team Leader

7-7-97

Date

Vispi P. Bhavnagri

Vispi P. Bhavnagri Ph. D., Review Chemist

7/2/97.

Date

CC:
NDA # 20-811
HFD-550/Division File
HFD-550/V.Bhavnagri
HFD-550/H.Patel
HFD-550/J.Holmes
HFD-550/W.Chambers
HFD-550/D.Bashaw
HFD-550/C.Fang
HFD-550/W.Coulter
HFD-830/C.Chen

APPROVABLE

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DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-811

REVIEW # 3 **DATE REVIEWED:** 9/08/97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUBMISSION	3/20/97	3/21/97	4/7/97
AMENDMENT			

NAME & ADDRESS OF APPLICANT:
Syntex (USA) Inc.
PO Box 10850
Palo Alto, CA 94303

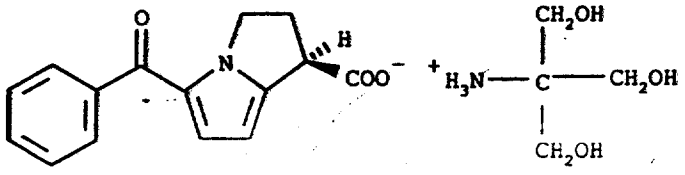
DRUG PRODUCT NAME
Proprietary: Acular® 0.5% Sterile Ophthalmic Solution, Preservative Free
Established: Ketorolac 0.5% Sterile Ophthalmic Solution, Preservative Free
Code Name/#:
Chem.Type/Ther.Class:

PHARMACOL. CATEGORY: Antiinflammatory
DOSAGE FORM: Sterile Ophthalmic Solution
STRENGTHS: 0.5%
ROUTE OF ADMINISTRATION: in to the eye
DISPENSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

Chemical Name:
(+)-5-benzoyl-2,3 dihydro lH-pyrrolizine-l-carboncylic acid, 2-amino-2 hydroxymethyl- l ,3-propanediol

5.4 Structural Formula:



Molecular Formula
$C_{19}H_{24}N_2O_6$

Molecular weight:
376.41

Physical Description:
A white to pale yellow powder.

SUPPORTING DOCUMENTS:

NDA #19-700,

RELATED DOCUMENTS

USP Dictionary (1996) pg. 387, Merck Index (12th ed.) 5319.

REMARKS:

The drug product will be manufactured by Allergan's Pharmaceuticals plant in Waco, Texas, under licence from Syntex (USA), which is a subsidiary of Roche Pharmaceuticals. As a result, the documents are from these various sources.

This NDA came in initially as a supplement to the approved NDA # 19-700. For administrative reasons this supplement was made into an NDA and given a new number (NDA # 20811). Therefore, the formulation in this NDA only differs from that of the approved NDA (NDA 19-700) in that this formulation does not contain the preservative benzalkonium chloride. This change was made to allow the use of the product by persons sensitive to benzalkonium chloride.

A number of deficiencies were found in the initial submission and have been addressed in this amendment.

In the amendment, the company provided the information asked for an EA. Subsequently the company has asked for a categorical exclusion under the new provision which went into effect on August 28, 1997. The basis for the categorical exclusion was found to be acceptable (see attachments from Hoffman La Roche and Allergan).

The firms answers to the microbiologist's questions were sent to the Microbiology Staff for evaluation.

At the time of the original review Allergen's PR facility was found to be in compliance. Subsequently a 483 was issued for the facility and on 4/30/97, a withhold was recommended by Compliance. The facility is again found to be acceptable as of 8/21/97.

CONCLUSIONS & RECOMMENDATIONS:

At the time of Review #2, the NDA was approvable, pending satisfactory completion of (1) the microbiology review and (2) acceptable sign-off of the FONSI by Nancy Sager.

Since then, the microbiology review was found to be acceptable and the company qualifies for a categorical exclusion of the EA under the revised policies and procedures of NEPA which were published in the Federal Register of July 29, 1997 and which went into effect on August 28, 1997.

The manufacturing facility is once again acceptable.

It is recommended that the NDA be approved.

Hasmukh Patel Ph. D., Team Leader

9/11/97
Date

Vispi P. Bhavnagri Ph. D., Review Chemist

9/5/97.
Date

CC:
NDA # 20-811
HFD-550/Division File
HFD-550/V.Bhavnagri
HFD-550/H.Patel
HFD-550/L.Lobianco
HFD-550/W.Chambers
HFD-550/D.Bashaw
HFD-550/C.Fang
HFD-550/W.Coulter
HFD-830/C.Chen

APPROVE

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20070/S-004, S-006

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

MAR 3 1 1997

NDA 19-700/SE1 010
Name of Drug: ACULAR (ketorolac tromethamine) 0.5% Sterile Ophthalmic Solution
Applicant: Hoffmann-La Roche Inc.
Indication: Reduction of Ocular Pain and Symptoms of Discomfort Following Incisional Refractive Surgery
Documents Reviewed: Statistical Section of NDA 19-700 (Vol. 15-Vol. 28) dated 12/13/96 by CDER
Reviewer: Laura Lu, Ph.D.
Date of Review: 3/31/97

I. Background

NDA 19-700 was approved on Nov. 9, 1992 for the relief of ocular itching due to seasonal allergic conjunctivitis. Over the past year, Allergan, Inc. had submitted the following clinical supplements to NDA 19-700: Supplements S-003, S-004, S-005 (submitted January 2, 1996, approved September 18, 1996) providing for an extension of the dosing period beyond one week of therapy (S-003), drafting labeling to reflect the changes (S-004) and an additional fill size of 10ml (S-005),

Two clinical studies, KETO-105-8718 and KETO-106-8718 were included in this submission to request approval of an indication for the reduction of ocular pain and symptoms of discomfort following incisional refractive surgery.

II. Description of Study Protocols

1. Study KETO-105-8718

This is a multi-center, double-masked, randomized, parallel-group, vehicle controlled clinical study. The object of this study is to evaluate the analgesic efficacy and safety of non-preserved, topical ketorolac tromethamine 0.5% compared with vehicle when used following radial keratotomy (RK). A total of 170 subjects will be included in this study with 86 subjects in the active treatment group and 84 subjects in the vehicle group. In the following description of the schedule of visits, measurements and dosing, the instillation of the masked study medication is always 5 minutes after the instillation of one drop of Ocuflox. Five minutes after the RK procedure, the subjects will be instructed to instill one drop of the masked study medication. Subjects will evaluate pain and fill out the subject diary at 30 and 60 minutes after surgery and then will be sent home. In the subject diary, pain intensity, pain relief, functional/activity assessment, and time that the escape medication (acetaminophen) is first taken are recorded. Subjects will evaluate pain intensity and pain relief at 2 hours after the RK procedure and fill out the subject diary. At three hours after the RK procedure, the subjects will fill out the subject diary

and instill one drop of the masked study medication. At four hours after the RK procedure, subjects will be instructed by nurses over the phone to fill out subject diary. The subjects will be asked to continue to instill one drop of masked study medication at meal times and bedtime, i.e., four times a day, and fill out subject diary each time right before Oduflox and masked study medication are instilled. The subjects will return to the investigator's office daily for interim visits until his/her last diary returns are 'No pain at all' for pain intensity at home and in the investigator's office or through Day 3, whichever comes first. During each interim visit, pain intensity, pain relief, biomicroscopy, use of escape medication, symptoms of ocular discomfort, quality of sleep, functional/activity assessment, ocular complication and adverse events will be recorded. At Day 7, subjects will return to the investigator's office for the last interim visit during which manifest refraction and visual acuity will be recorded additionally to those recorded in the previous visits. Subjects will be instructed to return for follow-up visits at 1, 3 and 12 months. The primary efficacy variables are pain intensity (7-scale variable) and pain relief (7-scale variable). The secondary efficacy measures include use of escape medication, symptoms of general discomfort (quality of sleep, headache, nausea, level of fatigue), and symptoms of ocular discomfort (foreign body sensation, photophobia, burning/stinging, tearing, itching).

2. Study KETO-106-8718

Study KETO-106-8718 is similar to KETO-105-8718 with the following differences:
a) A total of 170 subjects will be included in this study with 83 subjects in the ketorolac treatment group and 87 subjects in the vehicle group.
b) In the first four hours after the RK procedure, subjects will evaluate pain intensity and pain relief at Hour 1, 3 and 4 instead of Hour 0.5, 1, 2, 3, and 4.

III. Sponsor's Statistical Methods

Intent-to-treat analysis is the only analysis the sponsor used. Data recorded for patients who took acetaminophen escape medication, other nonsteriodal anti-inflammatory agent or other analgesic were to be included. The last observation will not be carried forward if the subject terminated due to lack of efficacy. In case where the last pain intensity response is 'no pain at all', the no-pain score is carried forward for analysis of subsequent pain-intensity time blocks. Similarly, response category 'complete', including 'complete' and 'no pain' in pain relief score, is carried forward. However, responses prior to the two-hour time block (which included data from 1.5 to 2.5 hours post surgery) are not carried forward, due to the effect of the anesthetic. Similarly, the survival analysis of time-to-no-pain and time-to-complete-relief disregarded scores for the first 1.5 hours. The statistical methods used are summarized as follows.

Variables	Statistical Method
Ordinal and continuous variables: pain intensity pain relief, number of acetaminophen tablets taken, hours of sleep, quality of life measures, visual acuity, age, and refractive error.	Descriptive statistics, Wilcoxon rank-sum test (Mann-Whitney U test).
Binomial variables: escape medication use, demography, medical history, adverse events, surgical complications, and incidences of pain intensity and pain relief, symptoms of ocular discomfort, biomicroscopy.	Descriptive statistics and/or response frequencies, 2x2 chi-square test/Fisher 2x2 exact test.
Survival times: time to no pain, time to complete relief of pain, and time to first use of escape medication.	Generalized Wilcoxon rank-sum test from survival analysis.

IV. Sponsor's Results

1. Results in Study KETO-105-8718

a) Efficacy Results

• Patient Disposition

The following results were all obtained by intent-to-treat analysis. Table 1 displays the disposition of patients.

Table 1 (KETO-105-8718). Patient Disposition

Disposition	Ketorolac N(%)	Vehicle N(%)	Total N(%)	P-value[a]
Total Patients Enrolled	86	84	170	
Completed Day 7:	84 (97.7%)	71 (84.5%)	155 (91.2%)	
Terminated:				
Lack of Efficacy	1 (1.2%)	12 (14.3%)	13 (7.6%)	0.001
Adverse Event	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Discontinued:				
Administrative Reason	1 (1.2%)	1 (1.2%)	2 (1.2%)	

[a] P-values for between-treatment comparisons of lack of efficacy analyzed by chi-square or Fisher's exact tests.

• **Demographics**

Among the patient **demographics**, only significant age and sex differences were found between the ketorolac group and the vehicle group. The differences are listed as follows.

Table 2 (KETO-105-8718). Demographics

Variable		Ketorolac	Vehicle	Total	P-value[a]
Age (Years)	N	86	84	170	0.038
	Mean	38.2	40.6	39.4	
	S.E.M.[b]	0.85	0.86	0.61	
	Min	24	25	24	
	Max	61	60	61	
Sex	Male	33 (38.4%)	45 (53.6%)	78 (45.9%)	0.047
	Female	53 (61.6%)	39 (46.4%)	92 (54.1%)	

[a] P-value for between-treatment comparisons. Age was analyzed by the Wilcoxon-Mann-Whitney ranksum test. Treatment-by-site interaction was not significant (p>0.10). Sex, race (Caucasian vs. non-Caucasian), and iris color (light: blue, green, hazel or gray vs. dark: brown or black) were analyzed by chi-square or Fisher's exact tests.
[b] S.E.M. - Standard error of mean.

• **Primary Efficacy Variables**

Figure 1-6 in the appendix show the results for pain intensity, incidence of no pain, pain relief and incidence of complete relief corresponding to the information on Table 8-13, Page 261-270 of Volume 17, KETO-105-8718. **Pain intensity** scores were significantly lower in the ketorolac-treated group than in the vehicle-treated group at every measurement point for the entire 72-hour period evaluated (all p<=0.047). Scores were both clinically (mean difference>=1 unit) and statistically significant at hours 2 to 12. **Time for patients to reach no pain** was significantly shorter in the ketorolac-treated group (median=18.1 hours) than in the vehicle group (median=45.9 hours). **Pain relief** was significantly greater at the time periods from 2 hours to 60 hours and from 67 hours to >72 hours (all p<=0.023), and both clinically (mean difference>=1 unit) and statistically significant at hours 2 to 54. **Time for patients to reach complete relief** was significantly shorter in the ketorolac-treated group than in the vehicle-treated group (median=21.6 hours) (p<=0.001).

• **Secondary Efficacy Variables**

Figure 7 in the appendix shows the Kaplan-Mejer estimator of the life-table curve of the time for **the first acetaminophen use** corresponding to the information on Table 14, Page 271 of Volume 17, KETO-105-8718. The time was significantly shorter in the vehicle group (median=4.5 hours) than in the ketorolac group (median time could not be calculated because fewer than 50% of the patients took acetaminophen tablets [p<=0.001]).

In Day 1, subjects in the ketorolac group were significantly less likely to be **awakened by pain** (p=.013), to have **trouble falling asleep** (p=0.006), and to take **additional pain medication to fall asleep** (p=0.001) (see Table 20, 22 and 23, Page 277, 279 and 280, Volume 17, KETO-15-8718).

Results on **ocular discomfort** are listed in Table 3 with those significantly favoring the ketorolac group marked with asterisks.

Table 3 (KETO-105-8718). Symptoms of Ocular Discomfort (p-values)

	4 hours Post-RK	Day1	Day2
Foreign Body Sensation	<=0.001*	0.126	0.631
Photophobia	<=0.001*	<=0.001*	0.003*
Burning/stinging	<=0.001*	0.008*	0.472
Tearing	<=0.001	0.296	0.024*
Itching	0.108	0.715	0.151

• Other Variables

The following **quality of life measures** at various time points are in favor of the ketorolec group: **read a newspaper or magazine** at hour 4 (p=0.01) and after hour 72 (p=0.048) (Table 35, Page 293, Volume 17, KETO-105-8718); **watch television** at hours 6 to 18 (all p<=0.039) (Table 37, Page 298, Volume 17, KETO-105-8718); **see steps** at hour 4 (p=0.013) (Table 40, Page 307, Volume 17, KETO-105-8718); **spend time in a well-lighted room** at hours 4, 6 to 12, and 55 to 60 (all p<=0.042) (Table 41, Page 310, Volume 17, KETO-105-8718); **spend time in daylight** at hours 4, 6 to 12, 19 to 30, and 43 to 48 (all p<=0.035) (Table 42, Page 313, Volume 17, KETO-105-8718).

b) Safety Results

• **Adverse Events**

During the study, 24.4% (21/86) of the patients treated with ketorolac and 19% (16/84) of the patients treated with vehicle experienced adverse events regardless of their causality. Treatment-related adverse events occurred in none of the patients treated with ketorolac and 1.2% (1/84) of the patients treated with vehicle. None of the ocular or systemic adverse events were serious and none of the patients were terminated from study participation because of adverse events. Detailed description of adverse events is in Table 4 and 5.

Table 4 (KETO-105-8718)

Patients with Any Adverse Event, by Relationship to Treatment[a]

No. of Subjects		Ketorolac 86	Vehicle 84	Total 170	
Category	Body System	N(%)	N(%)	N(%)	P-value[b]
Overall	Any	21 (24.4%)	16 (19.0%)	37 (21.8%)	>0.999
	Ocular	19 (22.1%)	13 (15.5%)	32 (18.6%)	0.270
	Systemic	3 (3.5%)	4 (4.8%)	7 (4.1%)	0.718
AE Related to Treatment[c]	Any	0 (0.0%)	1 (1.2%)	1 (0.6%)	0.494
	Ocular	0 (0.0%)	0 (0.0%)	0 (0.0%)	>0.999
	Systemic	0 (0.0%)	1 (1.2%)	1 (0.6%)	0.494
AE Not Related to Treatment[d]	Any	21 (24.4%)	15 (17.9%)	36 (21.2%)	0.295
	Ocular	19 (22.1%)	13 (15.5%)	32 (18.6%)	0.270
	Systemic	3 (3.5%)	3 (3.6%)	6 (3.5%)	>0.999

[a] Patient with multiple adverse events are only counted once in each category.
[b] P-value for between-treatment comparisons by chi-square or Fisher's exact tests.
[c] Includes definitely, probably, and possibly related to the study treatment.
[d] Includes not related, unlikely, and unknown.

