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*APPLICATION NUMBER:*  
**21-132**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA  
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Priority or Standard Standard

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Division / Office Division of Anti-Infective and  
Ophthalmology Products

Reviewer Name(s) William M. Boyd, M.D.  
Review Completion Date July 20, 2009

Established Name ketorolac tromethamine  
ophthalmic solution 0.45%  
(Proposed) Trade Name Acuvail  
Therapeutic Class nonsteroidal, anti-inflammatory  
Applicant Allergan, Inc.

Formulation(s) Ophthalmic solution  
Dosing Regimen Twice daily to the affected eye  
beginning 1 day prior to  
cataract surgery, continued on  
the day of surgery, and  
through the first 2 weeks of the  
postoperative period

Indication(s)	Treatment of pain and inflammation following cataract surgery
Intended Population(s)	Patients undergoing cataract surgery

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

It is recommended from a clinical prospective that NDA 22-427, Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% be approved for the treatment of pain and inflammation following cataract surgery.

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that patients receiving Acuvail had a significantly higher incidence of clearing of anterior chamber inflammation versus patients receiving vehicle at day 14. Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% was also significantly superior to vehicle in resolving ocular pain on Day 1 post cataract surgery.

The most common adverse events were reported in 1-6% of patients and included increased intraocular pressure, conjunctival hyperemia and/or hemorrhage, corneal edema, ocular pain, headache, tearing and vision blurred. Some of these events may be the consequence of the cataract surgical procedure.

### **1.2 Risk Benefit Assessment**

Since initial marketing approval in 1989 for Acular, 1997 for Acular PF, and 2003 for Acular LS, a combined maximum exposure estimate for the Acular product family is nearly (b) (4) patients.

For the primary efficacy endpoint in both phase 3 studies, patients receiving ketorolac 0.45% had a statistically significantly higher incidence of clearing of anterior chamber inflammation (SOIS = 0 on day 14) compared with patients receiving vehicle. For the secondary efficacy endpoints, ketorolac 0.45% was statistically significantly superior to vehicle in resolving ocular pain at day 1 post-cataract surgery in both studies. No statistically significant difference was observed between ketorolac 0.45% and vehicle in the inhibition of surgically induced miosis in either study.

Ketorolac 0.45% is a nonsteroidal anti-inflammatory (NSAID) ophthalmic solution. Characteristic adverse events of NSAIDs include increased bleeding time, delayed healing, and corneal effects. Increased bleeding time is due to interference with thrombocyte aggregation; ocularly applied NSAIDs may cause increase bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Healing may be slowed or delayed with topical NSAIDs as well as with topical corticosteroids; concomitant use of topical NSAIDs and topical steroids carries an increased risk of

healing problems. Corneal effects associated with topical NSAIDs include keratitis and sight threatening events: epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation.

Because of the nature of these adverse events characteristic of topical and ocularly applied NSAIDs, the studies that form the basis of this application were designed to include thorough ophthalmic evaluations. Evaluation of cataract surgery patients continued for 14 days following their surgery in the phase 3 studies.

The most common adverse events were reported in 1-6% of patients and included increased intraocular pressure, conjunctival hyperemia and/or hemorrhage, corneal edema, ocular pain, headache, tearing and vision blurred. Some of these events may be the consequence of the cataract surgical procedure.

### **1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies**

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

### **1.4 Recommendations for Postmarketing Requirements and Commitments**

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Established Name	ketorolac tromethamine ophthalmic solution 0.45%
(Proposed) Trade Name	Acuvail
Therapeutic Class	nonsteroidal anti-inflammatory drug (NSAID)

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug (NSAID) which has demonstrated analgesic, anti-inflammatory, and antipyretic activity when administered systemically. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. It has shown similar analgesic and anti-inflammatory effects in the eye.

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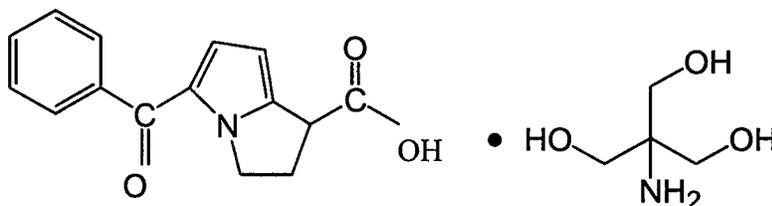
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Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Its chemical name is (±)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1), and its molecular weight is 376.41. Its molecular formula is C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>6</sub>. Its chemical structure is:



Per the recommended dosing, one drop of Acuvail should be applied by the patient to the affected eye twice daily beginning 1 day prior to cataract surgery, and continued through the first 2 weeks of the postoperative period.

Ketorolac been marketed as Acular (ketorolac tromethamine ophthalmic solution) 0.5%, Acular PF (ketorolac tromethamine ophthalmic solution) 0.5% [preservative free], and Acular LS (ketorolac tromethamine ophthalmic solution) 0.4%.

Acular is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis and for the treatment of postoperative inflammation following cataract extraction. Acular has been marketed in the European Union since 1989 and in the United States since 1990 for the treatment of inflammation and pain following cataract surgery. Acular PF is indicated for the reduction of ocular pain and photophobia following incisional refractive surgery. Acular LS is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery but is not approved for postoperative inflammation following cataract extraction.

The recommended dosage regimen for these other Acular products is 4 times daily.

## 2.2 Currently Available Treatments for Proposed Indication

### Currently Available Treatments

Name of Drug	Indication
Xibrom	XIBROM ophthalmic solution is indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
Voltaren	VOLTAREN Ophthalmic is indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.
Acular LS	ACULAR LS ophthalmic solution is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery.
Acular	ACULAR ophthalmic solution is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis. ACULAR ophthalmic solution is also indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction.
Nevanac	NEVANAC ophthalmic suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.
Vexol	VEXOL 1% is indicated for the treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis.
Durezol	DUREZOL ophthalmic emulsion is indicated for the treatment of inflammation and pain associated with ocular surgery

## 2.3 Availability of Proposed Active Ingredient in the United States

See Section 2.1 regarding other topical ophthalmic formulations of ketorolac tromethamine.

## 2.4 Important Safety Issues with Consideration to Related Drugs

Ketorolac tromethamine ophthalmic solution 0.45% is a topical nonsteroidal anti-inflammatory (NSAID). Characteristic adverse events of NSAIDs include increased bleeding time, delayed healing, and corneal effects. Increased bleeding time is due to interference with thrombocyte aggregation; ocularly applied NSAIDs may cause

increase bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Healing may be slowed or delayed with topical NSAIDs as well as with topical corticosteroids; concomitant use of topical NSAIDs and topical steroids carries an increased risk of healing problems. Corneal effects associated with topical NSAIDs include keratitis and sight threatening events: epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation.

Because of the nature of these adverse events characteristic of topical and ocularly applied NSAIDs, the studies that form the basis of this application were designed to include thorough ophthalmic evaluation. Evaluation of cataract surgery patients continued for 14 days following their surgery in the phase 3 studies. Prohibited medications included oral, injectable, or topical ophthalmic steroids; topical or oral NSAIDs (except once daily aspirin therapy); prostaglandins used ocularly; and depocorticosteroids used systemically.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The presubmission regulatory activity for this application and for ketorolac tromethamine ophthalmic solution 0.45 % is brief.

A Pre-NDA teleconference was held on February 22, 2008. Allergan planned to evaluate a new formulation of ketorolac tromethamine with the objective of decreasing dosing frequency to treat ocular inflammation and pain following cataract surgery. This new formulation, ketorolac tromethamine ophthalmic solution 0.45%, would be a preservative-free formulation. The proposed formulation contained ketorolac tromethamine, carboxymethylcellulose (b) (4), sodium chloride, sodium citrate, hydrochloric acid and/or sodium hydroxide to adjust pH, and purified water, and the drug product was to be packaged in a unit dose container.

Clinical studies 191578-004, 191578-005, and 191578-006 were conducted under IND 21,132.

## **2.6 Other Relevant Background Information**

The efficacy endpoints chosen for the phase 3 studies have been widely used in clinical studies of ophthalmic solutions and are recognized as reliable, accurate, and relevant for evaluation of the efficacy and safety of investigational products.

The primary efficacy analysis was the comparison of the proportion of patients with clearing of anterior chamber inflammation (SOIS = 0) between ketorolac 0.45% and vehicle on day 14 after cataract surgery. Secondary efficacy variables included the proportion of patients with no postoperative ocular pain (i.e, grade of pain = 0) at both

the morning and evening evaluation on day 1, and inhibition of surgically induced miosis as measured by the pupil area after irrigation and aspiration of the lens.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

No issues related to data quality or data integrity have been identified.

#### **3.2 Compliance with Good Clinical Practices**

The clinical trials reviewed in this application were conducted in accordance with good clinical trial practices.

#### **3.3 Financial Disclosures**

The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2.

There is no evidence to suggest that the results of the study were impacted by any financial payments.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Table 4.1 – Drug Product Composition

Composition of Ketorolac Tromethamine Ophthalmic Solution 0.45%			
Ingredient	Grade	Function	Concentration (% w/v)
Ketorolac Tromethamine	USP/Ph Eur	Active	0.45
Carboxymethylcellulose (b) (4) (b) (4)	USP/Ph Eur	(b) (4)	(b)
Carboxymethylcellulose (b) (4) (b) (4)	USP/Ph Eur	(b) (4)	(b)
Sodium Chloride	USP/Ph Eur	(b) (4)	(b)
Sodium Citrate Dihydrate	USP/Ph Eur	(b) (4)	(b)
Sodium Hydroxide (1N)	NF/Ph Eur	pH adjustment	Adjust to pH 6.8
Hydrochloric Acid (1N)	NF/Ph Eur	pH adjustment	Adjust to pH 6.8
Purified Water	USP/Ph Eur	(b) (4)	(b)

The proposed drug product, ketorolac tromethamine ophthalmic solution 0.45%, is a sterile, nonpreserved, clear, and colorless to pale yellow, isotonic ophthalmic solution. This formulation contains 0.45% (w/v) ketorolac tromethamine as drug substance. The inactive ingredients include carboxymethylcellulose (b) (4), sodium chloride (b) (4), and sodium citrate (b) (4). The pH of the bulk solution is adjusted using either 1N sodium hydroxide or 1N hydrochloric acid to a target pH of 6.8 for the final product. All ingredients are tested to USP/NF and Ph Eur criteria.

Table 4.1 – Drug Product Specifications (30 April 2009)

Test	In Process	Release	Shelf	Method
Physical Appearance	Not Performed	Clear, colorless to pale yellow solution	Clear, colorless to pale yellow solution	Section 3.2.P.5.2 Method AP-MS010 Visual Inspection
pH	(b) (4)	(b) (4)	(b) (4)	Section 3.2.P.5.2 USP <791>
Ketorolac Tromethamine HPLC Assay	(b) (4)	(b) (4)	(b) (4)	Section 3.2.P.5.2 Method AP-L236 HPLC
Ketorolac Tromethamine ID	(b) (4)	(b) (4)	(b) (4)	Section 3.2.P.5.2 Method ASET-DP-ID074 Identification by UV
Osmolality	(b) (4)	(b) (4)	(b) (4)	USP <785>
Ketorolac Tromethamine Impurities (%w/w):	(b) (4)	(b) (4)	(b) (4)	Section 3.2.P.5.2 Method AP-L236 HPLC
Particulate Matter (Count)	(b) (4)	(b) (4)	(b) (4)	Section 3.2.P.5.2 Method AP-Z003 Light Obscuration Particle Count USP <789>
Leachables: Specified and Identified	(b) (4)	(b) (4)	(b) (4)	Section 3.2.P.5.2 Method AP-G063 Volatile and Semi-Volatile Organic Leachable Compounds from (b) (4)
Sterility	Not Performed	Meets compendial acceptance criteria	Meets compendial acceptance criteria	Section 3.2.P.5.2 SOP WRM-100 Membrane Filtration USP <71>
Bacterial Endotoxins	Not Performed	NMT (b) (4)	NMT (b) (4)	Section 3.2.P.5.2 Analytical Procedure Endotoxin (b) (4)
Viscosity	(b) (4)	(b) (4)	(b) (4)	Section 3.2.P.5.2 Method AP-V008 Rotational Viscometry

An information request was sent to the applicant (5 November 2008) requesting validation data for the filling equipment and an endotoxin specification for the drug product. The equipment sterilization validation information and endotoxin specification were provided in amendment 0003 (dated 21 November 2008). Two endotoxin testing

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facilities were added in amendment 0007 (dated 30 April 2009). An additional endotoxin testing facility was added in amendment 0008 (dated 17 June 2009).