Table 5 (KETO-105-8718). Patients with Any Adverse Event[a], Grouped by Reaction Term

No. of Subjects			Ketorolac 86	Vehicle 84	Total 170	
Body System	Body Part	Reaction Term	N(%)	N(%)	N(%)	P-value[b]
Ocular	SS/EYE/APP	Blepharitis	2(2.3%)	1(1.2%)	3(1.8%)	>0.999
		Blepharospasm	0(0.0%)	1(1.2%)	1(0.6%)	0.494
		Edema Eyelid	1(1.2%)	1(1.2%)	2(1.2%)	>0.999
	SS/EYE/CON	Conjunctivitis-allergic	2(2.3%)	2(2.4%)	4(2.4%)	>0.999
		Hyperemia Conjunctival	1(1.2%)	0(0.0%)	1(0.6%)	>0.999
		Infection	0(0.0%)	1(1.2%)	1(0.6%)	0.494
	SS/EYE/COR	Corneal Infiltrates	1(1.2%)	0(0.0%)	1(0.6%)	>0.999
		Edema Corneal	9(10.5%)	3(3.6%)	12(7.1%)	0.133
		Keratitis (NOS)	1(1.2%)	1(1.2%)	2(1.2%)	>0.999
	SS/EYE/GEN	Eye Trauma	2(2.3%)	2(2.4%)	4(2.4%)	>0.999
		Foreign Body Sensation	1(1.2%)	0(0.0%)	1(0.6%)	>0.999
		Pain Eye	1(1.2%)	1(1.2%)	2(1.2%)	>0.999
	SS/EYE/VIS	Photophobia	1(1.2%)	2(2.4%)	3(1.8%)	0.619
Systemic	DIG/BUC	Pain	0(0.0%)	1(1.2%)	1(0.6%)	0.494
	DIG/GEN	Nausea	2(2.3%)	0(0.0%)	2(1.2%)	0.497
	NER/CNS/B	Hypertonia	0(0.0%)	1(1.2%)	1(0.6%)	0.494
	RES/GEN	Infection	1(1.2%)	0(0.0%)	1(0.6%)	>0.999
	SS/EAR/GEN	Pain Ear	0(0.0%)	1(1.2%)	1(0.6%)	0.494
	SS/HEAD[c]	Browache	0(0.0%)	1(1.2%)	1(0.6%)	0.494
		Edema Face	0(0.0%)	1(1.2%)	1(0.6%)	0.494

[a] Patients with multiple adverse events appear more than once in this table, once for each relevant reaction term.
[b] P-value for between-treatment comparisons by chi-square or Fisher's exact tests.
[c] (definitely, probably or possibly) related to the study treatment.

- **Safety Variables**

There were no statistically significant differences between ketorolac and vehicle regarding visual acuity, manifest refraction, or wound healing progression through Day 7. There were significant differences between ketorolac and vehicle in lid erythema (see Table 6) and lid edema (see Table 7) on Day 1, both favoring ketorolac.

Table 6 (KETO-105-8718). Lid Erythema: Incidence Mild or Greater[a]

Study Day	Ketorolac Overall=86 N/Total[b]	(%)	Vehicle Overall=84 N/Total	(%)	P-value[c]
Pre-op	0/86	(0.0%)	0/84	(0.0%)	>0.999
Day 1	0/85	(0.0%)	5/81	(6.2%)	0.026
Day 2	1/35	(2.9%)	0/50	(0.0%)	0.412
Day 3	0/15	(0.0%)	0/25	(0.0%)	>0.999
Day 4	0/5	(0.0%)	0/2	(0.0%)	N/A
Day 5	0/3	(0.0%)	0/0	(0.0%)	N/A
Day 6	0/1	(0.0%)	1/4	(25.0%)	N/A
Day 7	0/84	(0.0%)	0/80	(0.0%)	>0.999

[a] 0-4 Scale for None, Trace, Mild, Moderate, Severe.
[b] Non-missing total at each time period.
[c] P-values for between-treatment comparisons analyzed by chi-square or Fisher's exact tests.

Table 7 (KETO-105-8718). Lid Edema: Incidence Mild or Greater[a]

Study Day	Ketorolac Overall=86 N/Total[b] (%)	Vehicle Overall=84 N/Total (%)	P-value[c]
Pre-op	0/86 (0.0%)	0/84 (0.0%)	>0.999
Day 1	4/85 (4.7%)	21/81 (25.9%)	0.001
Day 2	1/35 (2.9%)	2/50 (4.0%)	>0.999
Day 3	0/15 (0.0%)	0/25 (0.0%)	>0.999
Day 4	0/5 (0.0%)	0/2 (0.0%)	N/A
Day 5	0/3 (0.0%)	0/0 (0.0%)	N/A
Day 6	0/1 (0.0%)	0/4 (0.0%)	N/A
Day 7	2/84 (2.4%)	3/80 (3.8%)	0.676

[a] 0-4 Scale for None, Trace, Mild, Moderate, Severe.
[b] Non-missing total at each time period.
[c] P-values for between-treatment comparisons analyzed by chi-square or Fisher's exact tests.

c) Subgroup Analysis

Sponsor's results of subgroup analysis are on Page 244-247, Volume 16. The results on primary efficacy variables and adverse events are summarized here.

- **Age**

The study variables were analyzed within the following age groups: <35, 35-44, >44. There was no senior citizen included in the study. In the subgroup <35 years, the ketorolac-treated patients were predominately female, while the vehicle-treated patients were predominantly male. There were no significant gender differences in the other two age subgroups. The between-treatment differences in subgroup analyses in pain intensity, pain relief, reports of adverse events and uncorrected visual acuity were consistent with the combined analysis (Appendix 10.6.2; Tables 74-80 , Page 67-99, Volume 18, KETO-105-8718).

- **Gender**

Within each gender subgroup, the results were consistent with the combined analysis (Appendix 10.6.2; Table 81-87, Page 100-121, Volume 18, KETO-105-8718). The female patients in the vehicle group (mean age: 42.7) were significantly older than the female patient in the ketorolac group (mean age: 38.5) (p=0.008).

- **Race**

Due to the small sample size, the non-Caucasian group (11 total, 6 in the ketorolac group, 5 in the vehicle group) lost the statistical significance for the between-treatment difference in pain relief at 3-18 hour, and the pain relief of the ketorolac group was not consistently greater than that in the vehicle group after 18 hours (Appendix 10.6.2; Table 92, Page 71-73, Volume 18). Other subgroup analysis results were consistent with the combined analysis.

• **Iris Color**

The results for between-treatment differences were consistent with the combined analysis within each iris color subgroup.

• **By Investigational Site**

Because of small sample sizes at two of the study sites, data from sites 2290 and 1345 were pooled for by-investigator tables and for any investigator-by-treatment interaction tests. In this pooled site, no notable trends in the between-group differences in pain intensity and pain relief were found. In the other three investigator sites, the results were in favor of the ketorolac group. The Yee and Grene sites had the highest incidence of patients with any adverse events (28.6%, [22/77] and 22.4%, [13/58] respectively).

2. Results in Study KETO-106-8718

a) Efficacy Results

Overall, the results of study KETO-106-8718 are in favor of the ketorolac group, but not as strong as the results of study KETO-105-8718.

• **Patient Disposition**

The following results are all obtained by intent-to-treat analysis. Table 8 displays the disposition of patients.

Table 8 (KETO-106-8718). Patient Disposition

Disposition	Ketorolac N(%)	Vehicle N(%)	Total N(%)	P-value[a]
Total Patient Enrolled	83	87	170	
Completed Day 7:	77 (97.7%)	77 (84.5%)	154 (91.2%)	
Terminated:				
Lack of Efficacy	0 (1.2%)	5 (14.3%)	5 (7.6%)	0.100
Adverse Event	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Discontinued:				
Administrative Reason	1 (1.2%)	0 (0.0%)	1 (0.6%)	

[a] P-values for between-treatment comparisons of lack of efficacy analyzed by chi-square or Fisher's exact tests.

• **Demographics**

Among the patients' demographics, the only significant difference was found in iris color between the ketorolac group and the vehicle group. The differences are listed as follows.

Table 9 (KETO-106-8718). Demographics

Variable		Ketorolac	Vehicle	Total	P-value[a]
Iris Color	Light	60	50	110	0.043
	Dark	23	37	60	

[a] P-value for between-treatment comparisons. Iris color (light: blue, green, hazel or grey vs. dark: brown or black) were analyzed by chi-square or Fisher's exact tests.

• **Primary Efficacy Variables**

Figure 8-14 in the appendix show the results for pain intensity, incidence of no pain, pain relief and incidence of complete relief corresponding to the information on Table 8-13, Page 351-360 of Volume 18, KETO-106-8718.

Pain intensity scores were significantly lower in the ketorolac-treated group than in the vehicle-treated group at hours 3 to 12, hours 25 to 36, and hours 49 to 54 (all p<=0.033). Scores were both clinically (mean difference>=1 unit) and statistically significant at hours 3 to 12.

Time for patients to reach no pain was significantly shorter in the ketorolac-treated group (median=21.5 hours) than in the vehicle-treated group (median=31.6 hours) (p=0.004).

Pain relief was significantly greater at the time periods from hours 3 to 12, 25 to 36, 49 to 60, and 67 to 72 (all p<=0.042). Scores were both clinically (mean difference >=1 unit) and statistically significant at hours 3 to 12 and 31 to 36.

Time for patients to reach complete relief was significantly shorter in the ketorolac-treated group (median=31.4 hours) than in the vehicle-treated group (median=44.6 hours) (p=0.015).

• **Secondary Efficacy Variables**

The time to the first acetaminophen use was significantly shorter in the vehicle group (median=4.0 hours) than the ketorolac group (median time could not be calculated because fewer than 50% of the patients took acetaminophen tablets [all p<=0.001]).

Patients treated with ketorolac took significantly less **additional medication to fall asleep** during Day 1 and Day 2, and had a significantly lower level of **fatigue** on Day 1. On Day 1, kerorolac-treated patients had significantly less difficulty **opening the surgical eye without topical anesthesia**, and significantly fewer ketorolac-treated patients required **topical anesthetic to open the surgical eye**.

Results on **ocular discomfort** are listed in Table 10 with those significantly favoring the ketorolac group marked with asterisks.

Table 10 (KETO-106-8718). Symptoms of Ocular Discomfort (p-values)

	4 hours Post-RK	day1	day2
Foreign Body Sensation	<=0.001*	0.443	0.028*
Photophobia	<=0.001*	0.007*	0.034*
Burning/stinging	<=0.001*	0.287	0.620
Tearing	<=0.001*	0.287	0.440
Itching	0.168	0.999	0.666

• **Other Variables**

There were trends that the ketorolac-treated patients had less difficulty than the vehicle-treated patients to do the following: **watch television** (statistically significant at hours 3 to 12, 31 to 36, and 43 to 48 [all p<=0.04]), **see traffic signs and signals** (statistically significant at hours 3 and 7 to 12 [all p<=0.048]), **see steps** (statistically significant at hours 3 an 7 to 12 [all p<=0.006]), **spend time in a well-lighted room** (statistically significant at hours 3 to 48, except hours 13 to 18 and 37 to 42 [all p<=0.03]), and **spend time outside in daylight** (statistically significant at hours 3 to 48, except hours 25 to 30 and 37 to 42 [all p<=0.035]).

b) Safety Results

During the study, 26.5% (22/83) of the patients treated with ketorolac and 16% (14/87) of the patients treated with vehicle experienced adverse events regardless of causality. Treatment related adverse events occurred in 3.6% (3/83) of the patients treated with ketorolac and 5.7% (5/87) of the patients treated with vehicle. Detailed description of adverse events is in Table 11 and 12. It is noticeable that the proportions of ocular adverse event not related with treatment were statistically different (p=0.022) and in favor of the vehicle-treated group.

Table 11 (KETO-106-8718) Patients with Any Adverse Event, by Relationship to Treatment[a]

No. of Subjects Category	Body System	Ketorolac 83 N(%)	Vehicle 87 N(%)	Total 170 N(%)	P-value[b]
Overall	Any	22 (26.5%)	14 (16.1%)	36 (21.2%)	>0.999
	Ocular	20 (24.1%)	11 (12.6%)	31 (18.1%)	0.058
	Systemic	3 (3.6%)	3 (3.4%)	6 (3.5%)	>0.999
AE Related to Treatment[c]	Any	3 (3.6%)	5 (5.7%)	8 (4.7%)	0.721
	Ocular	3 (3.6%)	4 (4.6%)	7 (4.1%)	>0.999
	Systemic	0 (0.0%)	1 (1.1%)	1 (0.6%)	>0.999
AE Not Related to Treatment[d]	Any	19 (22.9%)	9 (10.3%)	28 (16.5%)	0.027
	Ocular	17 (20.5%)	7 (8.0%)	24 (14.0%)	0.022
	Systemic	3 (3.6%)	2 (2.3%)	5 (2.9%)	0.678

[a] Patient with multiple adverse events are only counted once in each category.
[b] P-value for between-treatment comparisons by chi-square or Fisher's exact tests.
[c] Includes definitely, probably, and possibly related to the study treatment.
[d] Includes not related, unlikely, and unknown.

Table 12 (KETO-106-8718) Patients with Any Adverse Event[a], Grouped by Reaction Term

No. of Subjects			Ketorolac 83	Vehicle 87	Total 170	
Body System	Body Part	Reaction Term	N(%)	N(%)	N(%)	P-value[b]
Ocular	SS/EYE/APP	Eye Lid Edema	1 (1.2%)	1 (1.1%)	2 (1.2%)	>0.999
	SS/EYE/CON	Conjunctivitis-Allergic	1 (1.2%)	1 (1.1%)	2 (1.2%)	>0.999
	SS/EYE/COR	Corneal Infiltrate	2 (2.4%)	0 (0.0%)	2 (1.2%)	0.237
		Keratitis	1 (1.2%)	1 (1.1%)	2 (1.2%)	>0.999
		Keratoconjunct-ivitis Allergic	1 (1.2%)	0 (0.0%)	1 (0.6%)	0.488
	SS/EYE/GEN	Eye Dryness	0 (0.0%)	1 (1.1%)	1 (0.6%)	>0.999
		Eye Trauma	2 (2.4%)	0 (0.0%)	2 (1.2%)	0.237
		Pruritis Eye	0 (0.0%)	1 (1.1%)	1 (0.6%)	>0.999
		Inflammation Eye	10 (12.0%)	4 (4.6%)	14 (8.2%)	0.097
		Burning Sensation-in Eye	0 (0.0%)	1 (1.1%)	1 (0.6%)	>0.999
	SS/EYE/UVE	Iritis	3 (3.6%)	1 (1.1%)	4 (2.4%)	0.362
Systemic	BODY/HEAD	Sinus Headache	0 (0.0%)	1 (1.1%)	1 (0.6%)	>0.999
	BODY/NECK	Neck Pain	0 (0.0%)	1 (1.1%)	1 (0.6%)	>0.999
	CV/VASC/GEN	Syncope	1 (1.2%)	0 (0.0%)	1 (0.6%)	0.491
	DIG/GEN	Dyspepsia	0 (0.0%)	1 (1.1%)	1 (0.6%)	>0.999
	SKIN/DERM/ERY	Rash	1 (1.2%)	0 (0.0%)	1 (0.6%)	0.488
	UG/UT/GEN	Urinary Tract-Infection	1 (1.2%)	0 (0.0%)	1 (0.6%)	0.488

[a] Patients with multiple adverse events appear more than once in this table, once for each relevant reaction term.
[b] P-value for between-treatment comparisons by chi-square or Fisher's exact tests.

• Safety Variables

The safety variables in the study include **wound healing progression, visual acuity, refraction, keratometry and biomicroscopy. There was a noticeable difference in favor of vehicle in wound healing as expected** on Day 2 (see Table 13).

Table 13 (KETO-106-8718). Wound Healing as Expected

Study Day	Ketorolac (overall=83) N/Total[a] (%)	Vehicle (overall=87) N/Total (%)	P-value[b]
Day 1	75/83 (90.4%)	81/87 (93.1%)	0.516
Day 2	39/46 (84.8%)	51/52 (98.1%)	0.024
Day 3	12/13 (92.3%)	21/23 (91.3%)	>0.999
Day 4	2/5 (40.0%)	2/2 (100.0%)	N/A
Day 5	6/6 (100.0%)	5/6 (83.3%)	N/A
Day 6	4/5 (80.0%)	2/2 (100.0%)	N/A
Day 7	75/82 (91.5%)	82/84 (97.6%)	0.097

[a] Non-missing total.
[b] P-value for between-treatment comparisons by chi-square or Fisher's exact tests.

c) Subgroup Analysis

Sponsor's results of subgroup analysis are on Page 332-335, Volume 18. The results on primary efficacy variables and adverse events are summarized here.

- **Age**

The study variables were analyzed within the following age groups: <35, 35-44, >44. There was no senior citizen included in the study. In the subgroup <35 years , the ketorolac-treated patients were equally distributed in female and male, while the vehicle-treated patients were predominantly female (74.3%) (p=0.031). There were no significant gender differences in the other two age subgroups. The younger subgroup also had 75% light iris in the ketorolac-treated group (p=0.018). There were no notable differences between age subgroups in pain intensity, pain relief, and reports of adverse events.

- **Gender**

The male patients in the ketorolac group (mean age: 35) were significantly younger than the male patients in the vehicle group (mean age: 39.2) (p=0.046). There was a significant gender interaction (p=0.056) for overall adverse events, with females reporting fewer adverse events in the ketorolac group, and fewer overall events, while males reported more adverse events in the ketorolac-treated group, and more overall events. For males, this difference between treatment groups was significant with more total adverse events and more ocular adverse events in the ketorolac group (p<=0.015). There were no notable differences between males and females in operative report variables, pain intensity, and pain relief.