A kinetic turbidimetric LAL test will be used to test the drug product for endotoxin. The endotoxin limit is NMT (b) (4). The kinetic turbidimetric test method was validated by performing inhibition/enhancement testing with the drug product. A (b) (4) dilution allowed an endotoxin recovery that met the (b) (4), acceptance criteria. The (b) dilution will be used for testing the drug product.

A membrane filtration method is used for sterility testing of the finished drug product. The method is based on USP <71>. The method was validated for use with the drug product by performing bacteriostasis/fungistasis testing.

## 4.2 Clinical Microbiology

Not applicable to this review.

## 4.3 Preclinical Pharmacology/Toxicology

Allergan submitted an amendment for NDA 22-427 on March 10, 2009, identifying two leachables, (b) (4) in the drug product. They conducted a safety assessment for these leachables on ocular toxicity/irritation, systemic toxicity, and genotoxicity/carcinogenicity, based on the toxicity data obtained from literature.

Allergan stated that, because limited information is available on (b) (4), assessment on (b) (4) was conducted as the surrogates. Allergan assumed that the assessment of these alternative compounds was comparable to assessment of (b) (4) in providing the safety justification because of the structure similarities.

Based on the available information, it is concluded that (b) (4) present in the drug product as leachables up to (b) (4), respectively, do not pose a toxicological concern. The Pharmacology/Toxicology Reviewer concurred.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis.

### 4.4.2 Pharmacodynamics/Pharmacokinetics

The pharmacokinetics of ketorolac tromethamine ophthalmic solution 0.45% have not been assessed in humans.

Two drops of 0.5% ketorolac tromethamine ophthalmic solution instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved a mean ketorolac concentration of 95 ng/mL in the aqueous humor of 8 of 9 eyes tested (range 40 to 170 ng/mL).

One drop of 0.5% ketorolac tromethamine ophthalmic solution was instilled into 1 eye and 1 drop of vehicle into the other eye TID in 26 normal subjects. Five (5) of 26 subjects had detectable concentrations of ketorolac in their plasma (range 11 to 22 ng/mL) at Day 10 during topical ocular treatment. The range of concentrations following TID dosing of 0.5% ketorolac tromethamine ophthalmic solution are approximately 4 to 8% of the steady state mean minimum plasma concentration observed following four times daily oral administration of 10 mg ketorolac in humans ( $0.29 \pm 0.07$   $\mu\text{g/mL}$ ).

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 5.1 – Tabular Listing of all Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% Clinical Trials

Type of Study	Study Identifier	Location of Study	Objective(s) of the Study	Study Design and type of Control	Test Products; dosage Regimen; route of Administration	Number of Subjects	Healthy Subjects of Diagnosis of Patients	Duration of Treatment	Study Status; Type of report
Safety	004	United States	Safety and tolerability of 0.35% and 0.45% solutions compared with ACULAR LS® 0.4%	Randomized, paired-eye, active-controlled	Ketorolac tromethamine ophthalmic solution 0.35% and 0.45%, administered topically	39	Healthy Subjects	5 doses in both eyes over 1 day	Complete: full
Efficacy	005	United States	Safety and efficacy of ketorolac tromethamine 0.45% ophthalmic solution compared with vehicle	Randomized, double-masked, parallel, vehicle-controlled	Ketorolac tromethamine ophthalmic solution 0.45%, administered topically	248 (164 test drug, 84 vehicle)	Planned cataract extraction with posterior chamber IOL implant	16 days	Complete: full
Efficacy	006	United States	Safety and efficacy of ketorolac tromethamine 0.45% ophthalmic solution compared with vehicle	Randomized, double-masked, parallel, vehicle-controlled	Ketorolac tromethamine ophthalmic solution 0.45%, administered topically	263 (176 test drug, 87 vehicle)	Planned cataract extraction with posterior chamber IOL implant	16 days	Complete: full

### 5.2 Review Strategy

The September 29, 2008, submission was submitted electronically. Subsequent amendments were also submitted in electronically. All study reports were reviewed. The included clinical study reports, literature review, and package insert formed the basis for the review of efficacy and safety for the proposed indications.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Allergan, Inc. in this application for this indication.

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### **5.3 Discussion of Individual Studies/Clinical Trials**

#### **Clinical Trial 191578-005**

A Multi Center, Double Masked, Randomized Parallel Group Study Evaluating the Safety and Efficacy of a New Formulation of Ketorolac Tromethamine 0.45% Ophthalmic Solution Compared with Vehicle Administered Preoperatively and Twice-Daily Postoperatively for Two Weeks for the Treatment of Anterior Segment Inflammation, Pain, and Inhibition of Surgically Induced Miosis Following Cataract Extraction with Posterior Chamber Intraocular Lens (IOL) Implantation

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List of Investigators/Subinvestigators for -005

Principal Investigator Name (Number), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Gregg J. Berdy, MD (10001) Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131	(b) (4)	3	1192, 1193, 1268
Lisa Cibik, MD (10015) Associates In Ophthalmology 9970 Mountain View Drive, 2nd Floor West Mifflin, PA 15122		19	1021, 1022, 1026, 1033, 1034, 1050, 1057, 1058, 1070, 1150, 1182, 1183, 1185, 1199, 1200, 1201, 1216, 1253, 1273
David L. Cooke, MD (10002) Great Lakes Eye Care 2848 Niles Road St. Joseph, MI 49085		4	1171, 1176, 1202, 1206
Thomas L. Croley, MD (10025) Central Florida Eye Institute 3133 SW 32nd Ave Ocala, FL 34474		5	1209, 1210, 1211, 1212, 1241
John L. Davidson, MD (10003) Miramar Eye Specialists Medical Group 3085 Loma Vista Road. Ventura, CA 93003		4	1004, 1030, 1074, 1224
Eric Domenfeld, MD (10029) Ophthalmic Consultants of Long Island Ryan Medical Arts Building 2000 North Village Avenue, Ste 402 Rockville Centre, NY 11570		5	1165, 1172, 1173, 1195, 1223
Thoms R. Elmer, MD (10011) Fichte-Endl Eye Associates 2825 Niagara Falls Blvd. Amherst, NY 14228		23	1011, 1048, 1082, 1087, 1090, 1091, 1109, 1116, 1120, 1139, 1140, 1143, 1144, 1166, 1181, 1208, 1246, 1250, 1251, 1254, 1263, 1264, 1271
Richard M. Evans, MD (10022) Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX 78240		8	1187, 1188, 1220, 1221, 1222, 1239, 1247, 1248
Robert M. Feldman, MD (10017) Robert Cizik Eye Clinic 6400 Fannin Street Ste 1800 Houston, TX 77030		1	1256
Arthur M. Fishman, MD (10023) Eye Surgery Associates 603 N. Flamingo Rd. Ste 250 Pembroke Pines, FL 33028		11	1072, 1112, 1122, 1125, 1127, 1132, 1151, 1153, 1157, 1160, 1164
John Foley, MD (10030) Eastern Shore Eye Center 3297 Broad Street Exmore, VA 23350		2	1242, 1249

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Principal Investigator Name (Number), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
S. Lance Forstot, MD (10020) Corneal Consultants of Colorado 8381 Southpark Lane Littleton, CO 80120	(b) (4)	7	1015, 1049, 1068, 1073, 1080, 1154, 1163
Johnny L. Gayton, MD (10012) Eyesight Associates 216 Corder Road Warner Robins, GA 31088	(b) (4)	2	1031, 1138
David S. Grey, MD (10016) Grosinger, Spigelman and Grey 1750 Telegraph Road Ste 205 Bloomfield Hills, MI 48302	(b) (4)	3	1177, 1225, 1252
David R. Hardten, MD (10009) Minnesota Eye Consultants, PA 9801 Dupont Ave S., Suites 100 & 200 Bloomington, MN 55431	(b) (4)	3	1069, 1213, 1245
Mitchell A. Jackson, MD (10014) Jackson Eye 300 N Milwaukee Ave Ste. L Lake Villa, IL 60046	(b) (4)	12	1036, 1037, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1083, 1084, 1196
Ronald Landry, MD (10024) Eye Care Associates 4324 Veterans Blvd., Ste 102 Metairie, LA 70006	(b) (4)	14	1040, 1059, 1060, 1075, 1076, 1077, 1081, 1088, 1089, 1097, 1101, 1110, 1133, 1134
Jodi Luchs, MD (10010) South Shore Eye Care, LLP 2185 Wantagh Ave Wantagh, NY 11793	(b) (4)	12	1003, 1006, 1013, 1014, 1023, 1032, 1118, 1119, 1121, 1197, 1227, 1228
Louis D. Nichamin, MD (10008) Laurel Eye Clinic 50 Waterford Pike Brookville, PA 15825	(b) (4)	9	1102, 1115, 1168, 1174, 1190, 1230, 1244, 1260, 1262
Karl E. Olsen, MD (10021) Eye Center of Northern Colorado 1725 E. Prospect Rd Fort Collins, CO 80525	(b) (4)	11	1078, 1079, 1111, 1148, 1149, 1175, 1184, 1198, 1229, 1255, 1274
Michael B. Raizman, MD (10005) Ophthalmic Consultants of Boston 50 Staniford Street Ste 600 Boston, MA 02114	(b) (4)	7	1005, 1114, 1141, 1169, 1170, 1234, 1258
Harvey J. Reiser, MD (10007) Eye Care Specialists 703 Rutter Ave. Kingston, PA 18704	(b) (4)	27	1061, 1062, 1063, 1064, 1065, 1066, 1067, 1085, 1086, 1093, 1094, 1117, 1158, 1180, 1214, 1215, 1217, 1218, 1219, 1231, 1232, 1233, 1240, 1261, 1265, 1269, 1272

Clinical Review  
 William M. Boyd, M.D.  
 NDA 22-427  
 Acuvail (ketorolac tromethamine ophthalmic solution) 0.45%

Principal Investigator Name (Number), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Kenneth Sall, MD (10006) Sall Research Medical Center 11423 187th St. Ste. 200 Artesia, CA 90701	(b) (4)	28	1016, 1017, 1018, 1019, 1020, 1027, 1028, 1029, 1039, 1053, 1054, 1055, 1099, 1100, 1107, 1108, 1113, 1129, 1130, 1131, 1136, 1203, 1204, 1205, 1207, 1270, 1280, 1281
Scott Smetana, MD (10019) Colorado Eye Associates, PC 2920 North Cascade 2nd Floor Colorado Springs, CO 80907		19	1001, 1002, 1007, 1008, 1009, 1010, 1012, 1024, 1025, 1038, 1051, 1052, 1056, 1103, 1142, 1147, 1226, 1235, 1257
Lloyd R. Taustine, MD (10018) Taustine Eye Center The Medical Arts Building - Ste 3334 1169 Eastern Parkway Louisville, KY 40217		24	1035, 1071, 1095, 1096, 1098, 1104, 1135, 1137, 1152, 1155, 1156, 1159, 1178, 1179, 1186, 1189, 1191, 1194, 1259, 1275, 1276, 1277, 1278, 1279
John Wood, MD (10028) Vistar Eye Center 375 Hershberger Rd. Roanoke, VA 24012		18	1092, 1105, 1106, 1123, 1124, 1126, 1128, 1145, 1146, 1161, 1162, 1167, 1236, 1237, 1238, 1243, 1266, 1267

Study Plan for -005

Visits and Events	Screening (Week -4 to Day -2)	Randomization (Day-3 to Day -1)	Cataract Surgery Day	Day 1 Post-op	Day 3 Post-op	Day 7 Post-op	Day 14 Post-op/ Exit
Randomization		X					
ICF & Auth	X						
Hx & Demo <sup>a</sup>	X	X					
PR & BP	X						X
Pregnancy Test <sup>b</sup>		X					X
Begin Dosing <sup>c</sup>		X					
Surgical Day Dosing <sup>d</sup>			X				
Post-op Dosing <sup>e</sup>				X	X	X	X
Pupil Size Measure			X				
BCVA	X			X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X
Biomicroscopy	X			X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X
Ocular Pain Self- Assessment			X <sup>g</sup>	X <sup>h</sup>	X <sup>h</sup>	X <sup>h</sup>	X <sup>h</sup>
IOP	X			X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X
AEs		X	X	X	X	X	X
Dilated Fundus Exam	X <sup>i</sup>						X <sup>i</sup>
Assess Con Meds			X	X	X	X	X
D/C dosing							X

Abbreviations: AEs = Adverse Events; Auth = Authorization; BCVA = Best Corrected Visual Acuity; BP = Blood Pressure; Con Meds = concomitant medications; D/C = discontinue dosing; Hx & Demo = History & Demographics; ICF = Informed Consent Form; IOP = Intraocular Pressure; Post-op = postoperative; PR = Pulse Rate.