- **Race**

Caucasians had significantly more light iris in the ketorolac-treated group than in the vehicle group (p=0.028). Statistical significance was found in the age category, as the ketorolac-treated patients in the non-Caucasian subgroup were older than the vehicle-treated patients (p=0.043). Caucasian had a significant difference in adverse events between treatment groups. The ketorolac-treated group, for adverse events unrelated to treatment, had significantly more total events (p=0.026) and ocular events (p=0.039). The pain intensity and pain relief scores in the smaller, non-Caucasian subgroup did not show significant between-treatment differences.

- **Iris Color**

In the light iris-color subgroup there was a significant difference between treatment groups, favoring ketorolac, in pain intensity from hours 3 to 12 (all p<=0.001) and hours 49 to 60 (all p<=0.046). There was no significant difference between treatment groups for pain intensity in patients with dark iris.

- **By Investigational Site**

Because of small sample sizes at five of the study sites, data from sites 1773, 2391, 2510, 0360, and 2509 were pooled for by-investigator tables and for any investigator-by-treatment interaction tests. There were no significant differences in pain intensity scores at sites 0304, 2224, and 2438. Also, there were no significant differences in pain intensity scores at sites 0304, 2224, 2437, and

2438. Sites 0304, 2224, 2437, and 2438 were sites with relatively small sample sizes (N<=10). Scores for pain intensity and pain relief in other sites were consistent with the combined results.

Investigator 1289 had the highest incidence of patients with any adverse events (38.5%). This site had a significant difference between treatment groups for both overall adverse events and ocular adverse events (both: p=0.022).

V. Reviewer's Comments

The study design dose not allow for an observable baseline pain intensity since patients were instilled a drop of the study medication 5 minutes after the surgery when the anesthetics had not been worn off. For a meaningful interpretation of these studies, an assumption has to be made that randomization would have to produce a balance between the two treatment groups in pain intensity had it been observable. In studies KETO-105-8718 and KETO-106-8718, there are two problems with the measurement of pain relief:

1). The pain relief at each time point refers to the pain intensity in the previous instillation of the masked medicine instead of the first measurement of pain intensity (except at Hours 0.5, 1, 2, and 3) at Hour 0.5 post PK-procedure. Suppose both Patient A and Patient B had the same pain intensity 'extremely severe pain' at Hour .5, and the pain intensity and pain relief of A and B at Hours 3 and 4 are as follows.

	Patient A		Patient B	
	pain intensity	pain relief	pain intensity	pain relief
Hour 0.5	extremely severe pain		extremely severe pain	
Hour 3	mild pain	a great deal of relief	extremely severe pain	a little relief
Hour 4	very mild pain	a little relief	severe pain	a moderate relief

At Hour 4, Patient A had less pain then Patient B, but the pain relief score is in favor of Patient B, so the pain relief scores do not reflect patients' situation in pain recovery. Therefore, the reviewer concentrates more on the comparison of pain intensity scores.

2). The following inconsistencies are found in pain relief scores and pain intensity scores.

a). Some patients got pain relief although their pain intensity scores were getting worse. In study KETO-105-8718, a total of 105 (105/1950; 5.4%) inconsistent observations were found in 64 patients. In study KETO-106-8718, a total of 102 (102/1498; 6.8%) inconsistent observations were found in 67 patients. The frequencies in each treatment groups are listed as follows.

KETO-105-8718 Inconsistency (a)

Treatment	No. of Subjects	Percent	Cumulative Frequency	Cumulative Percent
ketorolac	37	57.8	37	57.8
vehicle	27	42.2	64	100.0

KETO-106-8718 Inconsistency (a)

Treatment	No. of subjects	Percent	Cumulative Frequency	Cumulative Percent
ketorolac	36	53.7	36	53.7
vehicle	31	46.3	67	100.0

The 105 observations in study KETO-105-8718 are listed in Table 22, and the 102 observations in study KETO-106-8718 are listed in Table 24 in the appendix with the following variables:
SBJ1A: patient number
KETO: treatment index with value 1(ketorolac treated group) and 2 (vehicle group).
VIS1N: visit number
PANEPR1F: current pain intensity
PANILAG: previous pain intensity
PANREL1F: pain relief from previous pain intensity
MELDSE1F: meal time (or bed time) of the current instillation
ISTTMELT: current instillation time
DRY1T: diary filling time
DRY1F: AM or PM index of time

b). Some patients got no pain relief although their pain intensity scores were getting better. In study KETO-105-8718, a total of 67 (67/1950; 3.4%) inconsistent observations were found in 36 patients. In study KETO-106-8718, a total of 42 (42/1498; 2.8%) inconsistent observations were found in 24 patients. The frequencies in each treatment groups are listed as follows.

KETO-105-8718 Inconsistency (b)

Treatment	No. of Subjects	Percent	Cumulative Frequency	Cumulative Percent
ketorolac	6	16.7	6	16.7
vehicle	30	83.3	36	100.0

KETO-106-8718 Inconsistency (b)

Treatment	No. of Subjects	Percent	Cumulative Frequency	Cumulative Percent
ketorolac	7	29.2	7	29.2
vehicle	17	70.8	24	100.0

The 67 observations in study KETO-105-8718 are listed in Table 23, and the 42 observations in study KETO-106-8718 are listed in Table 25 in the appendix with the same variables as those in Table 22.

In both studies, the observations of each patient in various time points are grouped into 6-hour blocks starting form the surgery time. For a given patient, if multiple observations occurred within the same block, only the first was included in the sponsor's statistical analysis and tables. An alternative analysis for pain intensity and pain relief was done by the reviewer using the last observation in each time block. The results are shown on Table 14-21 in the appendix, which are consistent to the sponsor's results (Tables 8, 9, 11 and 12 on Page 261-264 and Page 266-269, Volume 16, KETO-105-8718, Tables 8, 9, 11, and 12 on Page 351-354 and Page 356-359, Volume 18, KETO-106-8718).

VI. Conclusion

Assuming randomization had rendered a comparable mean pain intensity between treatment groups at an unobservable baseline, studies KETO-105-8718 and KETO-106-8718 showed that ketorolac tromethamine 0.5% Sterile Ophthalmic Solution is effective in the reduction of ocular pain (pain intensity) following incisional refractive surgery. There were less use of escape medicine (acetaminophen) and fewer symptoms of ocular discomfort, especially photophobia, in the ketorolac groups than in the vehicle groups. There were improvement in quality of life variables such as watching television', 'spending time in a well lighted room', and 'spend time outside in daylight'. No serious adverse events were found in the ketorolac treated groups.

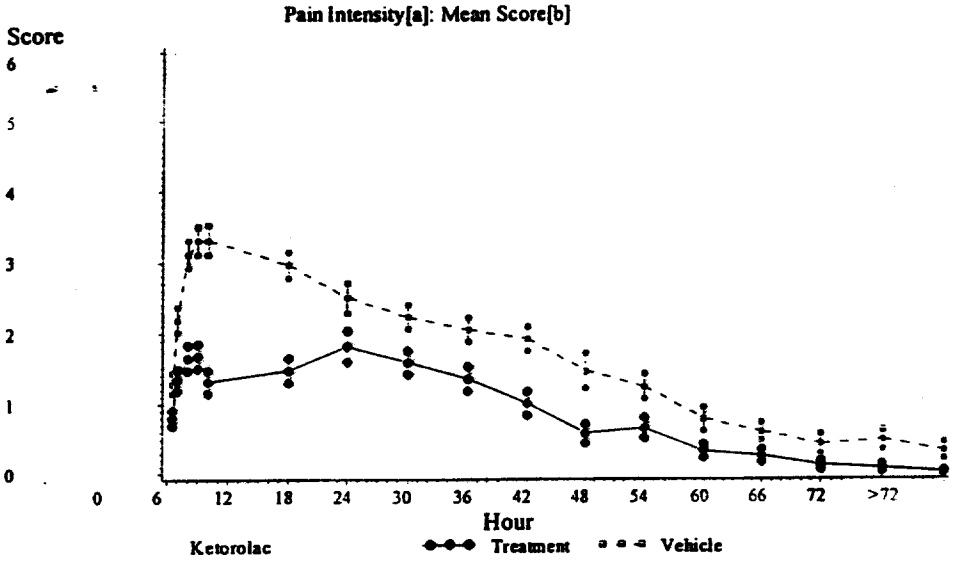
Laura Lu, Ph.D.
Mathematical Statistician

Concur:

Hoi M. Leung, Ph.D.
Team Leader

Archival: NDA 19-700/SE1-010
CC:
HFD-550/MO/Bull
HFD-550/Act. Dir./Chambers
HFD-550/PM/Holmes
HFD-550/Div. File
HFD-340/Div. Sci. Inv.
HFD-725/Lu
HFD-725/Leung
HFD-725/Div. File

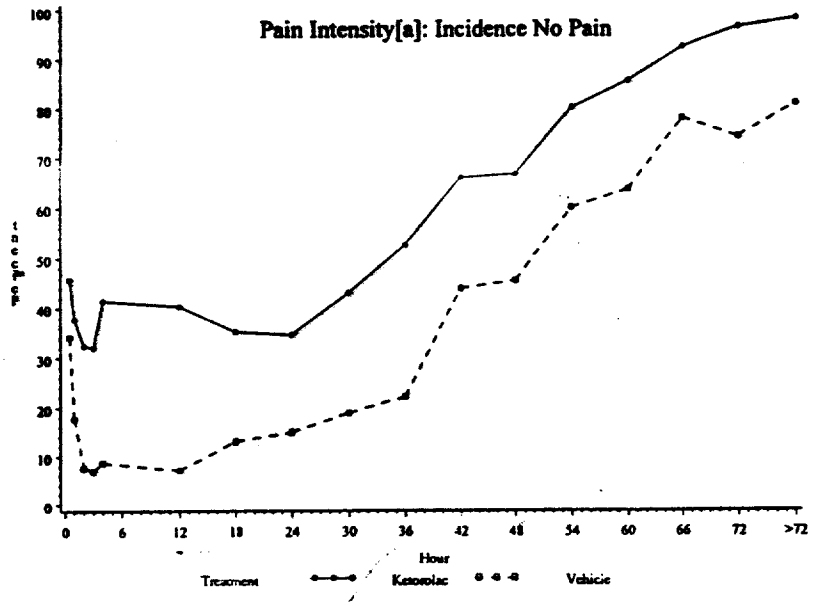
Figure 1 (keto-105-8718)
Pain Intensity[a]: Mean Score[b]



[a] 0-6 Scale (See table 8).
[b] Error bars are standard error of mean.
(K105F1.SAS)/ 10MAR97

SR(A1):KETO-105-8718

Figure 2 (keto-105-8718)

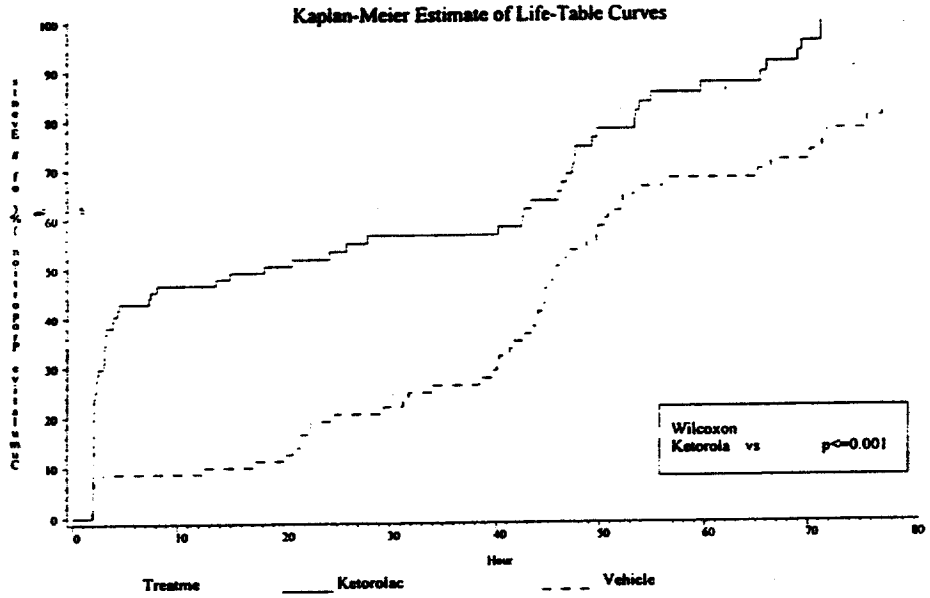


[a] 0-6 Scale (See table 9).
(K105F2.SAS)/ 01OCT96

SR:KETO-105-8718

Figure 3 (keto-105-8718)

Time (Hour) to First No Pain Intensity[a]
Kaplan-Meier Estimate of Life-Table Curves



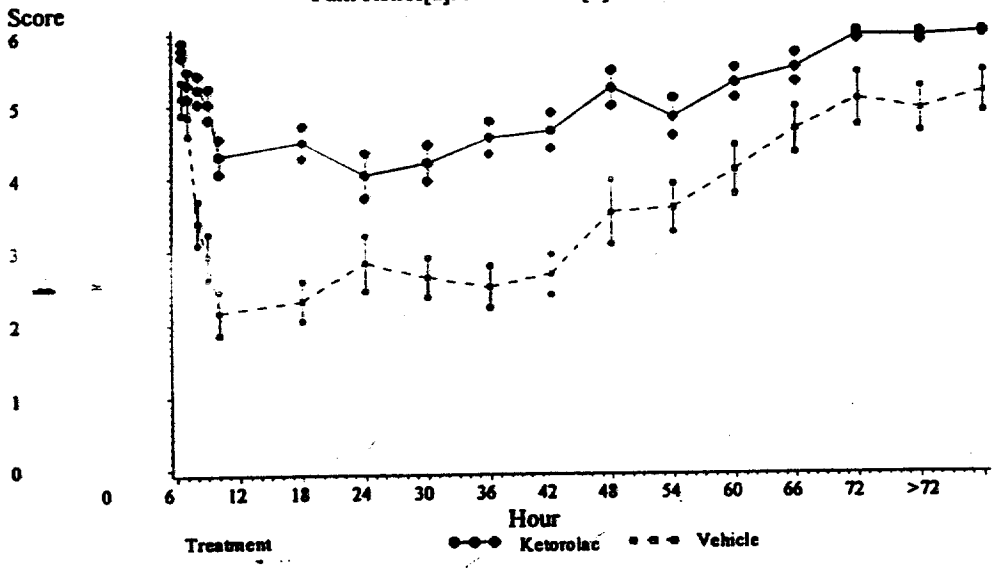
[a] 0-6 Scale (See table 10).

(K105F3.SAS)/30SEP96

SR:KETO-105-8718

Figure 4 (keto-105-8718)

Pain Relief[a]: Mean Score[b]



[a] 0-6 Scale (See table 11).

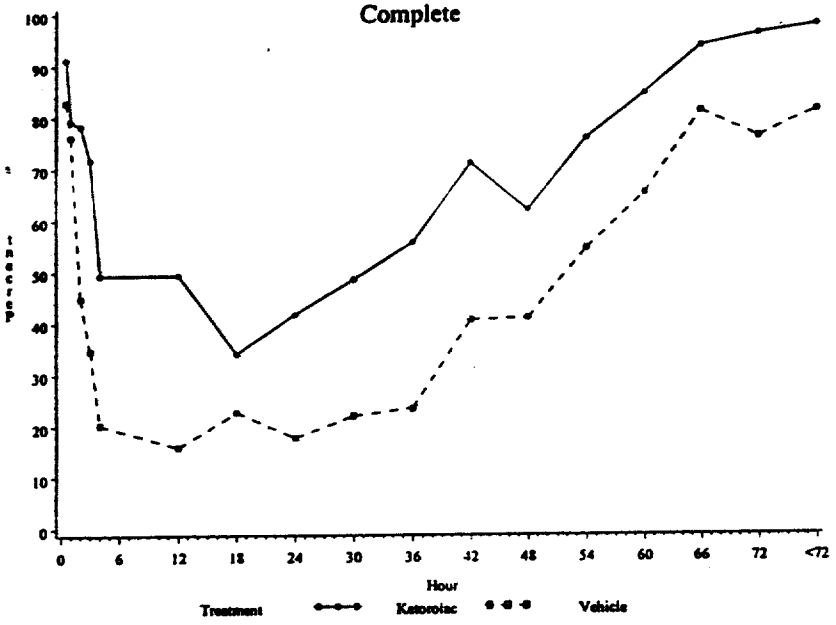
[b] Error bars are standard error of mean.