- a Patient histories (including ophthalmic, medical, and medication), demographics (including sex, date of birth, iris color, height and weight) and presence or absence of pain in the operative eye were assessed.
  - b Urine pregnancy test was to be performed for females of childbearing potential.
  - c Patients were instructed to begin twice daily dosing of study medication in the operative eye the day before surgery (Day -1) and to continue the regimen as per protocol.
  - d Patients were to instill 1 drop of study medication in the operative eye upon wakening. Presurgical dosing of study medication and gatifloxacin 0.3% by site personnel began 2 hr prior to surgery (for a total of 6 combined drops) with at least 10 min between instillations. Patients were instructed to continue the dosing regimen at home approximately 12 hr after their morning dose with 1 drop of study medication followed by gatifloxacin 0.3% approximately 10 min after.
  - e Patients were to instill 1 drop of study medication in the operative eye twice daily from day 1 to day 13. On day 14, patients were to instill 1 drop in the postoperative eye upon wakening. No additional drops were administered.
  - f Operative eye only
  - g In the evening, approximately 1 hr after the last dose of study medication on the cataract surgery day, patients were to record the severity of their ocular pain in the operative eye and the use of acetaminophen or other analgesics using the Interactive Voice Response System (IVRS).
  - h Patients were to record the severity of their ocular pain in the operative eye and the use of acetaminophen or other analgesics using the IVRS twice daily, approximately 1 hr after dosing on day 1 through day 13, and approximately 1 hr after the morning dose on day 14.
  - i Dilated fundus examination at screening was performed in both eyes after all study procedures were completed.
  - j Dilated fundus examination on day 14 was performed in the operative eye after all study procedures were completed.
- Note: For patients who discontinued the study early, all study procedures scheduled for the day 14/study exit visit were to be completed at the early exit visit.

Clinical Review  
William M. Boyd, M.D.  
NDA 22-427  
Acuvail (ketorolac tromethamine ophthalmic solution) 0.45%

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#### Clinical Trial 191578-006

A Multi Center, Double Masked, Randomized Parallel Group Study Evaluating the Safety and Efficacy of a New Formulation of Ketorolac Tromethamine 0.45% Ophthalmic Solution Compared with Vehicle Administered Preoperatively and Twice-Daily Postoperatively for Two Weeks for the Treatment of Anterior Segment Inflammation, Pain, and Inhibition of Surgically Induced Miosis Following Cataract Extraction with Posterior Chamber Intraocular Lens (IOL) Implantation

Clinical Review

William M. Boyd, M.D.

NDA 22-427

Acuvail (ketorolac tromethamine ophthalmic solution) 0.45%

List of Investigators/Subinvestigators for -006

Principal Investigator Name (Number), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Louis M. Alpern, MD (10027) The Cataract and Glaucoma Center 4171 N Mesa Bldg. D, Ste. 100 El Paso, TX 79902	(b) (4)	30	1015, 1021, 1022, 1030, 1039, 1064, 1065, 1095, 1097, 1141, 1142, 1160, 1161, 1162, 1195, 1241, 1242, 1244, 1245, 1258, 1259, 1261, 1267, 1268, 1269, 1270, 1271, 1272, 1274, 1276
Pranav Amin, MD (10029) Sutter North Medical Foundation 460 Plumas Blvd Ste 102 Yuba City, CA 95991		21	1055, 1056, 1057, 1058, 1059, 1109, 1113, 1129, 1169, 1170, 1177, 1178, 1179, 1202, 1203, 1204, 1237, 1239, 1243, 1246, 1250
Frank A. Bucci, MD (10021) Bucci Laser Vision Institute 158 Wilkes-Barre Township Blvd. Wilkes-Barre, PA 18702		1	1069
Y. Ralph Chu, MD (10012) Chu Vision Institute 7760 France Ave S. Ste 140 Edina, MN 55435		4	1048, 1157, 1158, 1206
Richard G. Cohen, MD (10016) Cohen Laser and Vision Center 3020 North Military Trail Ste 150 Boca Raton, FL 33431		15	1011, 1013, 1024, 1025, 1063, 1071, 1101, 1102, 1126, 1145, 1188, 1189, 1190, 1191, 1196
Steven J. Dell, MD (10024) Dell Laser Consultants 5717 Balcones Dr. Austin, TX 78731		2	1053, 1060
Monte S. Dirks, MD (10026) Black Hills Regional Eye Institute 2800 Third Street Rapid City, SD 57701		3	1148, 1159, 1256
Leonard Gurevich, MD (10013) Western New York Eye Center 301 Sterling Drive Orchard Park, NY 14127		27	1074, 1075, 1076, 1077, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1143, 1144, 1152, 1173, 1174, 1175, 1176, 1183, 1223, 1224, 1225, 1226, 1227
Robert Haverly, MD (10007) Laser Eye Surgery of Erie 311 W 24th St. Suite 301 Erie, PA 16502		17	1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1279, 1280, 1281, 1282, 1283, 1284
John D. Hunkeler, MD (10002) Hunkeler Eye Institute		20	1031, 1032, 1041, 1042, 1061, 1070,

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Principal Investigator Name (Number), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
7950 College Blvd Overland Park, KS 66210	(b) (4)		1083, 1098, 1100, 1103, 1108, 1163, 1164, 1165, 1199, 1200, 1218, 1252, 1260, 1262
Paul A. Jorizzo, MD (10003) Medical Eye Center 2727 Barnett Road Medford, OR 97504	(b) (4)	26	1001, 1002, 1003, 1004, 1005, 1012, 1035, 1040, 1045, 1046, 1047, 1066, 1067, 1079, 1186, 1198, 1219, 1221, 1222, 1233, 1234, 1249, 1254, 1273, 1275, 1278
Barry Katzman, MD (10015) West Coast Eye Care Associates 6945 El Cajon Blvd. San Diego, CA 92115	(b) (4)	12	1006, 1007, 1008, 1009, 1014, 1019, 1020, 1107, 1182, 1213, 1215, 1217
Michael S. Korenfeld (10004) Comprehensive Eye Care, Ltd 901 East Third Street Washington, MO 63090	(b) (4)	17	1010, 1023, 1052, 1054, 1080, 1081, 1105, 1106, 1111, 1147, 1150, 1181, 1185, 1197, 1235, 1251, 1285
W. Barry Lee, MD (10014) Eye Consultants of Atlanta 95 Collier Road, Ste 3000 Atlanta, GA 30309	(b) (4)	5	1016, 1017, 1038, 1078, 1085
Parag Majmudar, MD (10008) Chicago Cornea Consultants, Ltd. 1585 N Barrington Rd. Ste 502 Hoffman Estates, IL 60169	(b) (4)	12	1018, 1026, 1029, 1033, 1091, 1092, 1093, 1153, 1154, 1155, 1156, 1193
Francis W. Price, MD (10005) Price Vision Group and Cornea Research Foundation of America 9002 N Meridian St. Ste 100 & Basement Indianapolis, IN 46260	(b) (4)	1	1124
Rajesh K. Rajpal, MD (10017) Cornea Consultants/See Clearly Vision 8180 Greensboro Drive, Ste. 140 McLean, VA 22102	(b) (4)	11	1027, 1028, 1043, 1044, 1049, 1050, 1072, 1110, 1112, 1151, 1171
Steven Silverstein, MD (10009) Silverstein Eye Centers 4240 Blue Ridge Blvd Ste 1000 Kansas City, MO 64133	(b) (4)	16	1034, 1036, 1037, 1051, 1062, 1068, 1073, 1082, 1086, 1104, 1125, 1180, 1184, 1194, 1229, 1231
William B. Trattler, MD (10023) Center for Excellence in Eye Care Baptist Medical Arts Building, East Tower 8940 North Kendall Drive, Suite 400 E Miami, FL 33176	(b) (4)	16	1096, 1099, 1146, 1149, 1201, 1205, 1208, 1228, 1230, 1232, 1236, 1238, 1247, 1248, 1253, 1257
Kevin Waltz, MD (10019) Eye Surgeons of Indiana 8103 Clearvista Parkway Indianapolis, IN 46256	(b) (4)	8	1172, 1187, 1207, 1209, 1210, 1211, 1212, 1216

Clinical Review  
 William M. Boyd, M.D.  
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Principal Investigator Name (Number), Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
Arthur Weinstein, MD (10010) Eye Associates of New Mexico 5757 Harper Dr NE Albuquerque, NM 87109	(b) (4)	2	1214, 1240
Jon-Marc Weston, MD (10018) Roseburg Research Associates, LLC 2435 NW Kline St. Roseburg, OR 97470	(b) (4)	19	1084, 1087, 1088, 1089, 1090, 1094, 1127, 1128, 1166, 1167, 1168, 1192, 1220, 1255, 1263, 1264, 1265, 1266, 1277

The Study Plan for-006 is identical to the Study Plan for -005.

**Clinical Trial 191578-004**

A Single-center, Randomized, Double-masked, Paired-eye, Active Controlled Study to Evaluate the Safety and Tolerability of a New Formulation of Ketorolac Tromethamine Ophthalmic Solution 0.35% and 0.45% compared with Acular LS 0.4% Administered Five-times for 1 Day in Healthy Adult Volunteers

Site Number: 10001  
 Principle Investigator: David Wirta, MD  
 Address: Eye Research Foundation  
 1501 Superior Avenue, Suite 303  
 Newport Beach, CA 92663

Number of Patients Enrolled: 39  
 Patient Identification Numbers Assigned to Site: 1001-1048

Acuvail (ketorolac tromethamine ophthalmic solution) 0.45%

Study Plan for -004

Visits	Pre-Study Qualification Day -14 to -1	Dosing Day Day 1														
		Pre-dose	Hour 0	Hour 0.25	Hour 0.5	Hour 0.75	Hour 3.0	Hour 3.25	Hour 3.5	Hour 3.75	Hour 4.0	Hour 4.5	Hour 5.0 (Study Exit)			
Time points	Anytime															
ICF / authorization	X															
History, demographics, PE	X															
Pulse rate and blood pressure	X															X
Pregnancy test <sup>d</sup>		X														
Nonfasting laboratory tests <sup>b</sup>	X															
Subject Comfort Question <sup>c</sup>																
Ocular symptoms evaluation <sup>e</sup>	X/OU		X/OD			X/OS		X/OU		X/OU		X/OU		X/OU		
Macroscopic bulbar hyperemia grading <sup>d</sup>	X/OU		X/OD			X/OS		X/OU		X/OU		X/OU		X/OU		
Best corrected visual acuity <sup>f</sup>	X/OU		X/OD			X/OS		X/OU		X/OU		X/OU		X/OU		
Biometry	X/OU		X/OD			X/OS		X/OU		X/OU		X/OU		X/OU		
Intraocular pressure <sup>f</sup>	X/OU		X/OD			X/OS		X/OU		X/OU		X/OU		X/OU		
Ophthalmoscopy <sup>g</sup>	X															X/OU
Randomization		X														
Dosing <sup>h</sup>			X/OD		X/OS		X/OU <sup>i</sup>		X/OU <sup>i</sup>		X/OU <sup>i</sup>		X/OU <sup>i</sup>		X/OU <sup>i</sup>	
Adverse events																X

Abbreviations: ICF = informed consent form; OD = right eye; OS = left eye; OU = both eyes; PE = physical exam

a Urine pregnancy test was to be performed for females of childbearing potential.

b Prestudy nonfasting laboratory tests (which included blood chemistry panel, hematology including complete blood count, urine collection for urinalysis, and screening for drugs of potential abuse) were to be performed at any time within the prestudy window of 1 to 14 days prior to the dosing day visit as long as results were available for review at dosing day.

c Subject Comfort Questionnaires (if applicable) was to be performed before the ocular symptom evaluations and prior to any ophthalmic study procedures or instillation of any eye drops (if applicable). Subjects were to assess each eye separately.

d Macroscopic (gross) bulbar hyperemia grading (using the Allergan Bulbar Hyperemia Grading Guide) was to be performed after completion of the Subject Comfort Questionnaire (if applicable) and ocular symptoms evaluation and prior to any ophthalmic study procedures.

e Best-corrected visual acuity using manifest refraction obtained at screening was to be performed before biometry, intraocular pressure, and instillation of any eye drops.

f To be performed after the Subject Comfort Questionnaire, ocular symptoms evaluation, macroscopic (gross) bulbar hyperemia grading, best-corrected visual acuity, and biometry but prior to the dilated ophthalmoscopy examination (if applicable)

g Ophthalmoscopy exam with dilated pupil after all procedures were completed

h All dosing was to be administered at the clinic by site personnel. For the duration of the dosing day, the RIGHT eye was to receive instillation of study medication first followed by the LEFT. For dosing of both eyes beginning at hour 3.0, the LEFT eye was to receive medication immediately after the RIGHT eye.

i All study procedures were to be performed prior to instillation of any eye drops.

Note: For any subjects who exited the study early, at a minimum ocular symptoms evaluation, blood pressure/pulse rate, best-corrected visual acuity, biometry, and intraocular pressure were to be completed.

## **6 Review of Efficacy**

### **Efficacy Summary**

#### **6.1 Indication**

Two listed studies, 191578-005 and 191578-006, support the efficacy of Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% for the treatment of pain and inflammation following cataract surgery. The trials are identical in design.

##### **6.1.1 Methods**

###### **General Study Design for -005 and -006**

These were multicenter, randomized, double-masked, parallel group comparison studies to assess the safety and efficacy of ketorolac 0.45% compared with vehicle administered preoperatively and postoperatively in the treatment of anterior segment inflammation, pain, and inhibition of surgically induced miosis following cataract extraction with posterior chamber intraocular lens (IOL) implantation. The studies consisted of 7 scheduled visits: screening (week -4 to day -2), randomization (day -3 to day -1), cataract surgery day, day 1, day 3, day 7, and day 14/study exit.

Approximately 225 patients were to be randomized in each trial with a 2:1 ratio (ketorolac:vehicle) of treatment allocation in order to study approximately 201 patients per trial with an evaluation of inflammation in the operative eye after surgery.

Informed consent was obtained and screening procedures were performed at the screening visit. Qualified patients were randomized to either ketorolac 0.45% or vehicle at the randomization visit (day -3 to day -1). Because ketorolac 0.45% is a nonpreserved, unit-dose ophthalmic solution, all study medication was labeled for single use and packaged in sterile single-use containers to ensure masking. Patients were instructed to begin twice daily (BID) dosing of study medication in the operative eye the day before surgery (day -1) and to continue dosing on the day of surgery and day 1 through day 14 as per the protocol.

On the day before surgery (day -1), patients were also instructed to begin 4 times daily dosing of the ophthalmic antibiotic gatifloxacin 0.3%, and to continue dosing on the day of surgery and day 1 through day 7 as per protocol (see Section 9.4.5 for the detailed dosing regimen).

## Clinical Review

William M. Boyd, M.D.

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Acuvail (ketorolac tromethamine ophthalmic solution) 0.45%

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On the day of the surgery, the patient was to administer 1 drop of study medication upon waking followed by 1 drop of gatifloxacin 0.3% in the operative eye. Beginning 2 hr prior to surgery, study personnel administered 1 drop of study medication and 1 drop of gatifloxacin 0.3% in the operative eye approximately every 20 min, for a total of 3 drops each. When administering both study medication and gatifloxacin 0.3%, the study medication was instilled first, with at least 10 min between instillations. Beginning 1 hr prior to surgery, site personnel administered the mydriatic agents tropicamide 1% and phenylephrine 2.5% in the operative eye approximately every 15 min, for a total of 3 drops each. After cataract surgery just prior to discharge, study personnel administered 1 drop of study medication followed by 1 drop of gatifloxacin 0.3% in the operative eye. The patient was to administer the final dose on surgery day in the evening by instilling 1 drop of study medication followed by 1 drop of gatifloxacin 0.3% in the operative eye approximately 12 hr after the first morning dose.

Patients underwent unilateral, single procedure, uncomplicated phacoemulsification extracapsular cataract extraction with posterior chamber IOL implant under topical or intracameral anesthesia. Pupil area (via horizontal and vertical pupil diameters) was measured immediately pre-incision, post-irrigation and aspiration (I&A) of the lens, and after IOL placement. If miosis required an intraoperative intervention (such as additional phenylephrine or epinephrine) to safely complete the surgery, then the pupil diameters were to be measured prior to the intervention and recorded.

Patients recorded the severity of their ocular pain and the use of acetaminophen or other analgesics using an Interactive Voice Response System (IVRS) according to the following schedule: approximately 1 hr after the last evening dose of study medication on cataract surgery day, twice daily approximately 1 hr after dosing on day 1 through day 13, and approximately 1 hr after the morning dose on day 14. Patients were instructed to use acetaminophen if the pain relief following study medication was unacceptable. At the discretion of the investigator, patients could use other analgesics for pain relief. However, patients using anti-inflammatory medication were to be discontinued from the study.

Safety measurements were performed on days 1, 3, 7, and 14 and included assessments of adverse events, best-corrected visual acuity, biomicroscopy, and intraocular pressure. Dilated fundus examination in the operative eye was performed on day 14. The primary efficacy measurement, anterior segment inflammation assessment in the operative eye, was performed on days 1, 3, 7, and 14. The primary efficacy analysis was based on the anterior segment inflammation assessment on day 14. The secondary efficacy analyses were mean pupil area post-I&A of the lens and the percentage of patients with no ocular pain (grade = 0) on day 1.

Patients continued the BID use of study medication until Day 14 upon awakening.

**Inclusion Criteria:**

- 1) Male or female, at least 18 years of age and of legal age of consent.
- 2) Best-corrected visual acuity of 20/200 or better in the fellow eye.
- 3) No ocular pain at screening (week -4 to day -2) or at randomization (day -3 to day -1) in the operative eye.
- 4) Written informed consent and authorization obtained prior to any study-related procedures.
- 5) Planned unilateral, single procedure, uncomplicated phacoemulsification extracapsular cataract extraction with posterior chamber intraocular lens implant under topical or intracameral anesthesia at the start of the procedure with no capsular staining during phacoemulsification.
- 6) A negative urine pregnancy test result for females of child-bearing potential. A female was considered to be of childbearing potential unless she was postmenopausal or without a uterus and/or both ovaries.
- 7) Willingness and ability to comply with the investigator and protocol instructions and likelihood of completing all required visits.

**Exclusion Criteria:**

- 1) Any uncontrolled ocular disease in the study eye (eg, proliferative retinopathy, macular edema, rubeosis, neovascular membrane).
- 2) Active inflammation (cells or flare) in either eye.
- 3) History of chronic or recurrent inflammatory eye disease in the study eye (eg, iritis, scleritis, uveitis, iridocyclitis), ocular allergy requiring treatment, or history of ocular herpes.
- 4) Prior intraocular surgery in the operative eye except refractive surgery, which was allowed if performed at least 6 months prior to the screening visit.
- 5) Pseudoexfoliation lens syndrome, zonular weakness or compromise, or iris atrophy in the operative eye.
- 6) History of current or past Flomax use, or in the opinion of the investigator, at risk for
- 7) intraoperative floppy iris syndrome (IFIS) based on history of alpha blocker use or clinical findings.
- 8) Planned use of intraoperative intraocular irrigation fluid mixtures which have an effect on dilation other than intracameral lidocaine at the start of the procedure.
- 9) Planned use of any peribulbar or retrobulbar injection for anesthesia. Perioperative periorbital antibiotics were acceptable.
- 10) Need for postoperative patching of the operative eye.
- 11) Congenital ocular disease (e.g., aniridia, congenital cataract).
- 12) Intraocular pressure in the study eye of > 24 mm Hg at the screening visit.
- 13) Ocular use of prostaglandin (e.g., Lumigan, Travatan, Xalatan) within 14 days prior to randomization or anticipated use during the study.
- 14) Chronic use of analgesics within 14 days prior to randomization or anticipated use during the study.

- 15) Anticipated use of mast cell stabilizers, antihistamines, or preserved artificial tears (unpreserved artificial tears are allowed) during the study.
- 16) Use of oral, injectable, or topical ophthalmic steroids, NSAIDs, or immunosuppressants within 14 days prior to randomization, or anticipated use of these medications during the study (except chronic once daily use of acetyl salicylic acid 81 mg).
- 17) Systemic use of depo-corticosteroids within 45 days of randomization and during the study.
- 18) Use of an investigational IOL.
- 19) Insufficient pupil dilation using the standard dilating drops.
- 20) A nonfunctional fellow eye.
- 21) Intolerance to instillation of eye drops, history or known allergic hypersensitivity to any ingredients of the preparations used in this trial, or increased susceptibility to risk of complications from topical NSAIDs.
- 22) Contraindication to NSAIDs or acetaminophen.
- 23) Any uncontrolled systemic disease.
- 24) Females who were pregnant, nursing, or planning a pregnancy, or who were of childbearing potential and not using a reliable means of contraception.
- 25) Concurrent enrollment in an investigational drug or device study or participation in such a study within 30 days prior to the screening visit.
- 26) Presence of a condition or situation which, in the investigator's opinion, could have put the patient at significant risk, confounded the study results, or interfered significantly with the patient's participation in the study.
- 27) In the investigator's opinion, inability to perform self-assessment of ocular pain using the IVRS.

**Primary Efficacy Variable**

The percentage of patients with a summed ocular inflammation score (SOIS) of anterior chamber cell and flare equal to 0 on day 14 was evaluated as the primary efficacy analysis. The SOIS for a patient was calculated as the sum of the score for anterior chamber cells and the score for anterior chamber flare in the operative eye of the patient (see grade scale table below).

Anterior Chamber Cells		Anterior Chamber Flare	
Grade Score	Cell Count	Grade Score	Flare
0	0 cells	0	None: No flare seen
+0.5	1-5 cells (trace)	+1	Faint: Faint flare seen
+1	6-15 cells	+2	Moderate: Iris and lens details clear
+2	16-25 cells	+3	Marked: Iris and lens details hazy
+3	26-50 cells	+4	Intense: Fibrin or plastic aqueous
+4	> 50 cells		

## **Secondary Efficacy Measurements**

The following secondary efficacy measures were evaluated:

- Ocular pain as measured by a twice daily self-assessment by the patient within approximately 1 hr after dosing using a 5-point grade scale (0 = none, +1 = mild, +2 = moderate, +3 = severe, +4 = intolerable) was assessed. The percentage of patients with no pain (grade = 0) on day 1 was evaluated as a secondary efficacy analysis.
- Horizontal and vertical pupil diameters were measured immediately pre-incision, post-I&A of the lens, and after IOL placement. The mean pupil area post-I&A of the lens was evaluated as a secondary efficacy analysis.

## **Analysis Populations**

Four analysis populations were used in the analysis of the phase 3 studies: the intent-to-treat (ITT), modified intent-to-treat (mITT), per protocol (PP), and safety populations. All demographic data and some efficacy data were analyzed using the ITT population, which includes all randomized patients. Analyses using this population were based on the treatment to which the patient was randomized. The efficacy data were analyzed using the mITT and PP populations. The mITT population included all randomized patients who underwent cataract extraction surgery with posterior chamber IOL implantation in the operative eye. The PP population included all mITT patients with no major protocol deviations. PP exclusions were determined prior to the database lock. The safety population, which included all randomized patients who received at least 1 dose of study medication, was used to analyze all safety data. Safety analyses were based on the actual treatment that the patients received.

## 6.1.2 Demographics

Table 6.1.2a – Demographics and Baseline Characteristics  
 (Studies 191578-005 and 191578-006)