(K105F4.SAS)/ 10MAR97

SR(A1):KETO-105-8718

Figure 5 (keto-105-8718)

Pain Relief[a]: Incidence
Complete



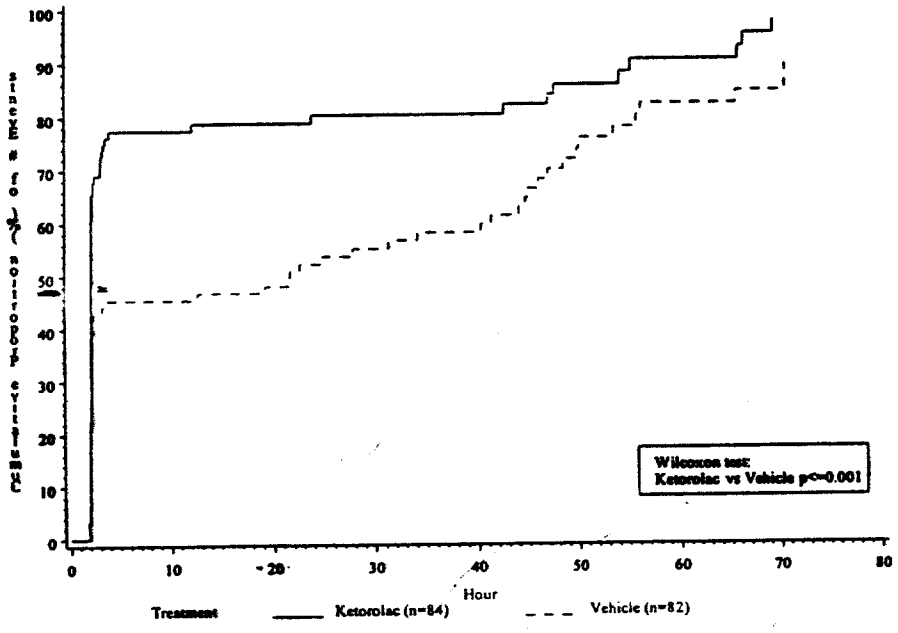
[a] 0-6 Scale (See table 12).
(K105F5.SAS)/ 01OCT96

SR:KETO-105-8718

Figure 6 (keto-105-8718)

Time (Hour) to First Complete Pain Relief[a]

Kaplan-Meier Estimate of Life-Table Curves

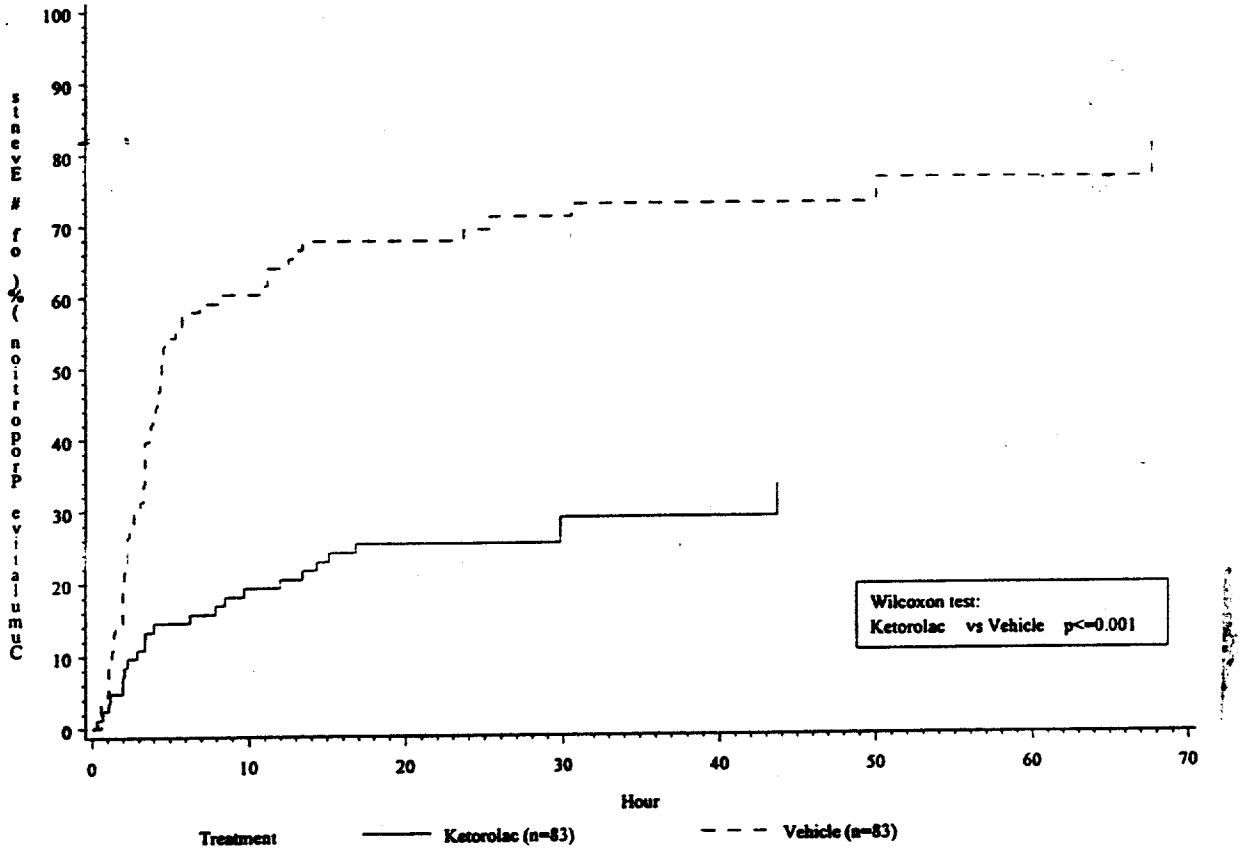


[a] 0-6 Scale (See table 13)
(K105F6.SAS)/30SEP96

SR:KETO-105-8718

Figure 7 (keto-105-8718)

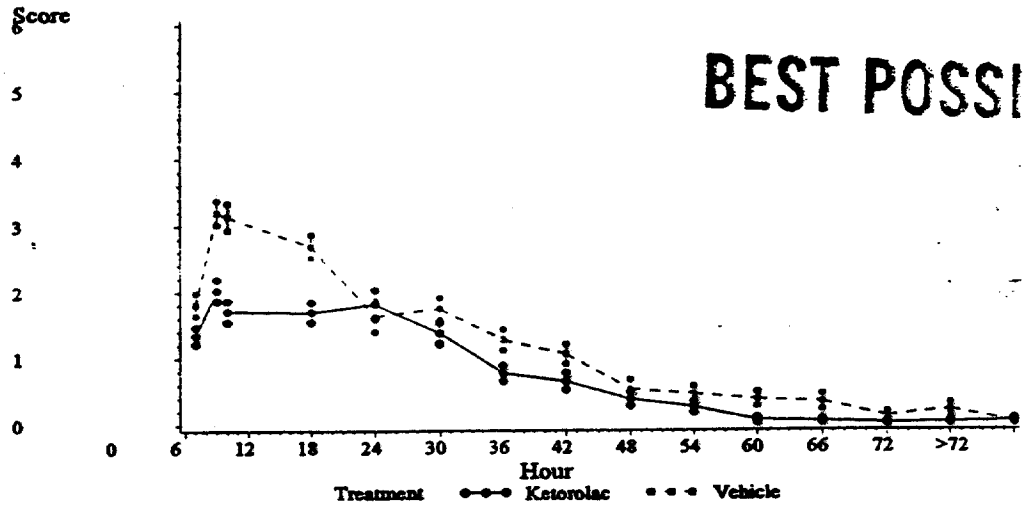
Time (Hour) to First Acetaminophen Taken
Kaplan-Meier Estimate of Life-Table Curves



(K105F7.SAS)/30SEP96

SR:KETO-105-8718

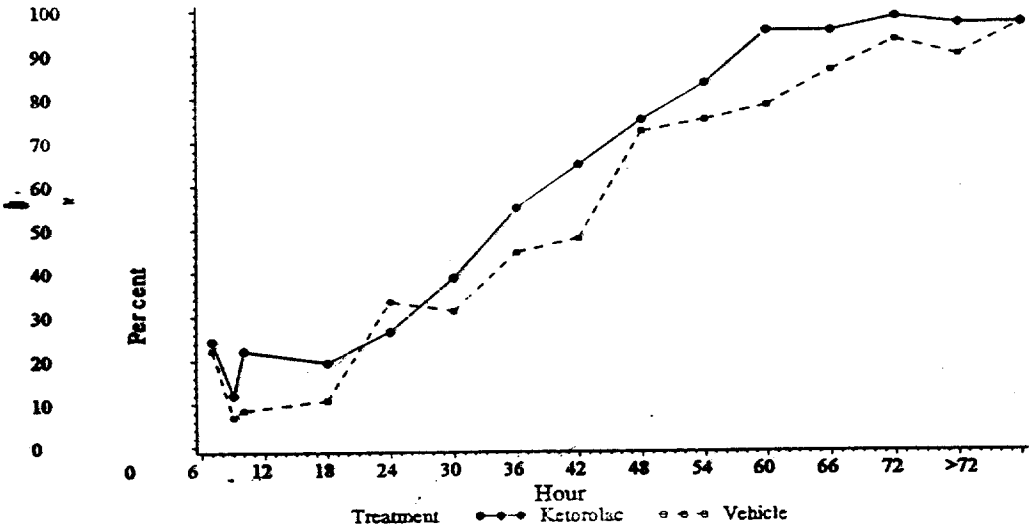
Figure 8 (keto-106-8718). Pain Intensity[a]: Mean Score[b]



[a] 0-6 Scales
[b] Error bars are standard error of mean.

KET106F1.SAS/06MAR97 SR:KETO-106-8718

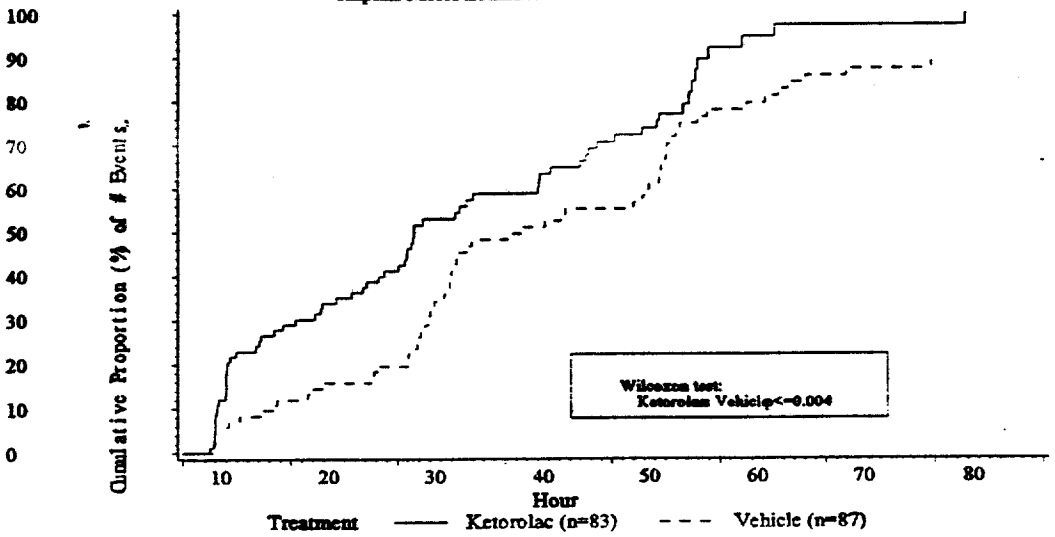
Figure 9 (keto-106-8718). Pain Intensity[a]: Incidence No Pain



[a] 0-6 Scales

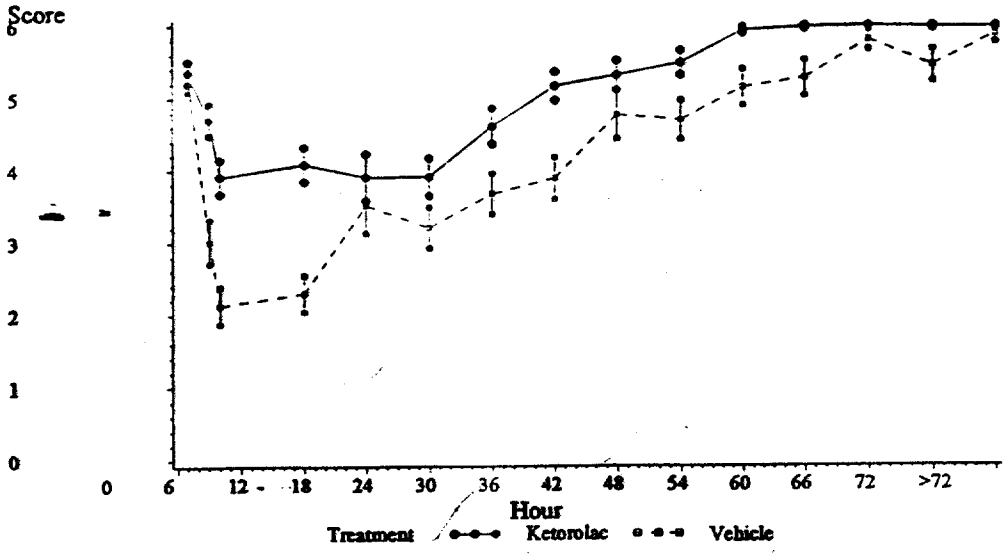
KET106F2.SAS/06MAR97 SR:KETO-106-8718

Figure 10 (keto-106-8718)
Time (Hour) to First No Pain Intensity[a]
Kaplan-Meier Estimate of Life-Table Curves



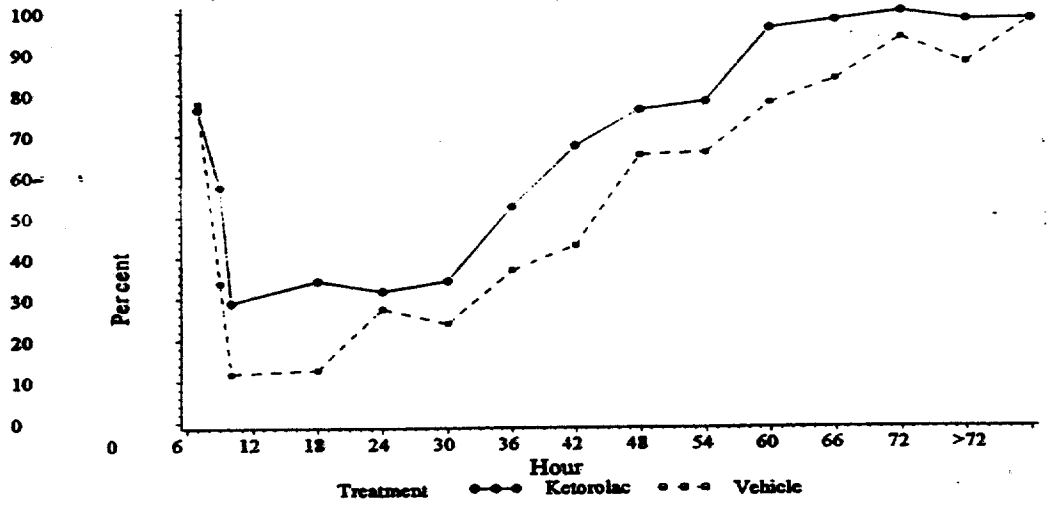
[a] 0-6 Scales
KET106F3.SAS/06MAR97
SR:KETO-106-8718

Figure 11 (keto-106-8718). Pain Relief[a]: Mean Score[b]



[a] 0-6 Scales
[b] Error bars are standard error of mean.
KET106F4.SAS/06MAR97
SR:KETO-106-8718

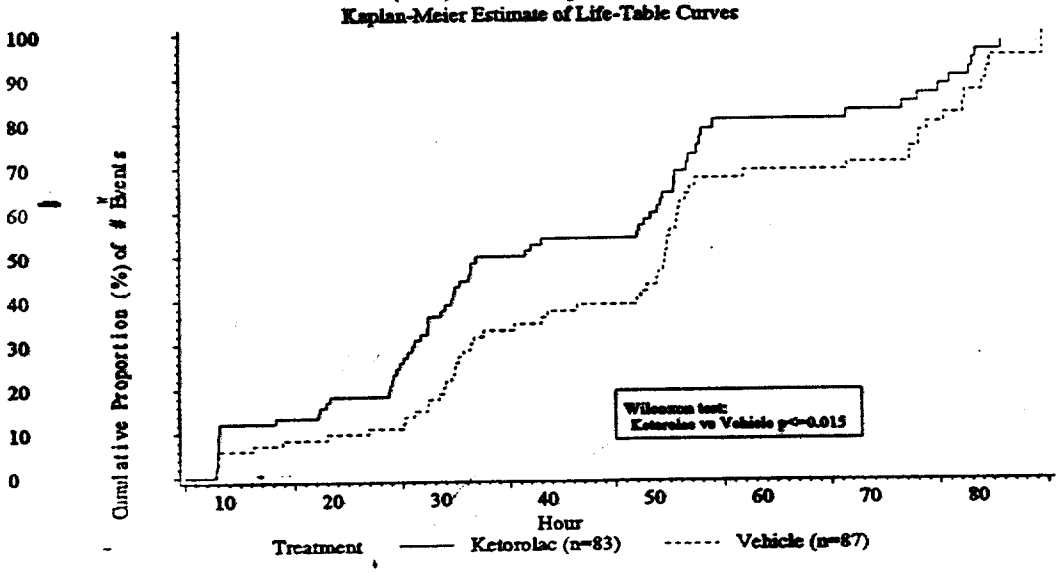
Figure 12 (keto-106-8718). Pain Relief[a]: Incidence Complete



[a] 0-6 Scales
KET106F5.SAS/06MAR97

SR:KETO-106-8718

Figure 13 (keto-106-8718)
Time (Hour) to First Complete Relief[a]
Kaplan-Meier Estimate of Life-Table Curves

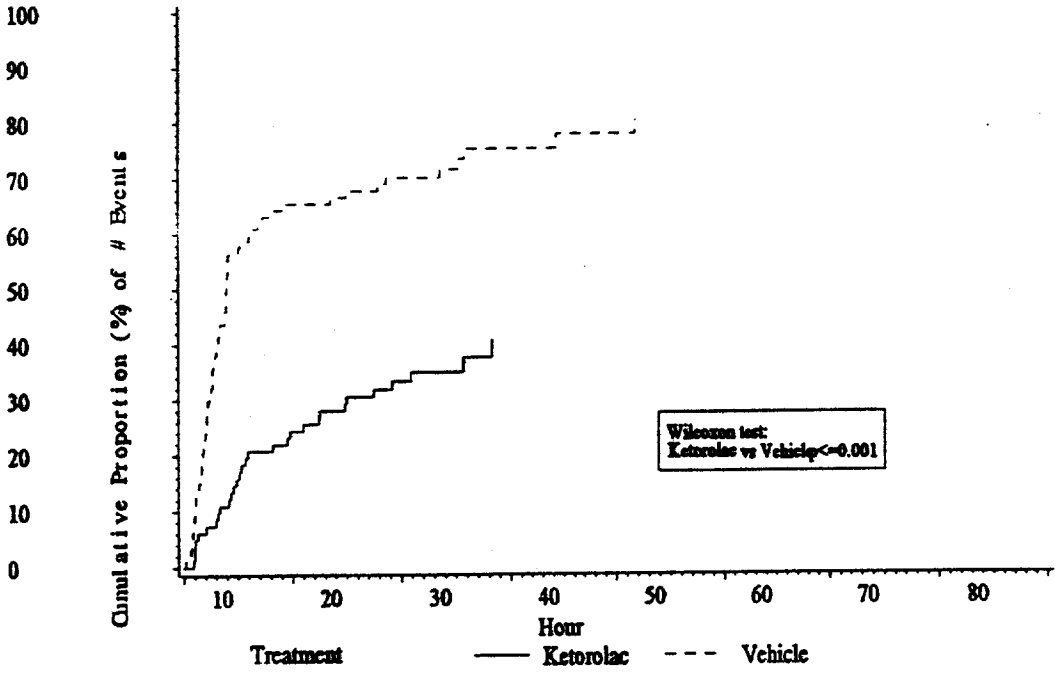


[a] 0-6 Scales
KET106F6.SAS/06MAR97

SR:KETO-106-8718

Figure 14 (keto-106-8718)

Time (Hour) to First Acetaminophen Taken[a]
Kaplan-Meier Estimate of Life-Table Curves



[a] The Ketorolac Curve is truncated and the median is not estimable because over half of the Ketorolac patients never took acetaminophen.

KET106F7.SAS/01OCT96 SR:KETO-106-8718

Table 14 (KETO-105-8718). Pain Intensity[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age
30 min	N	81	82	0.024	0.076	0.553	0.139
	Mean	0.8	1.3				
	S.E.M.	0.11	0.15				
	Min						
	Max						
1 hr	N	82	79	0.001	0.293	0.025	0.290
	Mean	1.4	2.2				
	S.E.M.	0.15	0.18				
	Min						
	Max						
2 hrs	N	77	78	0.0001	0.587	0.049	0.653
	Mean	1.6	3.1				
	S.E.M.	0.18	0.19				
	Min						
	Max						
3 hrs	N	79	72	0.0001	0.292	0.078	0.777
	Mean	1.7	3.3				
	S.E.M.	0.17	0.20				
	Min						
	Max						
4 hrs	N	70	70	0.0001	0.756	0.080	0.544
	Mean	1.3	3.3				
	S.E.M.	0.16	0.21				
	Min						
	Max						
7-12 hrs	N	72	69	0.0001	0.262	0.732	0.808
	Mean	1.6	2.9				
	S.E.M.	0.17	0.17				
	Min						
	Max						

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 14 (KETO-105-8718). Pain Intensity[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age
13-18 hrs	N	55	46	0.0224	0.247	0.103	0.415
	Mean	1.7	2.5				
	S.E.M.	0.22	0.21				
	Min						
	Max						
19-24 hrs	N	77	73	0.0011	0.760	0.531	0.911
	Mean	1.4	2.2				
	S.E.M.	0.17	0.17				
	Min						
	Max						
25-30 hrs	N	72	71	0.0008	0.418	0.486	0.521
	Mean	1.2	2.0				
	S.E.M.	0.16	0.17				
	Min						
	Max						
31-36 hrs	N	69	70	0.0001	0.207	0.867	0.191
	Mean	0.9	1.8				
	S.E.M.	0.14	0.17				
	Min						
	Max						
37-42 hrs	N	55	42	0.0024	0.242	0.753	0.846
	Mean	0.5	1.4				
	S.E.M.	0.12	0.25				
	Min						
	Max						
43-48 hrs	N	67	66	0.0021	0.041	0.508	0.810
	Mean	0.4	1.0				
	S.E.M.	0.11	0.17				
	Min						
	Max						

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 14 (KETO-105-8718). Pain Intensity[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age
49-54 hrs	N	66	65	0.0035	0.705	0.591	0.566
	Mean	0.2	0.7				
	S.E.M.	0.08	0.16				
	Min						
	Max						
55-60 hrs	N	67	62	0.0056	0.410	0.571	0.411
	Mean	0.2	0.5				
	S.E.M.	0.07	0.12				
	Min						
	Max						
61-66 hrs	N	64	52	0.032	0.416	0.261	0.253
	Mean	0.1	0.4				
	S.E.M.	0.05	0.13				
	Min						
	Max						
67-72 hrs	N	67	61	0.0008	0.349	0.926	0.616
	Mean	0.0	0.3				
	S.E.M.	0.03	0.11				
	Min						
	Max						
>72 hrs	N	66	59	0.0011	0.669	0.764	0.805
	Mean	0.0	0.3				
	S.E.M.	0.00	0.10				
	Min						
	Max						

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 15 (KETO-105-8718). Pain Intensity: Incidence No Pain[a]

Time Period	Ketorolac Overall=86 N/Total[b]	(%)	Vehicle Overall=84 N/Total	(%)	P-value[c]
30 min	37/81	(45.7%)	28/82	(34.1%)	0.133
1 hr	30/82	(36.6%)	14/79	(17.7%)	0.007
2 hrs	25/77	(32.5%)	6/78	(7.7%)	0.001
3 hrs	27/79	(34.2%)	5/72	(6.9%)	0.001
4 hrs	28/70	(40.0%)	6/70	(8.6%)	0.001
7-12 hrs	27/72	(37.5%)	4/69	(5.8%)	0.001
13-18 hrs	21/55	(38.2%)	6/46	(13.0%)	0.004
19-24 hrs	35/77	(45.5%)	13/73	(17.8%)	0.001
25-30 hrs	37/72	(51.4%)	15/71	(21.1%)	0.001
31-36 hrs	39/69	(56.5%)	18/70	(25.7%)	0.001
37-42 hrs	40/55	(72.7%)	20/42	(47.6%)	0.012
43-48 hrs	52/67	(77.6%)	35/66	(53.0%)	0.003
49-54 hrs	58/66	(87.9%)	43/65	(66.2%)	0.003
55-60 hrs	59/67	(88.1%)	42/62	(67.7%)	0.005
61-66 hrs	60/64	(93.8%)	42/52	(80.8%)	0.005
67-72 hrs	66/67	(98.5%)	49/61	(80.3%)	0.001
>72 hrs	66/66	(100.0%)	50/59	(84.7%)	0.001

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 16 (KETO-105-8718). Pain Relief[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age
30 min	N	80	82	0.0765	0.000	0.197	0.730
	Mean	5.8	5.1				
	S.E.M.	0.10	0.23				
	Min						
	Max						
1 hr	N	82	80	0.3476	0.005	0.951	0.367
	Mean	5.3	4.8				
	S.E.M.	0.18	0.25				
	Min						
	Max						
2 hrs	N	74	78	0.0001	0.178	0.533	0.032
	Mean	5.2	3.4				
	S.E.M.	0.20	0.30				
	Min						
	Max						
3 hrs	N	78	72	0.0001	0.241	0.256	0.220
	Mean	5.0	2.9				
	S.E.M.	0.21	0.30				
	Min						
	Max						
4 hrs	N	68	70	0.0001	0.951	0.089	0.649
	Mean	4.3	2.1				
	S.E.M.	0.24	0.28				
	Min						
	Max						
7-12 hrs	N	71	68	0.0001	0.420	0.709	0.730
	Mean	4.3	2.1				
	S.E.M.	0.23	0.25				
	Min						
	Max						

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] S.E.M. - standard error of mean.
[c] P-value for between-treatment comparisons analyzed byWilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 16 (KETO-105-8718). Pain Relief[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age
13-18 hrs	N	52	43	0.0031	0.434	0.284	0.351
	Mean	3.8	2.4				
	S.E.M.	0.30	0.35				
	Min						
	Max						
19-24 hrs	N	73	74	0.0001	0.068	0.933	0.971
	Mean	4.0	2.5				
	S.E.M.	0.25	0.27				
	Min						
	Max						
25-30 hrs	N	68	71	0.0001	0.037	0.807	0.881
	Mean	4.5	2.7				
	S.E.M.	0.23	0.29				
	Min						
	Max						
31-36 hrs	N	62	71	0.0001	0.275	0.762	0.270
	Mean	4.7	2.9				
	S.E.M.	0.23	0.28				
	Min						
	Max						
37-42 hrs	N	45	39	0.0048	0.166	0.089	0.777
	Mean	5.1	3.6				
	S.E.M.	0.25	0.41				
	Min						
	Max						
43-48 hrs	N	57	65	0.0238	0.553	0.154	0.858
	Mean	4.8	3.8				
	S.E.M.	0.26	0.31				
	Min						
	Max						

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] S.E.M. - standard error of mean.
[c] P-value for between-treatment comparisons analyzed byWilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 16 (KETO-105-8718). Pain Relief[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age
49-54 hrs	N	56	63	0.0071	0.793	0.053	0.580
	Mean	5.5	4.4				
	S.E.M.	0.18	0.30				
	Min						
	Max						
55-60 hrs	N	55	58	0.0258	0.442	0.095	0.234
	Mean	5.6	4.9				
	S.E.M.	0.16	0.26				
	Min						
	Max						
61-66 hrs	N	51	46	0.1018	0.740	0.215	0.167
	Mean	5.9	5.2				
	S.E.M.	0.05	0.29				
	Min						
	Max						
67-72 hrs	N	55	59	0.0059	0.437	0.162	0.143
	Mean	5.9	5.2				
	S.E.M.	0.06	0.24				
	Min						
	Max						
>72 hrs	N	53	56	0.0092	0.714	0.055	0.113
	Mean	6.0	5.3				
	S.E.M.	0.02	0.23				
	Min						
	Max						

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] S.E.M. - standard error of mean.
[c] P-value for between-treatment comparisons analyzed byWilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 17 (KETO-105-8718). Pain Relief: Incidence Complete[a]

Time Period	Ketorolac Overall=86 N/Total[b]	(%)	Vehicle Overall=84 N/Total	(%)	P-value[c]
30 min	73/80	(91.3%)	68/82	(82.9%)	0.115
1 hr	65/82	(79.3%)	60/80	(75.0%)	0.518
2 hrs	58/74	(78.4%)	35/78	(44.9%)	0.001
3 hrs	55/78	(70.5%)	25/72	(34.7%)	0.001
4 hrs	32/68	(47.1%)	13/70	(18.6%)	0.001
7-12 hrs	32/71	(45.1%)	8/68	(11.8%)	0.001
13-18 hrs	19/52	(36.5%)	9/43	(20.9%)	0.097
19-24 hrs	31/73	(42.5%)	16/74	(21.6%)	0.007
25-30 hrs	33/68	(48.5%)	18/71	(25.4%)	0.005
31-36 hrs	34/62	(54.8%)	20/71	(28.2%)	0.002
37-42 hrs	32/45	(71.1%)	18/39	(46.2%)	0.020
43-48 hrs	38/57	(66.7%)	32/65	(49.2%)	0.052
49-54 hrs	46/56	(82.1%)	39/63	(61.9%)	0.015
55-60 hrs	48/55	(87.3%)	41/58	(70.7%)	0.031
61-66 hrs	48/51	(94.1%)	39/46	(84.8%)	0.073
67-72 hrs	53/55	(96.4%)	47/59	(79.7%)	0.005
>72 hrs	52/53	(98.1%)	47/56	(83.9%)	0.009

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] Non-missing total at each time period.
[c] P-value for between-treatment comparisons analyzed by Chi-square or Fisher's exact tests.

Table 18 (KETO-106-8718). Pain Intensity[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d]			
					By Site	By Sex	By Age	By Iris Color
1 Hour	N	78	81	0.0676	0.773	0.378	0.876	0.686
	Mean	1.3	1.9					
	S.E.M.	0.13	0.17					
	Min							
	Max							
3 Hours	N	75	73	0.0001	0.306	0.833	0.642	0.281
	Mean	2.1	3.2					
	S.E.M.	0.16	0.18					
	Min							
	Max							
4 Hours	N	73	70	0.0001	0.014	0.580	0.315	0.112
	Mean	1.7	3.0					
	S.E.M.	0.16	0.19					
	Min							
	Max							
7-12 Hours	N	72	73	0.0028	0.142	0.757	0.836	0.345
	Mean	1.8	2.5					
	S.E.M.	0.15	0.18					
	Min							
	Max							
13-18 Hours	N	49	33	0.6694	0.078	0.902	0.152	0.147
	Mean	1.8	1.7					
	S.E.M.	0.21	0.23					
	Min							
	Max							

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 18 (KETO-106-8718). Pain Intensity[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age	By Iris Color
19-24 Hours	N	80	77	0.1409	0.107	0.985	0.384	0.952
	Mean	1.4	1.7					
	S.E.M.	0.16	0.17					
	Min							
	Max							
25-30 Hours	N	73	74	0.0342	0.039	0.885	0.778	0.597
	Mean	0.7	1.3					
	S.E.M.	0.11	0.16					
	Min							
	Max							
31-36 Hours	N	68	69	0.0460	0.334	0.404	0.715	0.325
	Mean	0.6	1.0					
	S.E.M.	0.11	0.14					
	Min							
	Max							
37-42 Hours	N	60	47	0.4742	0.224	0.541	0.153	0.833
	Mean	0.4	0.6					
	S.E.M.	0.10	0.14					
	Min							
	Max							
43-48 Hours	N	72	72	0.0863	0.290	0.808	0.928	0.711
	Mean	0.2	0.5					
	S.E.M.	0.07	0.11					
	Min							
	Max							

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 18 (KETO-106-8718). Pain Intensity[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age	By Iris Color
49-54 Hours	N	64	69	0.0069	0.629	0.978	0.686	0.687
	Mean	0.1	0.4					
	S.E.M.	0.04	0.11					
	Min							
	Max							
55-60 Hours	N	63	65	0.0667	0.596	0.965	0.450	0.544
	Mean	0.0	0.3					
	S.E.M.	0.03	0.11					
	Min							
	Max							
61-66 Hours	N	62	58	0.1474	0.716	0.210	0.210	0.450
	Mean	0.0	0.1					
	S.E.M.	0.02	0.07					
	Min							
	Max							
67-72 Hours	N	64	67	0.0939	0.751	0.944	0.756	0.609
	Mean	0.0	0.2					
	S.E.M.	0.02	0.10					
	Min							
	Max							
>72 Hours	N	67	63	0.9627	0.379	0.320	0.965	0.393
	Mean	0.0	0.0					
	S.E.M.	0.03	0.02					
	Min							
	Max							

[a] 0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 19 (KETO-106-8718). Pain Intensity[a]: Incidence No Pain

Time Period	Ketorolac Overall=83 N/Total[b] (%)	Vehicle Overall=87 N/Total[b] (%)	P-value[c]
1 Hour	19/78 (24.4%)	18/81 (22.2%)	0.750
3 Hours	9/75 (12.0%)	5/73 (6.8%)	0.284
4 Hours	16/73 (21.9%)	6/70 (8.6%)	0.027
7-12 Hour	14/72 (19.4%)	9/73 (12.3%)	0.241
13-18 Hours	12/49 (24.5%)	10/33 (30.3%)	0.560
19-24 Hours	32/80 (40.0%)	26/77 (33.8%)	0.419
25-30 Hours	40/73 (54.8%)	34/74 (45.9%)	0.283
31-36 Hours	45/68 (66.2%)	35/69 (50.7%)	0.067
37-42 Hours	45/60 (75.0%)	33/47 (70.2%)	0.580
43-48 Hours	61/72 (84.7%)	53/72 (73.6%)	0.101
49-54 Hours	61/64 (95.3%)	55/69 (79.7%)	0.007
55-60 Hours	60/63 (95.2%)	56/65 (86.2%)	0.078
61-66 Hours	61/62 (98.4%)	54/58 (93.1%)	0.148
67-72 Hours	62/64 (96.9%)	60/67 (89.6%)	0.098
>72 Hours	65/67 (97.0%)	61/63 (96.8%)	>0.999

0-6 Scale for None, Very Mild, Mild, Moderate, Severe, Very Severe, Extremely Severe. If a patient's last recorded score after 1 hour was no pain, a score of 0 was carried forward to subsequent time periods.
Non-missing total at each time period.
P-value for between-treatment comparisons analyzed by Chi-square or Fisher's exact tests.