Characteristic	Attribute	Study 191578-005			Study 191578-006			Pooled			p-value <sup>a</sup>
		Ketorolac 0.45% (N=157)	Vehicle (N=81)	Total (N=238)	Ketorolac 0.45% (N=173)	Vehicle (N=82)	Total (N=255)	Ketorolac 0.45% (N=330)	Vehicle (N=163)	Total (N=493)	
Age in Years	N	157	81	238	173	82	255	330	163	493	0.149
	Mean (SD)	68.7 (9.91)	67.7 (9.68)	68.4 (9.82)	68.5 (10.37)	66.7 (10.43)	67.9 (10.40)	68.6 (10.14)	67.2 (10.04)	68.1 (10.12)	
	Median	70.0	69.0	70.0	70.0	68.0	69.0	70.0	68.0	70.0	
	Min, Max	40, 89	43, 85	40, 89	28, 94	35, 85	28, 94	28, 94	35, 85	28, 94	
Age Category, n (%)	≤ 65	54 (34.4)	33 (40.7)	87 (36.6)	59 (34.1)	33 (40.2)	92 (36.1)	113 (34.2)	66 (40.5)	179 (36.3)	
	> 65	103 (65.6)	48 (59.3)	151 (63.4)	114 (65.9)	49 (59.8)	163 (63.9)	217 (65.8)	97 (59.5)	314 (63.7)	
Sex, n(%)	N	157	81	238	173	82	255	330	163	493	0.984
	Male	67 (42.7)	34 (42.0)	101 (42.4)	73 (42.2)	35 (42.7)	108 (42.4)	140 (42.4)	69 (42.3)	209 (42.4)	
	Female	90 (57.3)	47 (58.0)	137 (57.6)	100 (57.8)	47 (57.3)	147 (57.6)	190 (57.6)	94 (57.7)	284 (57.6)	
Race, n(%)	N	157	81	238	173	82	255	330	163	493	0.290
	Caucasian	143 (91.1)	69 (85.2)	212 (89.1)	144 (83.2)	67 (81.7)	211 (82.7)	287 (87.0)	136 (83.4)	423 (85.8)	
	Black	2 (1.3)	3 (3.7)	5 (2.1)	2 (1.2)	4 (4.9)	6 (2.4)	4 (1.2)	7 (4.3)	11 (2.2)	
	Asian	1 (0.6)	2 (2.5)	3 (1.3)	1 (0.6)	0 (0.0)	1 (0.4)	2 (0.6)	2 (1.2)	4 (0.8)	
	Hispanic	11 (7.0)	7 (8.6)	18 (7.6)	22 (12.7)	11 (13.4)	33 (12.9)	33 (10.0)	18 (11.0)	51 (10.3)	
	Other <sup>b</sup>	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.3)	0 (0.0)	4 (1.6)	4 (1.2)	0 (0.0)	4 (0.8)	
	Non-Caucasian	14 (8.9)	12 (14.8)	26 (10.9)	29 (16.8)	15 (18.3)	44 (17.3)	43 (13.0)	27 (16.6)	70 (14.2)	
Iris Color, n(%)	N	157	81	238	173	82	255	330	163	493	0.231
	Blue	52 (33.1)	30 (37.0)	82 (34.5)	56 (32.4)	30 (36.6)	86 (33.7)	108 (32.7)	60 (36.8)	168 (34.1)	
	Green	5 (3.2)	1 (1.2)	6 (2.5)	4 (2.3)	10 (12.2)	14 (5.5)	9 (2.7)	11 (6.7)	20 (4.1)	
	Hazel	39 (24.8)	17 (21.0)	56 (23.5)	30 (17.3)	16 (19.5)	46 (18.0)	69 (20.9)	33 (20.2)	102 (20.7)	
	Brown	57 (36.3)	33 (40.7)	90 (37.8)	81 (46.8)	26 (31.7)	107 (42.0)	138 (41.8)	59 (36.2)	197 (40.0)	
	Other <sup>c</sup>	4 (2.5)	0 (0.0)	4 (1.7)	2 (1.2)	0 (0.0)	2 (0.8)	6 (1.8)	0 (0.0)	6 (1.2)	
	Dark <sup>d</sup>	57 (36.3)	33 (40.7)	90 (37.8)	81 (46.8)	26 (31.7)	107 (42.0)	138 (41.8)	59 (36.2)	197 (40.0)	
	Light <sup>d</sup>	100 (63.7)	48 (59.3)	148 (62.2)	92 (53.2)	56 (68.3)	148 (58.0)	192 (58.2)	104 (63.8)	296 (60.0)	

Source: ISS Tables 2.7.4.7-2.2 and 2.7.4.7-2.3

SD = standard deviation

a p-value for ketorolac 0.45% compared with vehicle in the pooled data: for continuous variables, a 1-way analysis of variance model was used; for categorical variables, Pearson's chi-square test was used.

b Other races include Creole, East Indian, Greek, Pakistani

c Other iris colors include blue-green, blue-hazel, gray, grayish blue

d Dark: brown; Light: blue, green, hazel, other

Demographic and other baseline characteristics were similar across the 2 treatment groups in the pooled safety population for the phase 3 studies. Patients ranged from 28 to 94 years of age, with the majority being > 65 years of age (63.7% [314/493]). More than half of patients were women (57.6% [284/493]) and most patients were Caucasian (85.8% [423/493]).

Most of the patients had brown (40.0% [197/493]) or blue (34.1% [168/493]) eyes. The distribution of dark (brown) and light (blue, green, hazel, or other) iris color was in the ratio of 2:3 dark:light overall and was similar in the 2 treatment groups (differences of < 6%) after pooling (see table above). The distribution of dark and light iris color was similar across the treatment groups in study -005, but was statistically significantly different in study -006 where distribution of iris color in the ketorolac 0.45% group was close to equal between dark and light (46.8% [81/173] dark and 53.2% [92/173] light)

whereas distribution in the vehicle group was in a ratio of greater than 1:2 dark:light (31.7% [26/82] dark and 68.3% [56/82] light).

Table 6.1.2b – Demographics and Baseline Characteristics  
 (Studies 191578-004)

Characteristic	Attribute	Ketorolac 0.45% (N = 20)	Ketorolac 0.35% (N = 19)	Total (N = 39)	P-value <sup>a</sup>
Age (years)	N	20	19	39	0.642
	Mean (SD)	29.6 (12.12)	32.3 (13.78)	30.9 (12.85)	
	Median	24.5	24.0	24.0	
	Min, Max	19, 63	20, 60	19, 63	
Age category, n (%)	< 40	17 (85.0)	14 (73.7)	31 (79.5)	
	≥ 40	3 (15.0)	5 (26.3)	8 (20.5)	
Sex, n (%)	N	20	19	39	0.060
	Male	10 (50.0)	4 (21.1)	14 (35.9)	
	Female	10 (50.0)	15 (78.9)	25 (64.1)	
Race, n (%)	N	20	19	39	0.146
	Caucasian	15 (75.0)	10 (52.6)	25 (64.1)	
	Black	2 (10.0)	0 (0.0)	2 (5.1)	
	Hispanic	3 (15.0)	8 (42.1)	11 (28.2)	
	Other <sup>b</sup>	0 (0.0)	1 (5.3)	1 (2.6)	
	Caucasian Non-Caucasian	15 (75.0) 5 (25.0)	10 (52.6) 9 (47.4)	25 (64.1) 14 (35.9)	
Iris color, n (%)	N	20	19	39	0.079
	Blue	9 (45.0)	2 (10.5)	11 (28.2)	
	Green	1 (5.0)	1 (5.3)	2 (5.1)	
	Hazel	3 (15.0)	4 (21.1)	7 (17.9)	
	Brown	7 (35.0)	12 (63.2)	19 (48.7)	
	Dark <sup>c</sup>	7 (35.0)	12 (63.2)	19 (48.7)	
	Light <sup>c</sup>	13 (65.0)	7 (36.8)	20 (51.3)	

Source: ISS Table 2.7.4.7-2.1

SD = standard deviation

a Wilcoxon rank-sum test was used for continuous variables; Pearson's chi-square test or Fisher's exact test was used for categorical variables.

b Other races was mixed Caucasian, black, Hispanic, American Indian

c Dark: brown; Light: blue, green, or hazel

In Study 191578-004, the overall mean age of subjects was 31 years with a range of 19 to 63 years. The majority of subjects (64.1% [25/39]) were female. Overall, 64.1% (25/39) of subjects were Caucasian, 28.2% (11/39) were Hispanic, 5.1% (2/39) were black, and 1 (2.6%) subject was of mixed race. Approximately equal percentages of subjects had dark or light iris color. No statistically significant difference between the treatment groups was observed for any of the demographic or other baseline characteristics

### 6.1.3 Subject Disposition

Table 6.1.3a – Patient Disposition and Exit Status for 191578-005

Disposition, n (%)	Ketorolac 0.45% (N = 164)	Vehicle (N = 84)	Total (N = 248)
Included in Intent-to-Treat Population <sup>a</sup>	164	84	248
Completed	144 (87.8)	57 (67.9)	201 (81.0)
Discontinued	20 (12.2)	27 (32.1)	47 (19.0)
Adverse Event	7 (4.3)	20 (23.8)	27 (10.9)
Ocular	5 (3.0)	19 (22.6)	24 (9.7)
Non-Ocular	2 (1.2)	1 (1.2)	3 (1.2)
Lack of Efficacy	0 (0.0)	2 (2.4)	2 (0.8)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Lost to Follow-Up	1 (0.6)	0 (0.0)	1 (0.4)
Personal Reasons	5 (3.0)	0 (0.0)	5 (2.0)
Protocol Violations (anti-inflammatory)	4 (2.4)	2 (2.4)	6 (2.4)
Protocol Violations (other)	2 (1.2)	0 (0.0)	2 (0.8)
Other <sup>b</sup>	1 (0.6)	3 (3.6)	4 (1.6)
Modified Intent-to-Treat Population <sup>c</sup>	155	79	234
Per-Protocol Population (Inflammation) <sup>d</sup>	141	75	216
Per-Protocol Population (Pain) <sup>e</sup>	125	59	184
Safety Population <sup>f</sup>	157	81	238

Source: Tables 14.1-1.1 through 14.1-1.5, Listing 16.2.1-2

- a Includes all randomized patients.
- b “Other” reasons are listed in Listing 16.2.1-2.
- c Includes all randomized patients who underwent cataract extraction surgery with posterior chamber intraocular lens implantation in the operative eye.
- d Includes all patients with no major protocol deviations. Excludes randomized patients with all post-surgery data declared invalid due to major protocol violations.
- e Includes all patients with no major protocol deviations. Excludes randomized patients with morning and evening of day 1 postsurgery data declared invalid due to major protocol violations.
- f Includes all randomized and treated patients.

A total of 248 patients were randomly assigned to treatment in this study, including 164 assigned to ketorolac 0.45% and 84 assigned to vehicle. A higher percentage of patients in the ketorolac 0.45% group (87.8% [144/164]) than in the vehicle group (67.9% [57/84]) completed the study. In both treatment groups, the most common reason for discontinuation was adverse event (4.3% [7/164] of the ketorolac 0.45% group and 23.8% [20/84] of the vehicle group).

Table 6.1.3b – Patient Disposition and Exit Status for 191578-006

Disposition, n (%)	Ketorolac 0.45% (N = 176)	Vehicle (N = 87)	Total (N = 263)
Included in Intent-to-Treat Population <sup>a</sup>	176	87	263
Completed	163 ( 92.6)	59 ( 67.8)	222 ( 84.4)
Discontinued	13 ( 7.4)	28 ( 32.2)	41 ( 15.6)
Adverse Event	8 <sup>b</sup> ( 4.5)	11 ( 12.6)	19 ( 7.2)
Ocular	7 ( 4.0)	11 ( 12.6)	18 ( 6.8)
Non-Ocular	1 <sup>b</sup> ( 0.6)	0 ( 0.0)	1 ( 0.4)
Lack of Efficacy	0 ( 0.0)	8 ( 9.2)	8 ( 3.0)
Pregnancy	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Lost to Follow-Up	0 ( 0.0)	0 ( 0.0)	0 ( 0.0)
Personal Reasons	1 ( 0.6)	1 ( 1.1)	2 ( 0.8)
Protocol Violations (anti-inflammatory)	0 ( 0.0)	2 ( 2.3)	2 ( 0.8)
Protocol Violations (other)	1 ( 0.6)	1 ( 1.1)	2 ( 0.8)
Other <sup>c</sup>	3 ( 1.7)	5 ( 5.7)	8 ( 3.0)
Modified Intent-to-Treat Population <sup>d</sup>	173	82	255
Per-Protocol Population (Inflammation) <sup>e</sup>	161	75	236
Per-Protocol Population (Pain) <sup>f</sup>	145	54	199
Safety Population <sup>g</sup>	173	82	255

Source: Tables 14.1-1.1 through 14.1-1.5, Listing 16.2.1-2

- a Includes all randomized patients.
- b Includes Patient 10023-1228 who did not receive any study medication and was not included in the other analysis populations.
- c “Other” reasons are listed in Listing 16.2.1-2.
- d Includes all randomized patients who underwent cataract extraction surgery with posterior chamber intraocular lens implantation in the operative eye.
- e Includes all patients with no major protocol deviations. Excludes randomized patients with all post-surgery data declared invalid due to major protocol violations.
- f Includes all patients with no major protocol deviations. Excludes randomized patients with morning and evening of day 1 postsurgery data declared invalid due to major protocol violations.
- g Includes all randomized and treated patients.

A total of 263 patients were randomly assigned to treatment in this study, including 176 assigned to ketorolac 0.45% and 87 assigned to vehicle. A higher percentage of patients in the ketorolac 0.45% group (92.6% [163/176]) than in the vehicle group (67.8% [59/87]) completed the study. In both treatment groups, the most common reason for discontinuation was adverse event (4.5% [8/176] of the ketorolac 0.45% group and 12.6% [11/87] of the vehicle group).

Study 191578-004, all 39 randomized subjects completed the study.

#### 6.1.4 Analysis of Primary Endpoint(s)

Table 6.1.4a – Clearing of Anterior Chamber Inflammation: SOIS Score Equal to 0  
 (Modified Intent-to-Treat Population for 191578-005)

n (%)	Ketorolac 0.45% (N = 155)	Vehicle (N = 79)	P-value <sup>a</sup>
Day 1			
Yes	5 (3.4)	2 (2.6)	> 0.999 <sup>b</sup>
No	143 (96.6)	76 (97.4)	
Day 3			
Yes	21 (14.1)	6 (7.7)	0.157
No	128 (85.9)	72 (92.3)	
Day 7			
Yes	45 (30.2)	12 (15.4)	0.014
No	104 (69.8)	66 (84.6)	
Day 14			
Yes	69 (46.3)	20 (25.6)	0.002
No	80 (53.7)	58 (74.4)	

Source: Table 14.2-1; Listing 16.2.6-1

SOIS = summed ocular inflammation score

a P-value is from a 2-sided Pearson's chi-square test. Missing values were imputed by LOCF at the follow-up visits.

b A Fisher's Exact Test was performed.