Table 20 (KETO-106-8718). Pain Relief[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age	By Iris Color
1 Hour	N	76	81	0.9661	0.522	0.538	0.233	0.097
	Mean	5.4	5.2					
	S.E.M.	0.16	0.19					
	Min							
	Max							
3 Hours	N	75	71	0.0001	0.693	0.369	0.835	0.764
	Mean	4.6	3.0					
	S.E.M.	0.22	0.30					
	Min							
	Max							
4 Hours	N	69	67	0.0001	0.316	0.465	0.318	0.472
	Mean	3.8	2.0					
	S.E.M.	0.24	0.25					
	Min							
	Max							
7-12 Hours	N	72	72	0.0001	0.422	0.872	0.205	0.495
	Mean	4.1	2.4					
	S.E.M.	0.24	0.24					
	Min							
	Max							
13-18 Hours	N	44	29	0.3522	0.327	0.658	0.147	0.503
	Mean	3.9	3.5					
	S.E.M.	0.33	0.38					
	Min							
	Max							

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 20 (KETO-106-8718). Pain Relief[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age	By Iris Color
19-24 Hours	N	72	70	0.0708	0.137	0.747	0.658	0.916
	Mean	3.9	3.3					
	S.E.M.	0.26	0.28					
	Min							
	Max							
25-30 Hours	N	65	69	0.0290	0.337	0.785	0.401	0.847
	Mean	4.7	3.8					
	S.E.M.	0.24	0.27					
	Min							
	Max							
31-36 Hours	N	60	64	0.0032	0.304	0.911	0.348	0.616
	Mean	5.2	4.0					
	S.E.M.	0.19	0.29					
	Min							
	Max							
37-42 Hours	N	52	41	0.1270	0.541	0.769	0.486	0.615
	Mean	5.3	4.8					
	S.E.M.	0.19	0.32					
	Min							
	Max							
43-48 Hours	N	61	62	0.0516	0.235	0.860	0.579	0.578
	Mean	5.6	4.8					
	S.E.M.	0.13	0.26					
	Min							
	Max							

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 20 (KETO-106-8718). Pain Relief[a]: Mean Score

Time Period	Statistics[b]	Ketorolac	Vehicle	P-value[c]	Interaction P-value[d] By Site	By Sex	By Age	By Iris Color
49-54 Hours	N	52	60	0.0154	0.488	0.191	0.375	0.959
	Mean	5.9	5.3					
	S.E.M.	0.04	0.22					
	Min							
	Max							
55-60 Hours	N	51	56	0.0113	0.890	0.485	0.622	0.775
	Mean	6.0	5.3					
	S.E.M.	0.02	0.24					
	Min							
	Max							
61-66 Hours	N	50	49	0.0791	0.847	0.296	0.437	0.275
	Mean	6.0	5.8					
	S.E.M.	0.00	0.13					
	Min							
	Max							
67-72 Hours	N	51	57	0.0394	0.630	0.833	0.235	0.786
	Mean	6.0	5.5					
	S.E.M.	0.02	0.21					
	Min							
	Max							
>72 Hours	N	55	53	0.6044	0.105	0.134	0.747	0.651
	Mean	5.9	5.9					
	S.E.M.	0.06	0.11					
	Min							
	Max							

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] S.E.M. - Standard error of mean.
[c] P-value for between-treatment comparisons analyzed by Wilcoxon-Mann-Whitney rank sum tests.
[d] P-value for subgroup-by-treatment interaction from analysis of variance F-test, modeling response as a function of subgroup, treatment, and interaction.

Table 21 (KETO-106-8718). Pain Relief[a]: Incidence Complete

Time Period	Ketorolac Overall=83 N/Total[b] (%)	Vehicle Overall=87 N/Total[b] (%)	P-value[c]
1 Hour	58/76 (76.3%)	62/81 (76.5%)	0.973
3 Hours	42/75 (56.0%)	24/71 (33.8%)	0.007
4 Hours	20/69 (29.0%)	8/67 (11.9%)	0.014
7-12 Hours	25/72 (34.7%)	9/72 (12.5%)	0.002
13-18 Hours	14/44 (31.8%)	7/29 (24.1%)	0.478
19-24 Hours	27/72 (37.5%)	18/70 (25.7%)	0.131
25-30 Hours	35/65 (53.8%)	27/69 (39.1%)	0.088
31-36 Hours	41/60 (68.3%)	30/64 (46.9%)	0.016
37-42 Hours	40/52 (76.9%)	26/41 (63.4%)	0.154
43-48 Hours	49/61 (80.3%)	42/62 (67.7%)	0.112
49-54 Hours	50/52 (96.2%)	49/60 (81.7%)	0.017
55-60 Hours	50/51 (98.0%)	47/56 (83.9%)	0.012
61-66 Hours	50/50 (100.0%)	46/49 (93.9%)	0.076
67-72 Hours	50/51 (98.0%)	50/57 (87.7%)	0.041
>72 Hours	53/55 (96.4%)	52/53 (98.1%)	0.580

[a] 0-6 Scale for None, Little, Some, Moderate, Good Deal, Great Deal, Complete: complete or no pain. If a patient's last recorded score after 1 hour was complete relief, a score of 6 was carried forward.
[b] Non-missing total at each time period.
[c] P-value for between-treatment comparisons analyzed by Chi-square or Fisher's exact tests.

Table 22 (KETO-105-8718). Inconsistent data (a)

OBS	SBJ1A	KETO	VIS1N	PANILAG1	PANEPR1F	PANREL1F	MELDSE1F	ISTTME1T	DRY1T	DRY1F
1	101	1	2.00	moderate pain	Severe Pain	A Good Deal of Relief	Breakfast	1:30:00	1:30:00	AM
2	101	1	3.01	mild pain	Moderate Pain	A Great Deal of Relief	Breakfast	9:30:00	9:30:00	AM
3	106	2	2.00	mild pain	Moderate Pain	Some Relief	.	.	4:15:00	.
4	106	2	2.00	mild pain	Moderate Pain	Some Relief	Bedtime	9:30:00	9:30:00	PM
5	106	2	3.00	mild pain	Moderate Pain	Some Relief	Bedtime	9:35:00	9:30:00	PM
6	106	2	3.01	very mild pain	Mild Pain	Moderate Relief	Dinner	5:45:00	5:35:00	PM
7	108	2	2.00	no pain at all	Mild Pain	Some Relief	.	.	4:45:00	.
8	109	2	2.00	very mild pain	Mild Pain	A Great Deal of Relief	.	.	4:45:00	.
9	109	2	2.00	mild pain	Moderate Pain	A Great Deal of Relief	.	.	6:45:00	.
10	112	1	2.00	no pain at all	Very Mild Pain	Moderate Relief	Bedtime	9:10:00	9:10:00	PM
11	113	1	2.00	mild pain	Moderate Pain	Moderate Relief	Dinner	5:35:00	5:30:00	PM
12	113	1	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Bedtime	9:15:00	9:00:00	PM
13	113	1	3.00	moderate pain	Severe Pain	Moderate Relief	Lunch	11:00:00	11:00:00	AM
14	119	1	2.00	very mild pain	Moderate Pain	Moderate Relief	.	.	10:50:00	.
15	119	1	3.00	very mild pain	Mild Pain	Some Relief	Bedtime	9:00:00	8:55:00	PM
16	120	1	2.00	very mild pain	Moderate Pain	A Great Deal of Relief	.	.	4:00:00	.
17	120	1	2.00	moderate pain	Severe Pain	Moderate Relief	.	.	5:00:00	.
18	120	1	2.00	moderate pain	Severe Pain	A Good Deal of Relief	.	.	7:00:00	.
19	120	1	3.01	moderate pain	Severe Pain	Some Relief	Breakfast	9:30:00	9:30:00	AM
20	201	2	3.00	very mild pain	Severe Pain	A Good Deal of Relief	Breakfast	9:25:00	9:25:00	AM
21	203	2	2.00	no pain at all	Very Mild Pain	A Great Deal of Relief	.	.	2:16:00	.
22	203	2	2.00	very mild pain	Mild Pain	A Good Deal of Relief	Dinner	6:35:00	6:35:00	PM
23	204	1	2.00	very mild pain	Mild Pain	Moderate Relief	.	.	10:20:00	.
24	204	1	2.00	mild pain	Moderate Pain	Moderate Relief	Dinner	6:45:00	6:45:00	PM
25	207	1	3.00	very mild pain	Moderate Pain	A Good Deal of Relief	Breakfast	6:15:00	6:15:00	AM
26	301	1	3.00	very mild pain	Moderate Pain	A Great Deal of Relief	Breakfast	6:56:00	6:56:00	AM
27	305	1	2.00	mild pain	Moderate Pain	Moderate Relief	Dinner	6:00:00	6:00:00	PM
28	305	1	3.00	moderate pain	Severe Pain	Some Relief	Breakfast	6:00:00	6:00:00	AM
29	305	1	3.00	moderate pain	Severe Pain	Some Relief	Dinner	6:00:00	6:00:00	PM
30	305	1	3.02	very mild pain	Mild Pain	Moderate Relief	Breakfast	6:00:00	6:00:00	AM
31	309	2	2.00	very mild pain	Mild Pain	Some Relief	.	.	11:43:00	.
32	309	2	2.00	very mild pain	Mild Pain	Some Relief	.	.	2:20:00	.
33	310	2	3.00	very mild pain	Mild Pain	Some Relief	Lunch	12:00:00	12:00:00	PM
34	310	2	3.00	very mild pain	Mild Pain	Some Relief	Bedtime	9:00:00	9:00:00	PM
35	311	1	2.00	very mild pain	Mild Pain	A Great Deal of Relief	Bedtime	9:30:00	9:30:00	PM
36	319	2	3.00	mild pain	Moderate Pain	Moderate Relief	Lunch	1:00:00	1:00:00	PM
37	320	1	2.00	moderate pain	Very Severe Pain	A Good Deal of Relief	.	.	1:20:00	.
38	320	1	2.00	mild pain	Severe Pain	A Great Deal of Relief	Dinner	6:15:00	6:15:00	PM
39	321	2	2.00	no pain at all	Moderate Pain	Moderate Relief	.	.	3:10:00	.
40	321	2	2.00	moderate pain	Severe Pain	Some Relief	Bedtime	8:23:00	8:25:00	PM
41	321	2	3.00	very mild pain	Moderate Pain	A Good Deal of Relief	Bedtime	9:05:00	9:00:00	PM
42	322	1	2.00	mild pain	Moderate Pain	A Great Deal of Relief	.	.	5:46:00	.
43	322	1	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Bedtime	10:50:00	10:52:00	PM
44	322	1	3.00	mild pain	Moderate Pain	A Good Deal of Relief	Lunch	11:55:00	11:52:00	AM
45	323	2	2.00	mild pain	Moderate Pain	A Good Deal of Relief	.	.	12:00:00	.
46	323	2	2.00	moderate pain	Severe Pain	Moderate Relief	Lunch	1:10:00	1:05:00	PM
47	325	1	3.00	moderate pain	Severe Pain	A Good Deal of Relief	Dinner	5:43:00	5:40:00	PM
48	327	2	2.00	mild pain	Moderate Pain	Some Relief	.	.	4:00:00	.
49	327	2	2.00	moderate pain	Severe Pain	Some Relief	Dinner	6:00:00	6:00:00	PM
50	327	2	3.00	moderate pain	Severe Pain	Moderate Relief	Lunch	11:30:00	11:30:00	AM
51	327	2	3.01	very mild pain	Mild Pain	A Great Deal of Relief	Bedtime	11:40:00	11:40:00	PM
52	328	1	3.00	no pain at all	Severe Pain	Moderate Relief	Lunch	11:30:00	11:30:00	AM
53	328	1	3.02	very mild pain	Mild Pain	A Great Deal of Relief	Breakfast	.	7:15:00	.
54	328	1	3.02	no pain at all	Very Mild Pain	A Great Deal of Relief	Dinner	.	6:00:00	.

[illegible]	329	1	3.00	mild pain	Moderate Pain	A Good Deal of Relief	.	.	9:50:00	.
[illegible]	329	1	3.00	very mild pain	Mild Pain	A Great Deal of Relief	Bedtime	9:05:00	8:55:00	PM
[illegible]	330	2	2.00	mild pain	Severe Pain	Moderate Relief	.	4:30:00	4:30:00	PM
58	330	2	2.00	mild pain	Severe Pain	Moderate Relief	Dinner	7:05:00	7:05:00	PM
59	332	1	3.00	no pain at all	Moderate Pain	Moderate Relief	Lunch	11:25:00	11:25:00	AM
60	334	1	2.00	no pain at all	Very Mild Pain	A Good Deal of Relief	Lunch	2:30:00	2:30:00	PM
61	337	1	3.00	mild pain	Severe Pain	Some Relief	Breakfast	8:15:00	8:15:00	AM
62	340	2	2.00	moderate pain	Severe Pain	Some Relief	.	.	4:10:00	.
63	344	2	3.00	moderate pain	Severe Pain	A Good Deal of Relief	Breakfast	7:10:00	7:10:00	AM
64	345	2	3.01	mild pain	Moderate Pain	Moderate Relief	Lunch	11:55:00	11:55:00	AM
65	346	2	3.00	mild pain	Moderate Pain	A Good Deal of Relief	Bedtime	9:59:00	9:55:00	PM
66	347	1	2.00	very mild pain	Moderate Pain	Some Relief	.	.	11:25:00	.
67	348	1	2.00	mild pain	Moderate Pain	Moderate Relief	.	.	11:40:00	.
68	351	1	2.00	mild pain	Moderate Pain	Some Relief	Dinner	4:39:00	4:30:00	PM
69	351	1	2.00	mild pain	Severe Pain	A Good Deal of Relief	Bedtime	8:16:00	8:15:00	PM
70	351	1	3.00	moderate pain	Severe Pain	Some Relief	Dinner	5:25:00	5:22:00	PM
71	352	1	2.00	no pain at all	Mild Pain	A Great Deal of Relief	Lunch	2:00:00	2:10:00	PM
72	402	2	3.01	mild pain	Moderate Pain	Some Relief	Lunch	12:25:00	12:15:00	PM
73	404	1	3.01	very mild pain	Mild Pain	Some Relief	Breakfast	7:12:00	7:20:00	AM
74	405	1	3.00	mild pain	Moderate Pain	Some Relief	Bedtime	8:25:00	8:25:00	PM
75	410	1	3.00	mild pain	Moderate Pain	A Good Deal of Relief	Breakfast	6:35:00	6:30:00	AM
76	411	2	2.00	very mild pain	Mild Pain	A Great Deal of Relief	.	.	4:30:00	.
77	412	1	3.00	no pain at all	Severe Pain	A Great Deal of Relief	Breakfast	7:25:00	7:20:00	AM
78	415	2	2.00	very mild pain	Mild Pain	Moderate Relief	Dinner	6:31:00	6:30:00	PM
79	415	2	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Bedtime	9:06:00	9:01:00	PM
80	416	2	2.00	no pain at all	Very Mild Pain	A Great Deal of Relief	Bedtime	9:05:00	9:10:00	PM
81	420	1	3.00	moderate pain	Very Severe Pain	A Great Deal of Relief	Lunch	12:00:00	12:00:00	PM
82	424	1	2.00	very mild pain	Mild Pain	Moderate Relief	Bedtime	10:30:00	10:30:00	PM
83	425	1	2.00	very mild pain	Mild Pain	Some Relief	.	.	10:15:00	.
84	430	1	3.00	mild pain	Moderate Pain	Moderate Relief	Breakfast	7:00:00	7:00:00	AM
85	433	1	2.00	mild pain	Moderate Pain	Some Relief	Bedtime	9:30:00	9:30:00	PM
86	436	2	2.00	moderate pain	Severe Pain	A Great Deal of Relief	Dinner	5:15:00	5:15:00	PM
87	436	2	3.00	very mild pain	Mild Pain	A Good Deal of Relief	Lunch	1:10:00	1:05:00	PM
88	436	2	3.00	mild pain	Moderate Pain	A Good Deal of Relief	Dinner	8:05:00	8:07:00	PM
89	436	2	3.01	moderate pain	Severe Pain	Some Relief	Lunch	12:00:00	12:05:00	PM
90	437	2	3.00	moderate pain	Severe Pain	Some Relief	Bedtime	10:17:00	10:15:00	PM
91	441	1	3.00	mild pain	Moderate Pain	A Good Deal of Relief	Dinner	5:05:00	5:00:00	PM
92	443	1	2.00	very mild pain	Mild Pain	A Great Deal of Relief	Lunch	7:20:00	7:20:00	PM
93	452	2	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Dinner	6:30:00	6:30:00	PM
94	452	2	3.00	very mild pain	Mild Pain	A Good Deal of Relief	Dinner	11:00:00	11:00:00	PM
95	452	2	3.01	mild pain	Moderate Pain	Moderate Relief	Breakfast	9:00:00	9:00:00	AM
96	458	1	2.00	mild pain	Moderate Pain	Moderate Relief	Dinner	6:00:00	6:00:00	PM
97	458	1	2.00	moderate pain	Severe Pain	Moderate Relief	Bedtime	10:30:00	10:30:00	PM
98	459	2	2.00	very mild pain	Mild Pain	A Good Deal of Relief	Bedtime	9:45:00	9:45:00	PM
99	461	1	2.00	no pain at all	Mild Pain	A Great Deal of Relief	.	.	6:40:00	.
100	465	1	2.00	no pain at all	Mild Pain	Moderate Relief	Bedtime	11:00:00	11:00:00	PM
101	466	2	2.00	mild pain	Moderate Pain	A Good Deal of Relief	.	.	11:25:00	.
102	467	1	2.00	mild pain	Moderate Pain	Moderate Relief	Bedtime	.	10:15:00	.
103	468	2	2.00	mild pain	Moderate Pain	Some Relief	Bedtime	10:10:00	10:10:00	PM
104	469	2	2.00	no pain at all	Mild Pain	Moderate Relief	.	.	1:30:00	.
105	469	2	2.00	mild pain	Moderate Pain	Some Relief	Lunch	2:30:00	2:30:00	PM