For the primary efficacy endpoint, 46.3% (69/149) of patients receiving ketorolac 0.45% had clearing of anterior chamber inflammation (SOIS = 0) at day 14 compared to 25.6% of patients receiving vehicle (20/79) in the mITT population (p = 0.002).

Sensitivity analyses were performed in the PP and ITT populations to confirm the positive results observed in the mITT population. The percentage of patients in the PP population with a SOIS = 0 at day 14 was 49.6% in patients receiving ketorolac 0.45%, statistically significantly greater than the 27.8% of patients receiving vehicle (p = 0.002). In the ITT population, the percentage of patients with a SOIS = 0 at day 14 was 46.3% in patients receiving ketorolac 0.45%, statistically significantly greater than the 25.6% of patients receiving vehicle (p = 0.002).

Table 6.1.4b – Clearing of Anterior Chamber Inflammation: SOIS Score Equal to 0  
 (Modified Intent-to-Treat Population for 191578-006)

n (%)	Ketorolac 0.45% (N = 173)	Vehicle (N = 82)	P-value <sup>a</sup>
Day 1			
Yes	10 (5.9)	7 (9.1)	0.363
No	159 (94.1)	70 (90.9)	
Day 3			
Yes	21 (12.4)	11 (14.3)	0.688
No	148 (87.6)	66 (85.7)	
Day 7			
Yes	57 (33.7)	14 (18.2)	0.013
No	112 (66.3)	63 (81.8)	
Day 14			
Yes	98 (58.0)	21 (27.3)	< 0.001
No	71 (42.0)	56 (72.7)	

Source: Table 14.2-1; Listing 16.2.6-1

SOIS = summed ocular inflammation score

<sup>a</sup> P-value is from a 2-sided Pearson's chi-square test. Missing values were imputed by LOCF at the follow-up visits.

For the primary efficacy endpoint, 58.0% (98/169) of patients receiving ketorolac 0.45% had clearing of anterior chamber inflammation (SOIS = 0) at day 14 compared to 27.3% of patients receiving vehicle (21/77) in the mITT population ( $p < 0.001$ ).

Sensitivity analyses were performed in the PP and ITT populations to confirm the positive results observed in the mITT population. The percentage of patients in the PP population with a SOIS = 0 at day 14 was 60.6% in patients receiving ketorolac 0.45%, statistically significantly greater than the 30.0% of patients receiving vehicle ( $p < 0.001$ ). In the ITT population, the percentage of patients with a SOIS = 0 at day 14 was 58.0% in patients receiving ketorolac 0.45%, statistically significantly greater than the 27.3% of patients receiving vehicle ( $p < 0.001$ ).

6.1.5 Analysis of Secondary Endpoints(s)

Table 6.1.5a – Ocular Pain Resolution: Pain Score Equal to 0  
 (Modified Intent-to-Treat Population for 191578-005)

n (%)		Ketorolac 0.45% (N = 155)	Vehicle (N = 79)	P-value <sup>a</sup>
Day 1	Yes	114 (75.0)	32 (41.0)	< 0.001
	No	38 (25.0)	46 (59.0)	
Day 2	Yes	127 (83.0)	39 (51.3)	< 0.001
	No	26 (17.0)	37 (48.7)	
Day 3	Yes	123 (80.9)	44 (59.5)	< 0.001
	No	29 (19.1)	30 (40.5)	
Day 4	Yes	130 (86.1)	46 (62.2)	< 0.001
	No	21 (13.9)	28 (37.8)	
Day 5	Yes	130 (86.7)	39 (53.4)	< 0.001
	No	20 (13.3)	34 (46.6)	
Day 6	Yes	123 (82.6)	40 (54.8)	< 0.001
	No	26 (17.4)	33 (45.2)	
Day 7	Yes	125 (84.5)	41 (58.6)	< 0.001
	No	23 (15.5)	29 (41.4)	
Day 8	Yes	122 (82.4)	44 (62.9)	0.002
	No	26 (17.6)	26 (37.1)	
Day 9	Yes	124 (84.4)	38 (59.4)	< 0.001
	No	23 (15.6)	26 (40.6)	
Day 10	Yes	124 (84.9)	43 (67.2)	0.003
	No	22 (15.1)	21 (32.8)	
Day 11	Yes	124 (84.9)	40 (63.5)	< 0.001
	No	22 (15.1)	23 (36.5)	
Day 12	Yes	126 (86.9)	41 (64.1)	< 0.001
	No	19 (13.1)	23 (35.9)	
Day 13	Yes	119 (82.6)	44 (69.8)	0.038
	No	25 (17.4)	19 (30.2)	
Day 14	Yes	124 (88.6)	43 (71.7)	0.003
	No	16 (11.4)	17 (28.3)	

Source: Table 14.2-2; Listing 16.2.6-2

<sup>a</sup> P-value is from a 2-sided Pearson's chi-square test. Missing values were imputed as described in Section 9.7.1.3.

There was a statistically significantly greater proportion of patients who were ocular pain-free at day 1 in the ketorolac 0.45% group, 75.0% (114/152 patients), compared to the vehicle group, 41.0% (32/78 patients) (p < 0.001).

A sensitivity analysis performed on the PP population at day 1 revealed that 89.6% of ketorolac 0.45% patients were free of ocular pain, statistically significantly greater than the 55.2% of patients receiving vehicle (p < 0.001).

Table 6.1.5b – Inhibition of Surgically Induced Miosis: Pupil Area (mm<sup>2</sup>)  
 (Modified Intent-to-Treat Population for 191578-005)

	Ketorolac 0.45% (N = 155)	Vehicle (N = 79)	P-value <sup>a</sup>
<b>Pre-Incision</b>			
N	155	78	
Mean (SD)	52.3 (11.8)	52.9 (12.8)	0.723
Median	50.9	52.8	
Min-Max	(b) (4)	(b) (4)	
<b>Post-I&amp;A</b>			
N	154	78	
Mean (SD)	41.8 (12.6)	41.1 (14.0)	0.706
Median	41.2	41.6	
Min-Max	(b) (4)	(b) (4)	
<b>Post-IOL Placement</b>			
N	153	78	
Mean (SD)	39.4 (12.4)	39.4 (14.9)	0.999
Median	38.5	41.2	
Min-Max	(b) (4)	(b) (4)	

Source: Table 14.2-3; Listing 16.2.6-3.1 and Listing 16.2.6-3.2

I&A = irrigation and aspiration; IOL = intraocular lens; SD = standard deviation

<sup>a</sup> P-value is from a 1-way analysis of variance model.

The mean pupil area measured post-I&A was not statistically significantly different between the two treatment groups (p = 0.706). Mean pupil area post-I&A was 41.8 mm<sup>2</sup> in the ketorolac 0.45% group and 41.1 mm<sup>2</sup> in the vehicle group.

Table 6.1.5c – Ocular Pain Resolution: Pain Score Equal to 0  
 (Modified Intent-to-Treat Population for 191578-006)

n (%)		Ketorolac 0.45% (N = 173)	Vehicle (N = 82)	P-value <sup>a</sup>
Day 1	Yes	119 (70.0)	30 (38.5)	< 0.001
	No	51 (30.0)	48 (61.5)	
Day 2	Yes	135 (79.9)	35 (44.9)	< 0.001
	No	34 (20.1)	43 (55.1)	
Day 3	Yes	138 (82.1)	48 (64.9)	0.003
	No	30 (17.9)	26 (35.1)	
Day 4	Yes	138 (83.1)	50 (68.5)	0.011
	No	28 (16.9)	23 (31.5)	
Day 5	Yes	140 (83.8)	47 (64.4)	< 0.001
	No	27 (16.2)	26 (35.6)	
Day 6	Yes	139 (83.7)	45 (63.4)	< 0.001
	No	27 (16.3)	26 (36.6)	
Day 7	Yes	143 (85.6)	44 (62.0)	< 0.001
	No	24 (14.4)	27 (38.0)	
Day 8	Yes	141 (84.9)	46 (67.6)	0.003
	No	25 (15.1)	22 (32.4)	
Day 9	Yes	141 (86.0)	47 (73.4)	0.025
	No	23 (14.0)	17 (26.6)	
Day 10	Yes	147 (89.1)	50 (78.1)	0.032
	No	18 (10.9)	14 (21.9)	
Day 11	Yes	143 (87.2)	50 (79.4)	0.139
	No	21 (12.8)	13 (20.6)	
Day 12	Yes	147 (89.1)	45 (75.0)	0.008
	No	18 (10.9)	15 (25.0)	
Day 13	Yes	145 (88.4)	45 (73.8)	0.007
	No	19 (11.6)	16 (26.2)	
Day 14	Yes	139 (88.5)	44 (78.6)	0.066
	No	18 (11.5)	12 (21.4)	

Source: Table 14.2-2; Listing 16.2.6-2

a P-value is from a 2-sided Pearson's chi-square test. Missing values were imputed as described in Section 9.7.1.3.

There was a statistically significantly greater proportion of patients who were ocular pain-free at day 1 in the ketorolac 0.45% group, 70.0% (119/170 patients), compared to the vehicle group, 38.5% (30/78 patients) (p < 0.001).

A sensitivity analysis performed on the PP population at day 1 revealed that 82.3% of ketorolac 0.45% patients were free of ocular pain, statistically significantly greater than the 53.8% of patients receiving vehicle (p < 0.001).

Table 6.1.5d – Inhibition of Surgically Induced Miosis: Pupil Area (mm<sup>2</sup>)  
 (Modified Intent-to-Treat Population for 191578-006)

	<b>Ketorolac 0.45%</b> (N = 173)	<b>Vehicle</b> (N = 82)	<b>P-value<sup>a</sup></b>
<b>Pre-Incision</b>			
N	173	81	
Mean (SD)	50.7 (12.3)	49.5 (12.0)	0.463
Median	50.3	50.3	
Min-Max	(b) (4)	(b) (4)	
<b>Post-I&amp;A</b>			
N	173	81	
Mean (SD)	37.9 (12.0)	36.5 (13.5)	0.413
Median	38.5	38.3	
Min-Max	(b) (4)	(b) (4)	
<b>Post-IOL Placement</b>			
N	173	80	
Mean (SD)	36.1 (12.1)	34.3 (13.4)	0.300
Median	35.8	36.6	
Min-Max	(b) (4)	(b) (4)	

Source: Table 14.2-3; Listing 16.2.6-3.1 and Listing 16.2.6-3.2

I&A = irrigation and aspiration; IOL = intraocular lens; SD = standard deviation

a P-value is from a 1-way analysis of variance model.

The mean pupil area measured post-I&A was not statistically significantly different between the two treatment groups (p = 0.413). Mean pupil area post-I&A was 37.9 mm<sup>2</sup> in the ketorolac 0.45% group and 36.5 mm<sup>2</sup> in the vehicle group.

### 6.1.6 Other Endpoints

Not applicable.

### 6.1.7 Subpopulations

The primary efficacy endpoint for the two phase 3 studies, clearing of anterior chamber inflammation (SOIS = 0 on day 14), was analyzed for the pooled mITT population by age, sex, race, and iris color. For all subgroups, patients receiving ketorolac 0.45% had a statistically significantly higher incidence of clearing of anterior chamber inflammation compared with patients receiving vehicle ( $p \leq 0.002$ ).

Table 6.1.7a –Clearing of Anterior Chamber Inflammation by Age, Sex, Race, and Iris Color: SOIS Equal to 0 on Day 14 (Modified Intent-to-Treat Population)

Characteristic, n/N (%)	Ketorolac 0.45%	Vehicle	P-value <sup>a</sup>
Age ≤ 65	47/107 (43.9)	11/62 (17.7)	< 0.001
Age > 65	120/211 (56.9)	30/93 (32.3)	< 0.001
Male	61/135 (45.2)	14/63 (22.2)	0.002
Female	106/183 (57.9)	27/92 (29.3)	< 0.001
Caucasian	142/276 (51.4)	39/130 (30.0)	< 0.001
Non-Caucasian	25/42 (59.5)	2/25 (8.0)	< 0.001
Dark Iris Color <sup>b</sup>	69/133 (51.9)	10/56 (17.9)	< 0.001
Light Iris Color <sup>b</sup>	98/185 (53.0)	31/99 (31.3)	< 0.001

Source: ISE Tables 2.7.3.6-7.1.1 through 2.7.3.6-7.4.2.

a P-values are from a 2-sided Pearson's chi-square test.

b Dark iris color: brown; light iris color: blue, green, or hazel.

The pooled mITT population was also analyzed by age, sex, race, and iris color for the secondary endpoints of ocular pain and mean pupil area post-irrigation and aspiration. With the exception of non-Caucasians, patients in all subgroups receiving ketorolac 0.45% had a statistically significantly higher incidence of ocular pain resolution at day 1 compared with patients receiving vehicle ( $p < 0.001$ ). Non-Caucasians receiving ketorolac 0.45% had a numerically higher incidence of ocular pain resolution at each of days 1 through 14 compared with non-Caucasians receiving vehicle, but the difference was not statistically significant on any of the days due to the small number of non-Caucasians in the studies.

Consistent with the overall results, no statistically significant difference was seen between treatment groups for any of the subgroups for pupil area post-irrigation and aspiration.

Table 6.1.7b – Ocular Pain Resolution: Pain Score Equal to 0 on Day 1 (Modified Intent-to-Treat Population)

Characteristic, n/N (%)	Ketorolac 0.45%	Vehicle	P-value <sup>a</sup>
Age ≤ 65	85/112 (75.9)	24/63 (38.1)	< 0.001
Age > 65	148/210 (70.5)	38/93 (40.9)	< 0.001
Male	104/137 (75.9)	29/65 (44.6)	< 0.001
Female	129/185 (69.7)	33/91 (36.3)	< 0.001
Caucasian	212/281 (75.4)	50/132 (37.9)	< 0.001
Non-Caucasian	21/41 (51.2)	12/24 (50.0)	0.924
Dark Iris Color <sup>b</sup>	93/134 (69.4)	23/55 (41.8)	< 0.001
Light Iris Color <sup>b</sup>	140/188 (74.5)	39/101 (38.6)	< 0.001

Source: ISE Tables 2.7.3.6-9.1.1 through 2.7.3.6-9.4.2.

a P-values are from a 2-sided Pearson's chi-square test.

b Dark iris color: brown; light iris color: blue, green, or hazel.

Table 6.1.7c – Inhibition of Surgically Induced Miosis: Mean Pupil Area (mm<sup>2</sup>) Post-Irrigation and Aspiration (Modified Intent-to-Treat Population)

Characteristic, mean (SD)	Ketorolac 0.45%	Vehicle	P-value <sup>a</sup>
Age ≤ 65	43.6 (12.5)	40.0 (14.2)	0.083
Age > 65	37.7 (11.9)	37.9 (13.7)	0.895
Male	39.2 (13.5)	38.1 (15.8)	0.583
Female	40.0 (11.6)	39.2 (12.3)	0.595
Caucasian	40.0 (12.6)	39.0 (13.6)	0.433
Non-Caucasian	37.4 (10.7)	37.5 (15.7)	0.998
Dark Iris Color <sup>b</sup>	38.5 (11.5)	38.0 (14.4)	0.790
Light Iris Color <sup>b</sup>	40.6 (13.0)	39.2 (13.6)	0.389

Source: ISE Tables 2.7.3.6-11.1.1 through 2.7.3.6-11.4.2.

SD = standard deviation

a P-values are from a 1-way analysis of variance model.

b Dark iris color: brown; light iris color: blue, green, or hazel.

Table 6.1.7d – Freedom from Postoperative Ocular Pain by Race: Pain Score = 0  
 Race = Non-Caucasian Phase 3 Clinical Studies (Modified Intent-to-Treat Population)

		Pooled		
		Ketorolac 0.45% (N=43)	Vehicle (N=26)	P-value [a]
Day 1 Post-op	N	41	24	0.924
	Yes	21 ( 51.2%)	12 ( 50.0%)	
	No	20 ( 48.8%)	12 ( 50.0%)	
Day 2 Post-op	N	41	24	0.208
	Yes	27 ( 65.9%)	12 ( 50.0%)	
	No	14 ( 34.1%)	12 ( 50.0%)	
Day 3 Post-op	N	40	22	0.469
	Yes	29 ( 72.5%)	14 ( 63.6%)	
	No	11 ( 27.5%)	8 ( 36.4%)	
Day 4 Post-op	N	37	20	0.530
	Yes	27 ( 73.0%)	13 ( 65.0%)	
	No	10 ( 27.0%)	7 ( 35.0%)	
Day 5 Post-op	N	38	20	0.602
	Yes	29 ( 76.3%)	14 ( 70.0%)	
	No	9 ( 23.7%)	6 ( 30.0%)	
Day 6 Post-op	N	35	19	0.314
	Yes	25 ( 71.4%)	11 ( 57.9%)	
	No	10 ( 28.6%)	8 ( 42.1%)	
Day 7 Post-op	N	39	19	0.213 [b]
	Yes	31 ( 79.5%)	12 ( 63.2%)	
	No	8 ( 20.5%)	7 ( 36.8%)	
Day 8 Post-op	N	39	19	0.502 [b]
	Yes	32 ( 82.1%)	14 ( 73.7%)	
	No	7 ( 17.9%)	5 ( 26.3%)	

Note: Pooled data are from phase 3 clinical studies 191578-005 and 191578-006.  
 Ocular pain resolution: Pain Score = 0. Missing values are imputed according to the imputation method described in Section 5.3 of the analysis plan.  
 [a] P-value is from a 2 sided Pearson's chi-square test.  
 [b] A Fisher's exact test is performed.

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		Pooled		
		Ketorolac 0.45% (N=43)	Vehicle (N=26)	P-value [a]
Day 9 Post-op	N	39	17	0.739 [b]
	Yes	30 ( 76.9%)	12 ( 70.6%)	
	No	9 ( 23.1%)	5 ( 29.4%)	
Day 10 Post-op	N	39	17	0.480 [b]
	Yes	32 ( 82.1%)	12 ( 70.6%)	
	No	7 ( 17.9%)	5 ( 29.4%)	
Day 11 Post-op	N	38	18	0.524 [b]
	Yes	29 ( 76.3%)	12 ( 66.7%)	
	No	9 ( 23.7%)	6 ( 33.3%)	
Day 12 Post-op	N	39	18	0.087 [b]
	Yes	33 ( 84.6%)	11 ( 61.1%)	
	No	6 ( 15.4%)	7 ( 38.9%)	
Day 13 Post-op	N	38	17	0.479 [b]
	Yes	32 ( 84.2%)	13 ( 76.5%)	
	No	6 ( 15.8%)	4 ( 23.5%)	
Day 14 Post-op	N	37	16	0.148 [b]
	Yes	32 ( 86.5%)	11 ( 68.8%)	
	No	5 ( 13.5%)	5 ( 31.3%)	

Note: Pooled data are from phase 3 clinical studies 191578-005 and 191578-006.  
 Ocular pain resolution: Pain Score = 0. Missing values are imputed according to the imputation method described in Section 5.3 of the analysis plan.  
 [a] P-value is from a 2 sided Pearson's chi-square test.  
 [b] A Fisher's exact test is performed.

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### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Ketorolac tromethamine ophthalmic solution 0.5% has been approved and marketed for cataract surgery for over 15 years and has demonstrated an acceptable efficacy and safety profile. The ketorolac 0.45% formulation tested BID in these phase 3 clinical studies was developed in order to decrease dosing frequency from QID to treat ocular inflammation and pain following cataract surgery.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Due to the brief duration of dosing in studies 191578-005 and 191578-006 (16 days), neither the persistence of efficacy nor tolerance effects were evaluated.

### 6.1.10 Additional Efficacy Issues/Analyses

Summaries of additional sensitivity analyses for the primary and secondary endpoints are located in relevant portions of Sections 6.1.4 and 6.1.5.

## 7 Review of Safety

### Safety Summary

#### 7.1 Methods

##### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

All three clinical trials found in the table in Section 5.1 were utilized to evaluate the safety of Acuvail.

See Section 6.1.1 for General Study Designs for -005 and -006.

##### **General Study Design for -004**

This was a single-center, randomized, double-masked, paired-eye, active-controlled study to assess the safety and tolerability of ketorolac 0.35% and ketorolac 0.45% when administered for 1 day (5 doses), compared with Acular LS, in healthy adult subjects.

The study consisted of 2 scheduled visits: screening (day -14 to day -1) and dosing day/exit (day 1).

Approximately 36 subjects were to be enrolled. Informed consent was obtained and screening procedures were performed at the screening visit. On day 1, qualified subjects were randomized to receive either the ketorolac 0.35% or ketorolac 0.45% treatment regimen. Within each treatment regimen, subjects were randomized to receive ketorolac in either the right or left eye with the contralateral eye receiving Acular LS. 0.4%.

Following randomization, subjects were dosed with 1 drop of study medication per eye by site personnel beginning at hour 0. At each dosing interval, the right eye was dosed first followed by the left eye. Since ketorolac 0.35% and 0.45% were nonpreserved, and to ensure masking, all study medication bottles were labeled for single use.

Approximately 15 min after the subjects received the first dose of study medication in the right eye, the subject was given the Subject Comfort Questionnaire followed by the Ocular Symptom Evaluation. Macroscopic (gross) bulbar hyperemia grading (using the Allergan Bulbar Hyperemia Grading Guide) and best-corrected visual acuity, using manifest refraction obtained at screening, were performed after the Ocular Symptom Evaluation and prior to dosing of the left eye. The left eye then followed the same procedure as the right eye.

The second dose was administered approximately 3 hr later (hour 3), followed by the third, fourth, and fifth doses at approximately 15-min intervals (hour 3.25, hour 3.5, and hour 3.75, respectively). For each of these doses, the right eye received study medication first, followed immediately by the left eye. Approximately 15 min after each dose and prior to instillation of the next dose, subjects were given the Subject Comfort Questionnaire followed by the Ocular Symptom Evaluation. At hour 4, after the subjects had completed the Subject Comfort Questionnaire and the Ocular Symptom Evaluation, macroscopic (gross) bulbar hyperemia grading, best-corrected visual acuity (using the manifest refraction obtained at screening), and biomicroscopy were also performed. Approximately 30 min later (hour 4.5), pulse rate, blood pressure, and intraocular pressures were measured. At hour 5, subjects exited the study after a final adverse event query.

### 7.1.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) nomenclature was used to code AEs.

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

See Section 7.4.1.

## 7.2 Adequacy of Safety Assessments

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

Table 2.1 – Treatment Exposure by Cumulative Time Interval (Safety Populations, Studies 191578-005 and 191578-006)

Duration, n (%) <sup>a</sup>	Study 191578-005		Study 191578-006	
	Ketorolac 0.45% (N=157)	Vehicle (N=81)	Ketorolac 0.45% (N=173)	Vehicle (N=82)
≥ 1 day	157 (100.0)	81 (100.0)	173 (100.0)	82 (100.0)
≥ 2 days	156 (99.4)	81 (100.0)	173 (100.0)	82 (100.0)
≥ 3 days	154 (98.1)	79 (97.5)	169 (97.7)	80 (97.6)
≥ 4 days	152 (96.8)	77 (95.1)	166 (96.0)	79 (96.3)
≥ 5 days	152 (96.8)	76 (93.8)	166 (96.0)	75 (91.5)
≥ 6 days	150 (95.5)	73 (90.1)	166 (96.0)	74 (90.2)
≥ 7 days	150 (95.5)	69 (85.2)	166 (96.0)	73 (89.0)
≥ 8 days	149 (94.9)	68 (84.0)	166 (96.0)	72 (87.8)
≥ 9 days	147 (93.6)	66 (81.5)	166 (96.0)	70 (85.4)
≥ 10 days	147 (93.6)	60 (74.1)	163 (94.2)	65 (79.3)
≥ 11 days	147 (93.6)	57 (70.4)	163 (94.2)	59 (72.0)
≥ 12 days	147 (93.6)	57 (70.4)	163 (94.2)	58 (70.7)
≥ 13 days	146 (93.0)	57 (70.4)	163 (94.2)	57 (69.5)
≥ 14 days	146 (93.0)	57 (70.4)	163 (94.2)	55 (67.1)

Source: Reports 191578-005, Table 14.3-1, Listings 16.2.9-1 and Report 191578-006, Table 14.3-1, Listings 16.2.9-1.

a Treatment duration is defined as duration (days) = (date of last treatment) – (date of first treatment) + 1. If date of last dose was missing, the exit date was used.

The safety population from the phase 3 studies that form the basis of this application consisted of patients undergoing cataract extraction with posterior chamber intraocular lens implantation. From 93% to 94% of patients in the ketorolac 0.45% groups and from 67% to 70% of patients in the vehicle groups received at least 14 days of exposure.

The patient exposure and safety assessments were adequate.

### 7.2.2 Explorations for Dose Response

Ketorolac been marketed as Acular (ketorolac tromethamine ophthalmic solution) 0.5%, Acular PF (ketorolac tromethamine ophthalmic solution) 0.5% [preservative free], and Acular LS (ketorolac tromethamine ophthalmic solution) 0.4%.

Both a ketorolac tromethamine ophthalmic solution 0.35% and a 0.45% formulation were evaluated in -004 as compared to Acular LS.