Table 23 (KETO-105-8718). Inconsistent data (b)

OBS	SBJIA	KETO	VISIN	PANJIAGI	PANEPRIF	PANRELIF	MEDSE1F	ISTTME1T	DRY1T	DRY1F
1	102	2	2.00	severe pain	Moderate Pain	No Relief	.	.	5:35:00	.
2	102	2	3.00	severe pain	Moderate Pain	No Relief	Breakfast	6:20:00	6:15:00	AM
3	102	2	3.00	severe pain	Moderate Pain	No Relief	Bedtime	9:00:00	8:54:00	PM
4	104	2	2.00	very severe pa	Moderate Pain	No Relief	Lunch	1:35:00	1:35:00	PM
5	104	2	2.00	moderate pain	Mild Pain	No Relief	Bedtime	10:45:00	10:50:00	PM
6	104	2	3.00	severe pain	Very Mild Pain	No Relief	Lunch	.	11:00:00	.
7	116	2	3.00	severe pain	Mild Pain	No Relief	Lunch	1:30:00	1:25:00	PM
8	121	2	3.00	moderate pain	Very Mild Pain	No Relief	Lunch	1:00:00	1:00:00	PM
9	201	2	2.00	very severe pa	Moderate Pain	No Relief	Dinner	6:30:00	6:30:00	PM
10	201	2	3.01	mild pain	Very Mild Pain	No Relief	Lunch	1:15:00	1:15:00	PM
11	201	2	3.02	very mild pain	No Pain	No Relief	Breakfast	7:50:00	7:50:00	AM
12	204	1	3.01	severe pain	Moderate Pain	No Relief	Bedtime	1:00:00	1:00:00	AM
13	207	1	3.01	very mild pain	No Pain	No Relief	Dinner	6:00:00	6:00:00	PM
14	313	2	2.00	extremely seve	Very Severe Pain	No Relief	Bedtime	8:30:00	8:30:00	PM
15	313	2	3.00	very severe pa	Moderate Pain	No Relief	Dinner	4:30:00	4:30:00	PM
16	316	2	3.00	severe pain	Moderate Pain	No Relief	Breakfast	8:45:00	8:50:00	AM
17	323	2	2.00	very severe pa	Moderate Pain	No Relief	Dinner	6:10:00	6:10:00	PM
18	323	2	3.00	severe pain	Mild Pain	No Relief	Breakfast	6:50:00	6:50:00	AM
19	324	1	3.00	severe pain	Moderate Pain	No Relief	Breakfast	7:42:00	7:42:00	AM
20	325	1	3.01	moderate pain	Mild Pain	No Relief	Lunch	12:47:00	12:45:00	PM
21	331	2	3.02	mild pain	Very Mild Pain	No Relief	Breakfast	7:30:00	7:30:00	AM
22	335	2	2.00	moderate pain	Mild Pain	No Relief	Dinner	5:53:00	5:51:00	PM
23	335	2	3.01	mild pain	Very Mild Pain	No Relief	Breakfast	6:46:00	6:44:00	AM
24	335	2	3.01	very mild pain	No Pain	No Relief	Lunch	12:05:00	11:57:00	PM
25	339	2	3.00	severe pain	Moderate Pain	No Relief	Breakfast	8:05:00	8:00:00	PM
26	339	2	3.00	moderate pain	Mild Pain	No Relief	Lunch	1:00:00	1:00:00	PM
27	339	2	3.00	mild pain	Very Mild Pain	No Relief	Bedtime	8:30:00	8:30:00	PM
28	339	2	3.01	mild pain	Very Mild Pain	No Relief	Lunch	1:45:00	1:45:00	PM
29	339	2	3.01	very mild pain	No Pain	No Relief	Dinner	6:00:00	6:00:00	PM
30	345	2	2.00	very severe pa	Severe Pain	No Relief	Dinner	5:00:00	5:00:00	PM
31	346	2	2.00	extremely seve	Severe Pain	No Relief	.	.	6:17:00	.
32	347	1	3.00	very severe pa	Severe Pain	No Relief	Breakfast	8:00:00	8:00:00	AM
33	354	2	3.00	severe pain	Mild Pain	No Relief	Lunch	1:15:00	1:05:00	PM
34	402	2	2.00	severe pain	Moderate Pain	No Relief	Bedtime	9:20:00	9:10:00	PM
35	402	2	3.00	moderate pain	Mild Pain	No Relief	Breakfast	7:20:00	7:15:00	AM
36	407	2	3.00	moderate pain	Mild Pain	No Relief	Dinner	6:30:00	6:30:00	PM
37	409	2	3.01	very mild pain	No Pain	No Relief	Breakfast	7:10:00	7:05:00	AM
38	417	2	3.00	very severe pa	Severe Pain	No Relief	Breakfast	7:20:00	7:15:00	AM
39	417	2	3.00	severe pain	Moderate Pain	No Relief	Lunch	12:50:00	12:50:00	PM
40	417	2	3.01	moderate pain	Mild Pain	No Relief	Breakfast	7:30:00	7:30:00	AM
41	422	2	2.00	extremely seve	Very Mild Pain	No Relief	Dinner	5:30:00	5:30:00	PM
42	423	2	3.00	moderate pain	Mild Pain	No Relief	Breakfast	6:15:00	6:15:00	AM
43	423	2	3.00	mild pain	Very Mild Pain	No Relief	Lunch	12:00:00	12:00:00	PM
44	429	2	2.00	very severe pa	Severe Pain	No Relief	.	.	5:45:00	.
45	429	2	3.00	very severe pa	Severe Pain	No Relief	Bedtime	10:30:00	10:30:00	PM
46	429	2	3.01	severe pain	Moderate Pain	No Relief	Lunch	12:45:00	12:45:00	PM
47	429	2	3.01	severe pain	Moderate Pain	No Relief	Bedtime	10:30:00	10:30:00	PM
48	429	2	3.02	moderate pain	Mild Pain	No Relief	Breakfast	7:35:00	7:35:00	AM
49	433	1	3.00	severe pain	Moderate Pain	No Relief	Bedtime	10:30:00	10:30:00	PM
50	433	1	3.01	moderate pain	Mild Pain	No Relief	Breakfast	10:00:00	10:00:00	AM
51	435	2	3.00	extremely seve	Severe Pain	No Relief	Breakfast	6:45:00	6:50:00	AM
52	435	2	3.00	severe pain	Moderate Pain	No Relief	Dinner	5:05:00	5:00:00	PM
53	435	2	3.01	moderate pain	Mild Pain	No Relief	Breakfast	7:40:00	7:30:00	AM

54	435	1	1.01	mild pain	Very Mild Pain	No Relief	Lunch	11:35:00	11:30:00	AM
55	444	1	1.00	extremely seve	Very Severe Pain	No Relief	.	.	7:40:00	.
56	444	2	3.00	very severe pa	Moderate Pain	No Relief	Lunch	11:15:00	11:15:00	AM
57	444	2	3.00	moderate pain	Mild Pain	No Relief	Bedtime	10:10:00	10:10:00	PM
58	448	2	3.02	extremely seve	Very Severe Pain	No Relief	Breakfast	7:30:00	7:30:00	AM
59	463	2	3.00	severe pain	No Pain	No Relief	Breakfast	8:00:00	8:00:00	AM
60	466	2	3.00	moderate pain	Mild Pain	No Relief	Bedtime	10:08:00	10:05:00	PM
61	466	2	3.01	mild pain	No Pain	No Relief	Breakfast	6:15:00	6:20:00	AM
62	470	2	3.01	very severe pa	Severe Pain	No Relief	.	.	9:15:00	.
63	475	2	3.00	very mild pain	No Pain	No Relief	.	.	3:27:00	.
64	476	2	2	very severe pa	Severe Pain	No Relief	Dinner	6:25:00	6:25:00	PM
65	478	2	3	severe pain	Moderate Pain	No Relief	Breakfast	2:00:00	2:10:00	AM
66	478	2	3	moderate pain	Mild Pain	No Relief	Lunch	7:55:00	7:55:00	AM
67	478	2	3	mild pain	No Pain	No Relief	Bedtime	7:20:00	7:30:00	PM

APPEARS THIS WAY

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 24 (KETO-106-8718). Inconsistent data (a)

OBS	BBJIA	KETO	VISIN	PANILAGI	PANKIRIF	PANRELIF	MELDBEIF	ISTTMEIT	DRYIT	DRYIF
1	201	8	2.00	very mild pain	Mild Pain	Moderate Relief	Bedtime	9:30:00	.	PM
2	207	1	2.00	no pain at all	Moderate Pain	A Great Deal of Relief	Dinner	7:15:00	.	PM
3	214	1	2.00	very mild pain	Mild Pain	A Great Deal of Relief	.	.	9:30:00	.
4	216	1	2.00	mild pain	Moderate Pain	Moderate Relief	Dinner	7:23:00	.	PM
5	216	1	2.00	moderate pain	Severe Pain	Moderate Relief	Bedtime	9:40:00	.	PM
6	302	2	2.00	moderate pain	Very Severe Pain	Moderate Relief	Bedtime	10:15:00	.	PM
7	302	2	3.01	severe pain	Very Severe Pain	Moderate Relief	Breakfast	7:45:00	.	AM
8	303	1	3.00	moderate pain	Very Severe Pain	Moderate Relief	Breakfast	8:10:00	.	AM
9	303	1	3.00	moderate pain	Severe Pain	A Good Deal of Relief	Dinner	6:20:00	.	PM
10	304	1	2.00	very mild pain	Moderate Pain	A Great Deal of Relief	Lunch	1:55:00	.	PM
11	306	1	3.00	no pain at all	Very Mild Pain	A Good Deal of Relief	Lunch	12:50:00	.	PM
12	308	2	2.00	very mild pain	Moderate Pain	A Good Deal of Relief	Lunch	2:30:00	.	PM
13	312	1	2.00	no pain at all	Moderate Pain	A Good Deal of Relief	Bedtime	10:30:00	.	PM
14	313	1	2.00	mild pain	Moderate Pain	Some Relief	Lunch	1:50:00	.	PM
15	313	1	2.00	very mild pain	Mild Pain	A Great Deal of Relief	Bedtime	10:40:00	.	PM
16	317	2	3.00	mild pain	Moderate Pain	Moderate Relief	Breakfast	7:00:00	.	AM
17	317	2	3.00	mild pain	Moderate Pain	Moderate Relief	Dinner	5:00:00	.	PM
18	318	2	2.00	very mild pain	Severe Pain	A Good Deal of Relief	Lunch	12:30:00	.	PM
19	318	2	2.00	severe pain	Extremely Severe Pain	A Good Deal of Relief	.	.	1:00:00	.
20	319	1	2.00	very mild pain	Mild Pain	Moderate Relief	Lunch	1:55:00	.	PM
21	323	1	2.00	very mild pain	Mild Pain	A Great Deal of Relief	.	.	4:15:00	.
22	325	1	3.00	very mild pain	Mild Pain	A Great Deal of Relief	Lunch	12:30:00	.	PM
23	327	2	2.00	very mild pain	Moderate Pain	A Great Deal of Relief	Lunch	2:45:00	.	PM
24	329	2	2.00	moderate pain	Severe Pain	Some Relief	Dinner	8:00:00	.	PM
25	332	1	2.00	mild pain	Moderate Pain	Some Relief	Lunch	4:55:00	.	PM
26	333	1	2.00	mild pain	Moderate Pain	Moderate Relief	Dinner	7:55:00	.	PM
27	335	2	2.00	mild pain	Moderate Pain	Some Relief	Bedtime	10:15:00	.	PM
28	335	2	3.00	mild pain	Moderate Pain	A Good Deal of Relief	Dinner	4:30:00	.	PM
29	336	2	2.00	very mild pain	Moderate Pain	A Good Deal of Relief	.	.	4:50:00	.
30	336	2	2.00	very mild pain	Moderate Pain	A Good Deal of Relief	Bedtime	10:00:00	.	PM
31	339	2	2.00	mild pain	Extremely Severe Pain	Some Relief	Lunch	3:35:00	.	PM
32	339	2	3.00	very mild pain	Mild Pain	Moderate Relief	Bedtime	7:30:00	.	PM
33	402	1	2.00	very mild pain	Moderate Pain	A Good Deal of Relief	Dinner	7:00:00	.	PM
34	402	1	3.01	no pain at all	Very Mild Pain	A Great Deal of Relief	Breakfast	7:30:00	.	AM
35	402	1	3.01	very mild pain	Mild Pain	A Great Deal of Relief	Lunch	1:00:00	.	PM
36	403	1	2.00	very mild pain	Mild Pain	A Great Deal of Relief	Bedtime	11:30:00	.	PM
37	403	1	3.00	mild pain	Moderate Pain	A Great Deal of Relief	Breakfast	8:00:00	.	AM
38	405	1	3.00	very mild pain	Mild Pain	Moderate Relief	Dinner	5:00:00	.	PM
39	408	1	2.00	very mild pain	Mild Pain	A Good Deal of Relief	Bedtime	11:00:00	.	PM
40	408	1	3.00	no pain at all	Mild Pain	Some Relief	Lunch	12:45:00	.	PM
41	408	1	3.01	no pain at all	Moderate Pain	Some Relief	Breakfast	7:55:00	.	AM
42	502	1	2.00	very mild pain	Mild Pain	A Great Deal of Relief	Dinner	5:45:00	.	PM
43	502	1	3.00	very mild pain	Moderate Pain	A Great Deal of Relief	Breakfast	6:10:00	.	AM
44	503	2	2.00	no pain at all	Moderate Pain	A Good Deal of Relief	Bedtime	7:00:00	.	PM
45	503	2	3.00	very mild pain	Mild Pain	A Good Deal of Relief	Dinner	5:00:00	.	PM
46	505	2	2.00	very mild pain	Moderate Pain	Moderate Relief	Dinner	5:30:00	.	PM
47	505	2	3.00	mild pain	Moderate Pain	Moderate Relief	Bedtime	8:45:00	.	PM
48	507	1	2.00	no pain at all	Moderate Pain	Moderate Relief	Bedtime	7:45:00	.	PM
49	507	1	3.00	mild pain	Moderate Pain	Moderate Relief	Breakfast	7:15:00	.	AM
50	509	2	3.01	mild pain	Moderate Pain	Some Relief	Breakfast	7:30:00	.	AM
51	602	1	2.00	mild pain	Moderate Pain	Some Relief	Lunch	11:45:00	.	AM
52	602	1	2.00	very mild pain	Moderate Pain	A Good Deal of Relief	Bedtime	10:00:00	.	PM
53	603	2	2.00	moderate pain	Severe Pain	A Good Deal of Relief	.	.	6:00:00	.
54	604	1	2.00	no pain at all	Mild Pain	A Great Deal of Relief	Bedtime	8:55:00	.	PM

55	604	1	3.00	mild pain	Moderate Pain	A Great Deal of Relief	Dinner	4:00:00	.	PM
56	606	1	3.00	mild pain	Moderate Pain	Moderate Relief	.	.	1:00:00	.
57	610	1	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Dinner	3:30:00	.	PM
58	613	2	2.00	no pain at all	Moderate Pain	Some Relief	Lunch	2:00:00	.	PM
59	614	1	2.00	no pain at all	Very Mild Pain	A Great Deal of Relief	Dinner	6:30:00	.	PM
60	614	1	2.00	very mild pain	Mild Pain	A Great Deal of Relief	Bedtime	10:30:00	.	PM
61	614	1	3.00	mild pain	Moderate Pain	A Great Deal of Relief	Breakfast	7:00:00	.	AM
62	617	1	2.00	very mild pain	Moderate Pain	A Good Deal of Relief	Lunch	3:10:00	.	PM
63	619	2	2.00	no pain at all	Moderate Pain	Moderate Relief	Lunch	4:00:00	.	PM
64	619	2	3.00	very mild pain	Mild Pain	A Good Deal of Relief	Breakfast	9:15:00	.	AM
65	620	2	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Lunch	1:00:00	.	PM
66	620	2	2.00	very mild pain	Moderate Pain	A Great Deal of Relief	Dinner	6:00:00	.	PM
67	702	1	2.00	very mild pain	Mild Pain	Some Relief	Lunch	11:55:00	.	AM
68	702	1	2.00	mild pain	Moderate Pain	Some Relief	Dinner	5:15:00	.	PM
69	703	2	2.00	very mild pain	Severe Pain	A Great Deal of Relief	Lunch	11:35:00	.	AM
70	708	2	2.00	very mild pain	Moderate Pain	Moderate Relief	Lunch	12:15:00	.	PM
71	712	1	2.00	very mild pain	Mild Pain	Some Relief	Lunch	12:11:00	.	PM
72	712	1	3.00	very mild pain	Mild Pain	A Great Deal of Relief	Dinner	5:45:00	.	PM
73	715	2	2.00	very mild pain	Moderate Pain	Some Relief	Lunch	12:01:00	.	PM
74	716	2	2.00	very mild pain	Moderate Pain	Moderate Relief	Lunch	12:12:00	.	PM
75	716	2	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Bedtime	9:30:00	.	PM
76	720	2	2.00	very mild pain	Moderate Pain	A Great Deal of Relief	Lunch	12:33:00	.	PM
77	720	2	3.00	very mild pain	Mild Pain	A Great Deal of Relief	Dinner	6:10:00	.	PM
78	721	2	2.00	no pain at all	Severe Pain	A Great Deal of Relief	Lunch	1:30:00	.	PM
79	723	1	2.00	no pain at all	Very Mild Pain	A Great Deal of Relief	Bedtime	10:14:00	.	PM
80	724	1	2.00	no pain at all	Very Mild Pain	A Great Deal of Relief	Lunch	12:00:00	.	PM
81	724	1	2.00	very mild pain	Mild Pain	A Great Deal of Relief	.	.	1:05:00	.
82	725	2	3.01	very mild pain	Moderate Pain	Some Relief	Dinner	5:35:00	.	PM
83	733	2	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Lunch	12:16:00	.	PM
84	736	1	2.00	moderate pain	Severe Pain	Moderate Relief	Lunch	12:30:00	.	PM
85	801	2	3.00	mild pain	Moderate Pain	A Good Deal of Relief	Bedtime	9:20:00	.	PM
86	804	2	2.00	severe pain	Very Severe Pain	Some Relief	.	.	2:05:00	.
87	805	2	2.00	very severe pa	Extremely Severe Pain	Some Relief	Dinner	5:40:00	.	PM
88	807	2	3.00	no pain at all	Mild Pain	A Great Deal of Relief	Lunch	12:00:00	.	PM
89	808	1	2.00	very mild pain	Mild Pain	A Great Deal of Relief	Dinner	4:30:00	.	PM
90	A01	2	2.00	no pain at all	Mild Pain	A Great Deal of Relief	Lunch	12:54:00	.	PM
91	A01	2	3.00	no pain at all	Mild Pain	A Good Deal of Relief	Breakfast	3:15:00	.	AM
92	A01	2	3.00	no pain at all	Mild Pain	A Good Deal of Relief	Bedtime	10:00:00	.	PM
93	A03	1	2.00	mild pain	Moderate Pain	Moderate Relief	Bedtime	9:30:00	.	PM
94	A07	1	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Lunch	12:15:00	.	PM
95	A07	1	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Dinner	5:30:00	.	PM
96	A07	1	3.00	moderate pain	Severe Pain	Some Relief	Breakfast	9:45:00	.	AM
97	A07	1	3.00	very mild pain	Mild Pain	A Good Deal of Relief	Dinner	7:00:00	.	PM
98	A07	1	3.01	very mild pain	Mild Pain	A Great Deal of Relief	Breakfast	7:00:00	.	AM
99	A08	1	2.00	mild pain	Moderate Pain	A Good Deal of Relief	Bedtime	9:40:00	.	PM
100	A09	1	3.00	very mild pain	Mild Pain	Moderate Relief	Dinner	7:20:00	.	PM
101	B02	1	2.00	moderate pain	Severe Pain	Some Relief	Dinner	4:45:00	.	PM
102	C04	2	2.00	moderate pain	Very Severe Pain	Some Relief	Lunch	12:00:00	.	PM

Table 25 (KETO-106-8718). Inconsistent data (b)

OBS	SBJIA	KETO	VISIN	PANILAG1	PANEPR1F	PANREL1F	MELDSE1F	ISTTME1T	DRY1T	DRY1F
1	204	1	2.00	extremely seve	Severe Pain	No Relief	.	.	10:35:00	.
2	204	1	3.00	severe pain	Moderate Pain	No Relief	Breakfast	9:00:00	.	AM
3	205	2	2.00	severe pain	Moderate Pain	No Relief	.	1:40:00	.	AM
4	211	1	3.00	severe pain	Mild Pain	No Relief	Breakfast	9:00:00	.	AM
5	215	2	3.00	extremely seve	Severe Pain	No Relief	Breakfast	9:00:00	.	AM
6	215	2	3.00	severe pain	Moderate Pain	No Relief	Lunch	2:00:00	.	PM
7	215	2	3.00	moderate pain	.	No Relief	Dinner	.	.	.
8	215	2	3.01	moderate pain	Mild Pain	No Relief	Dinner	5:00:00	.	PM
9	215	2	3.01	mild pain	Very Mild Pain	No Relief	Bedtime	9:00:00	.	PM
10	314	2	3.00	moderate pain	Mild Pain	No Relief	Lunch	11:50:00	.	AM
11	314	2	3.00	severe pain	Moderate Pain	No Relief	Bedtime	10:00:00	.	PM
12	314	2	3.01	moderate pain	Mild Pain	No Relief	Lunch	12:15:00	.	PM
13	321	2	2.00	severe pain	Moderate Pain	No Relief	Dinner	6:55:00	.	PM
14	321	2	2.00	moderate pain	.	No Relief	Bedtime	10:20:00	.	PM
15	324	2	2.00	severe pain	Moderate Pain	No Relief	Dinner	6:00:00	.	PM
16	324	2	3.00	moderate pain	Mild Pain	No Relief	Breakfast	8:20:00	.	AM
17	324	2	3.00	mild pain	Very Mild Pain	No Relief	Bedtime	10:00:00	.	PM
18	327	2	3.00	severe pain	Moderate Pain	No Relief	Lunch	12:00:00	.	AM
19	327	2	3.00	moderate pain	Very Mild Pain	No Relief	Bedtime	6:30:00	.	PM
20	327	2	3.01	very mild pain	No Pain	No Relief	Breakfast	7:00:00	.	AM
21	328	2	2.00	extremely seve	Severe Pain	No Relief	Dinner	6:00:00	.	PM
22	406	2	3.00	severe pain	Mild Pain	No Relief	Breakfast	8:44:00	.	AM
23	406	2	3.00	mild pain	Very Mild Pain	No Relief	Dinner	8:00:00	.	PM
24	504	1	3.00	severe pain	Moderate Pain	No Relief	Dinner	6:00:00	.	PM
25	512	2	2.00	extremely seve	Very Severe Pain	No Relief	Bedtime	10:20:00	.	PM
26	601	2	3.00	severe pain	Moderate Pain	No Relief	Lunch	12:30:00	.	PM
27	601	2	3.00	moderate pain	Mild Pain	No Relief	Dinner	5:15:00	.	PM
28	601	2	3.00	mild pain	Very Mild Pain	No Relief	Bedtime	9:40:00	.	PM
29	615	1	2.00	severe pain	Moderate Pain	No Relief	Bedtime	10:25:00	.	PM
30	615	1	3.00	moderate pain	Mild Pain	No Relief	Dinner	6:30:00	.	PM
31	701	1	2.00	mild pain	Very Mild Pain	No Relief	Bedtime	9:10:00	.	PM
32	713	1	3.00	severe pain	Very Mild Pain	No Relief	Breakfast	8:38:00	.	AM
33	722	2	3.00	extremely seve	Severe Pain	No Relief	Breakfast	7:04:00	.	AM
34	731	2	2.00	moderate pain	Mild Pain	No Relief	Dinner	6:50:00	.	PM
35	732	1	3.00	moderate pain	Mild Pain	No Relief	Breakfast	9:30:00	.	AM
36	732	1	3.00	mild pain	Very Mild Pain	No Relief	Breakfast	9:30:00	.	AM
37	735	2	2.00	severe pain	Mild Pain	No Relief	Dinner	7:41:00	.	PM
38	801	2	2.00	extremely seve	Very Severe Pain	No Relief	Bedtime	8:00:00	.	PM
39	801	2	3.00	very severe pa	Moderate Pain	No Relief	Breakfast	8:00:00	.	AM
40	A11	2	3.00	mild pain	Very Mild Pain	No Relief	Bedtime	9:35:00	.	PM
41	B08	2	3.00	very severe pa	Severe Pain	No Relief	Breakfast	9:00:00	.	AM
42	C05	2	2.00	severe pain	Moderate Pain	No Relief	Bedtime	9:25:00	.	PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20070/S-004, S-006

MICROBIOLOGY REVIEW(S)

JAN 22 1997

REVIEW TO HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF SUPPLEMENT

January 22, 1997

A. 1. NDA 20-811 (Formerly NDA 19-700/S-008)

Applicant: Syntex (USA) Inc.
3401 Hillview Avenue
P.O. Box 10850
Palo Alto, CA 94303

Manufacturer: Allergan, Inc.
8301 Mars Drive
P.O. Box 2675
Waco, Texas

2. **PRODUCT NAMES:** Acular® (ketorolac tromethamine) 0.5%
Sterile Ophthalmic Solution

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:**
Sterile ophthalmic packaged in low density polyethylene unit dose vials with 0.4 mL fill volume. The sterile product does not contain a preservative system.

4. PHARMACOLOGICAL CATEGORY:

5. **METHOD OF STERILIZATION:**

6. **RELATED DOCUMENTS:**

B. 1. **DATE OF INITIAL SUBMISSION:** July 26, 1996
2. **DATE OF AMENDMENT #1:** October 25, 1996
3. **ASSIGNED FOR REVIEW:**
INITIAL SUBMISSION: November 18, 1996
AMENDMENT #1: January 2, 1997

C. **REMARKS:** The supplement NDA 19-700/S-008 originally submitted on July 26, 1996 was administratively reassigned a new number, NDA 20-811. This NDA provides for a new formulation of the drug product without the preservative, benzalkonium chloride, in a single dose container. An amendment to the NDA was submitted on October 25, 1996 to provide validation information for the to be used to commercially manufacture the drug product. The amendment replaces Section 3.6.2-2 and Appendices D and E of the initial submission.

D. **CONCLUSIONS:** The NDA 20-811 is not recommended for approval from the standpoint of microbiology.

1/22/97

Patricia F. Hughes, Ph.D.
Review Microbiologist

1/22/97

cc.: Original NDA 20-811
HFD-160/Consult File
HFD-160/PFHughes
HFD-550/Division File
HFD-550/J. Holmes
Drafted by P.F.Hughes/01/22/97
R/D initialed by P. Cooney/01/22/97

MAY 2 2 1997

REVIEW TO HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF AMENDMENT

MAY 22, 1997

A. 1. NDA 20-811 (Formerly NDA 19-700/S-008)

Applicant: Syntex (USA) Inc.
3401 Hillview Avenue
P.O. Box 10850
Palo Alto, CA 94303

Manufacturer: Allergan, Inc.
8301 Mars Drive
P.O. Box 2675
Waco, Texas

2. PRODUCT NAMES: Acular® (ketorolac tromethamine) 0.5%
Sterile Ophthalmic Solution

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile ophthalmic packaged in low density polyethylene unit dose vials with 0.4 mL fill volume. The sterile product does not contain a preservative system.

4. PHARMACOLOGICAL CATEGORY:

5. METHOD OF STERILIZATION:

6. RELATED DOCUMENTS:

B. 1. DATE OF INITIAL SUBMISSION: July 26, 1996
2. DATE OF AMENDMENT #1: October 25, 1996
3. DATE OF AMENDMENT #2: March 20,1997 (Subject of this review)

4. ASSIGNED FOR REVIEW:
INITIAL SUBMISSION: November 18, 1996
AMENDMENT #1: January 2, 1997
AMENDMENT # 2: April 22, 1997

C. REMARKS: This amendment dated March 20, 1997 is in response to the Agency's "Not Approvable Letter" dated January 28, 1997 and contains responses to microbiology deficiencies found in NDA 20-811 and in Amendment # 1, dated October 25, 1996. Responses to other deficiencies are not reviewed here

D. CONCLUSIONS: All microbiology deficiencies found in the original submission and in the amendment dated January 2, 1997 have been adequately addressed by the applicant. The NDA 20-811 is recommended for approval from the standpoint of microbiology.

PR 5/24/97

Patricia F. Hughes, Ph.D.
Review Microbiologist

PFH 6/4/97

cc.: Original NDA 20-811
HFD-160/Consult File
HFD-160/PFHughes
HFD-550/Division File
HFD-550/J. Holmes
Drafted by P.F.Hughes/05/22/97
R/D initialed by P. Cooney/05/22/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20070/S-004,S-006

ADMINISTRATIVE DOCUMENTS

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair, (HFD-530) CRP2

FROM: Division of Anti-inflammatory, Analgesic and Ophthalmic Products, HFD-550
Attention: Vispi P. Bhavnagri Phone: 827-2509

DATE: May 14, 1997

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Acular® 0.5% Preservative-Free (From Acular® PF 0.5%)

Company Name: Roche Pharmaceuticals

Established name, including dosage form: Ketorolac tromethamine ophthalmic solution

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy):
It is used for the treatment of pain.

Initial comments from the submitter (concerns, observations, etc.):
The company wishes to change the name from Acular® PF 0.5% to Acular® 0.5% Preservative-Free

Rev 04/96

PATENT INFORMATION

ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-free
NDA 20-811

Syntex Laboratories, Inc. submits the following patent information, as required by 21 U.S.C. 355(b) and in compliance with 21 CFR 314.53(c) and the notice at 62 FR 22216.

The following patents are relevant to this New Drug Application:

Patent No. 4,089,969; expires May 16, 1997;	drug, drug product, method of use;
Patent No. 4,454,151; expires March 22, 2002;	drug product, method of use;

The owner of the patents is:

Syntex (U.S.A.) Inc.
3401 Hillview Avenue
P.O. Box 10850
Palo Alto, California 94303

DECLARATION

The undersigned declares that U.S. Patents Nos. 4,089,969 and 4,454,151 cover the formulation, composition, and/or method of use of ACULAR® (ketorolac tromethamine ophthamic solution) 0.5% Preservative-free. This product is the subject of this application for which approval is being sought.

Lynn Devenezia-Tobias

Lynn Devenezia-Tobias

EXCLUSIVITY SUMMARY for NDA # 20-811 **SUPPL #** 0A

Trade Name Acular 0.5% ophthalmic soln **Generic Name** Ketorolac tromethamine

Applicant Name Hoffmann LaRoche HFD- 550

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /X/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /X/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS **ON PAGE 8 (even if a study was required for the upgrade).**

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-700 _____

NDA # 19-645 _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. **Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.**

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. **A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.**

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_✓_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_✓_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_✓_/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # KETO 105-871R

Investigation #2, Study # KETO 106-871R

Investigation #3, Study # _____

3. **In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.**

a) **For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")**

Investigation #1	YES /___/	NO /_✓_/
Investigation #2	YES /___/	NO /_✓_/
Investigation #3	**YES /___/**	**NO /___/**

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ **Study #** _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	**YES /___/**	**NO /_✓_/**
Investigation #2	**YES /___/**	**NO /_✓_/**
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ **Study #** _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # KETO 105 8718

Investigation #2, Study # KETO 106 8718

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # YES /✓/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____

_____

_____

NO /___/ Explain _____

_____

_____

(c) **Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)**

YES /___/ NO /V/

If yes, explain: _____

_____

_____

_____

Signature
Title: Project Manager

9/17/97
Date

MD
Signature of Division Director
Deputy

9/17/97
Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-811 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 550 Trade (generic) name/dosage form: Acular PF (ketorolac tromethamine) ophthalmic solution 0.5% Preservative-Free Action: (AP) AE NA

Applicant Hoffmann-LaRoche Therapeutic Class 35

Indication(s) previously approved _____

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application reduction of ocular pain and photophobia following incisional refractive surgery

(For supplements, answer the following questions in relation to the proposed indication.)

✓ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 3. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in children.
- ___ Explain, on the back of this form, why pediatric studies are not needed.

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

Signature of Preparer and Title (PM, CSO, MO, other) 10/16/97 Date

cc: Orig NDA/PLA # 20-811
HFD 550 /Div File
NDA/PLA Action Package
HFD-550/Troendle (paper, for CSO, APS and ADS, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

SIBS

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (714) 752-4500

DEBARRMENT CERTIFICATION

REF: Acular® (ketorolac tromethamine) 0.5% Ophthalmic Solution
NDA 19-700

Under the provisions of Section 306(k) of the Federal Food, Drug and Cosmetic Act, Allergan, Inc. has made a diligent effort to insure that no individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Act, as referenced above, has provided any services in connection with this application. This effort included identifying all employees of Allergan, Inc. connected with this application and requiring each of them to certify that he or she has not been debarred. This effort also included a requirement that all persons not employed by Allergan, Inc. who provided services in connection with this application certify to us that neither they nor any person employed by them has been disbarred. Relying, in part, on these certifications to us, Allergan, Inc. certifies that it did not and will not use, in any capacity, the services of any individual, corporation, partnership or association debarred under Section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this New Drug Application.

Peter Kresel

Peter Kresel
Vice President, Global Regulatory Affairs
Allergan, Inc.

March 14, 1996
Date