### 7.2.3 Special Animal and/or In Vitro Testing

There was no special animal and/or in vitro testing indicated or performed.

### 7.2.4 Routine Clinical Testing

This drug product is a topical ophthalmic solution for the treatment of pain and inflammation following cataract surgery.

There was adequate monitoring of the anterior and posterior segments of the eye, intraocular pressure, and visual acuity.

Clinical laboratory evaluations were not performed for any of the studies.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance and interaction were not performed due to the negligible systemic absorption of ketorolac tromethamine given by the topical route of administration and the well established safety profile when placed in the eye.

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

The routine clinical assessments, testing and monitoring of study subjects was adequate to elicit potential adverse events for similar drugs in the drug class.

The following ophthalmic evaluations were performed in the 3 clinical studies that support this application: intraocular pressure measurement; visual acuity measurement; biomicroscopic slit-lamp examinations through an undilated pupil to evaluate condition of the lid/lashes, conjunctiva, cornea, anterior chamber, iris/pupil, and lens; and ophthalmoscopic (dilated fundus) examinations to evaluate fundus and vitreous pathology.

In the phase 3 studies at screening and on post-operative days 1, 3, 7, and 14, biomicroscopic slit-lamp examinations were performed and intraocular pressure and visual acuity were evaluated. Ophthalmoscopic (dilated fundus) examinations were performed at screening and on postoperative day 14.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

No patient or subject deaths occurred during the conduct of the two Phase 3 clinical studies and the additional safety study that form the basis of this application.

#### 7.3.2 Nonfatal Serious Adverse Events

Table 7.3.2 – All Serious Adverse Events by Treatment (Pooled)

Study-Subject	Age/Sex Race	Eye	Abbrev. SOC	Preferred Term\ Investigator Term	Onset/Max Severity\ Related to Study Drug/ Led to Discontinua- tion	Onset Day\ Duration	Seriousness Criteria
<b>Treatment: Ketorolac 0.45%</b>							
191578006-10002-1163	62/Male Caucasian	Non-ocular	Inj&P	Post procedural haemorrhage Post Colonoscopy intestinal bleeding	Severe/Severe No/No	7 3	Hospitalization
191578005-10006-1270	69/Male Caucasian	Non-ocular	Card	Angina unstable unstable angina	Severe/Severe No/Yes	18 —	Hospitalization
191578005-10015-1182	72/Male Caucasian	Non-ocular	Card	Cardiac arrest asystole	Severe/Severe No/Yes	12 1	Life-Threatening, Hospitalization
		Non-ocular	Card	Coronary artery occlusion coronary artery blockage	Severe/Severe No/Yes	13 1	Hospitalization
<b>Treatment: Vehicle</b>							
191578005-10011-1048	55/Male Caucasian	Non-ocular	Card	Coronary artery disease Coronary Artery Disease	Severe/Severe No/Yes	4 6	Life-Threatening, Hospitalization

Source: ISS Table 2.7.4.7-13.2: Listing 14.3.2 (Reports 191578-005 and -006); Listing 16.2.7-1 (Reports 191578-005 and -006)

SOC = abbreviated System Organ Class of MedDRA; Card = Cardiac disorders; Inj&P = Injury, poisoning and procedural complications

Four patients in the pooled phase 3 studies and none in the phase 1 study experienced serious adverse events. All of the serious adverse events were non-ocular in nature.

7.3.3 Dropouts and/or Discontinuations

Table 7.3.3 - Subject Disposition and Exit Status for Phase 3 Clinical Studies (Safety Population)  
 191578-005/191578-006

Disposition	Study 191578-005		Study 191578-006	
	Ketorolac 0.45% Vehicle (N=157)	Total (N=238)	Ketorolac 0.45% Vehicle (N=173)	Total (N=255)
Enrolled[a]	157	238	173	255
Completed	144 ( 91.7%)	201 ( 84.5%)	163 ( 94.2%)	222 ( 87.1%)
Discontinued	13 ( 8.3%)	37 ( 15.5%)	10 ( 5.8%)	33 ( 12.9%)
Adverse Event	7 ( 4.5%)	27 ( 11.3%)	7 ( 4.0%)	18 ( 7.1%)
Ocular	5 ( 3.2%)	24 ( 10.1%)	7 ( 4.0%)	18 ( 7.1%)
Non-Ocular	2 ( 1.3%)	3 ( 1.3%)	0 ( 0.0%)	0 ( 0.0%)
Lack of Efficacy	0 ( 0.0%)	2 ( 0.8%)	0 ( 0.0%)	8 ( 3.1%)
Pregnancy	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
Lost to Follow-Up	1 ( 0.6%)	1 ( 0.4%)	0 ( 0.0%)	0 ( 0.0%)
Personal Reasons	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)	0 ( 0.0%)
Protocol Violation (Anti-Inflammatory)	3 ( 1.9%)	4 ( 1.7%)	0 ( 0.0%)	2 ( 0.8%)
Protocol Violation (Other)	1 ( 0.6%)	1 ( 0.4%)	1 ( 0.6%)	1 ( 0.4%)
Other[b]	1 ( 0.6%)	2 ( 0.8%)	2 ( 1.2%)	4 ( 1.6%)

[a] Includes all randomized subjects who received at least 1 dose of study medication and analyzed according to the medication actually received.

[b] Other reasons for discontinuation are presented in Table 2.7.3.6-1.3.

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This is a pooled table. For individual study patient disposition, see Section 6.1.3.

### 7.3.4 Significant Adverse Events

See Section 7.3.2.

### 7.3.5 Submission Specific Primary Safety Concerns

Table 7.3.5 – Visual Acuity in Operative Eye: Final Evaluation Compared with Baseline (Safety Population) in Phase 3 Trials

Change (lines) <sup>a</sup>	Study 191578-005		Study 191578-006		Pooled	
	Ketorolac 0.45% (N=157)	Vehicle (N=81)	Ketorolac 0.45% (N=173)	Vehicle (N=82)	Ketorolac 0.45% (N=330)	Vehicle (N=163)
N	153	78	167	80	320	158
≥ +3	91 (59.5)	36 (46.2)	95 (56.9)	29 (36.3)	186 (58.1)	65 (41.1)
< +3	62 (40.5)	42 (53.8)	72 (43.1)	51 (63.8)	134 (41.9)	93 (58.9)
≥ +2 to < +3	17 (11.1)	12 (15.4)	21 (12.6)	7 (8.8)	38 (11.9)	19 (12.0)
≥ +1 to < +2	28 (18.3)	12 (15.4)	31 (18.6)	19 (23.8)	59 (18.4)	31 (19.6)
≥ 0 to < +1	12 (7.8)	7 (9.0)	10 (6.0)	13 (16.3)	22 (6.9)	20 (12.7)
≥ -1 to < 0	4 (2.6)	4 (5.1)	5 (3.0)	6 (7.5)	9 (2.8)	10 (6.3)
≥ -2 to < -1	1 (0.7)	5 (6.4)	3 (1.8)	6 (7.5)	4 (1.3)	11 (7.0)
> -3 to < -2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≤ -3	0 (0.0)	2 (2.6)	2 (1.2)	0 (0.0)	2 (0.6)	2 (1.3)

In the two phase 3 studies pooled, more than 2/3 of patients in both treatment groups experienced at least 1 line of improvement in visual acuity from baseline to final evaluation. Two patients in each treatment group had a decrease in visual acuity of > 3 lines (0.6% [2/320] of ketorolac 0.45% patients, 1.3% [2/158] of vehicle patients).

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Table 7.4.1a – Adverse Events by Decreasing Incidence: Phase 3 Clinical Studies, Pooled (Safety Population)

Clinical Review  
 William M. Boyd, M.D.  
 NDA 22-427  
 Acuvail (ketorolac tromethamine ophthalmic solution) 0.45%

Adverse Event (Preferred Term) <sup>a</sup> n (%)	SOC Abbrev.	Ketorolac 0.45% (N=330)	Vehicle (N=163)
Overall		116 (35.2)	79 (48.5)
Intraocular pressure increased	Inv	19 (5.8)	3 (1.8)
Anterior chamber cell	Eye	17 (5.2)	10 (6.1)
Conjunctival hyperaemia	Eye	15 (4.5)	23 (14.1)
Eye pain	Eye	14 (4.2)	25 (15.3)
Iritis	Eye	14 (4.2)	12 (7.4)
Anterior chamber flare	Eye	12 (3.6)	8 (4.9)
Corneal oedema	Eye	11 (3.3)	10 (6.1)
Foreign body sensation in eyes	Eye	11 (3.3)	9 (5.5)
Headache	Nerv	10 (3.0)	6 (3.7)
Lacrimation increased	Eye	4 (1.2)	4 (2.5)
Conjunctival haemorrhage	Eye	4 (1.2)	1 (0.6)
Vision blurred	Eye	4 (1.2)	1 (0.6)
Photophobia	Eye	3 (0.9)	16 (9.8)
Conjunctival oedema	Eye	3 (0.9)	4 (2.5)
Eye irritation	Eye	3 (0.9)	4 (2.5)
Eye pruritus	Eye	3 (0.9)	3 (1.8)
Corneal abrasion	Inj&P	3 (0.9)	1 (0.6)
Vitreous detachment	Eye	3 (0.9)	1 (0.6)
Posterior capsule rupture	Eye	3 (0.9)	0 (0.0)
Vitreous floaters	Eye	3 (0.9)	0 (0.0)
Anterior chamber fibrin	Eye	2 (0.6)	2 (1.2)
Cataract operation complication	Inj&P	2 (0.6)	1 (0.6)
Macular oedema	Eye	2 (0.6)	1 (0.6)
Nausea	Gastr	2 (0.6)	1 (0.6)
Punctate keratitis	Eye	2 (0.6)	1 (0.6)
Anterior chamber inflammation	Eye	1 (0.3)	6 (3.7)
Iris haemorrhage	Eye	1 (0.3)	2 (1.2)
Eyelid oedema	Eye	0 (0.0)	3 (1.8)
Facial pain	Genrl	0 (0.0)	3 (1.8)
Uveitis	Eye	0 (0.0)	3 (1.8)

Source: ISS Table 2.7.4.7-9.2

SOC = abbreviated System Organ Class of MedDRA; Eye = eye disorders; Inv = investigations; Nerv = nervous system disorders; Inj&P = injury, poisoning and procedural complications; Gastr = gastrointestinal disorders; Genrl = general disorders and administration site conditions

a Adverse events occurring in 3 or more patients

The most common adverse events were reported in 1-6% of patients and included increased intraocular pressure, conjunctival hyperemia and/or hemorrhage, corneal edema, ocular pain, headache, tearing and vision blurred. Some of these events may be the consequence of the cataract surgical procedure.

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Of the most frequently occurring adverse events in the 2 pooled phase 3 studies, the incidences of eye pain ( $p < 0.001$ ), conjunctival hyperemia ( $p < 0.001$ ), and photophobia ( $p < 0.001$ ) were statistically significantly higher in the vehicle group than in the ketorolac 0.45% group.

For one of the most frequently occurring adverse events in the pooled phase 3 studies, intraocular pressure increased, incidence was higher in the ketorolac 0.45% group than in the vehicle group (5.8% [19/330] of the ketorolac 0.45% group compared with 1.8% [3/163] of the vehicle group). This was a statistically significant difference ( $p = 0.048$ ); no other adverse event in the pooled phase 3 studies was statistically significantly more prevalent in the ketorolac 0.45% group than in the vehicle group (original source - ISS Table 2.7.4.7-9.2). The mean increase of 2.7 mm Hg (Acuvail) vs. 0.2 mm Hg (vehicle) is not clinically significant.

Table 7.4.1b –Number (Percentage) of Subjects with Adverse Events: Study -004 (Safety Population)

Adverse Event (Preferred Term)	KETO 0.45%		KETO 0.35%	
	Ketorolac Eye (N = 20)	ACULAR LS® Eye (N = 20)	Ketorolac Eye (N = 19)	ACULAR LS® Eye (N = 19)
Eye irritation	2 (10)	3 (15)	3 (16)	3 (16)
Lacrimation increased	1 (5)	0	0	0
Foreign body sensation in eyes	0	1 (5)	1 (5)	0
Vision blurred	0	0	1 (5)	0
Conjunctival hyperaemia	0	0	0	1 (5)
Hypoaesthesia eye	0	0	0	1 (5)

Source: Table 14.3-3.1 and Table 14.3-3.2; Listing 16.2.7

In safety study -004, eye irritation was the most commonly reported ocular adverse event, occurring in 2 (10%) ketorolac 0.45%-treated eyes, in 3 (16%) ketorolac 0.35%-treated eyes, and in 6 (15%) subjects over both treatment groups receiving Acular LS. One subject in each treatment group reported irritation in both the ketorolac eye and the Acular LS eye. No other ocular adverse events occurred in more than 1 subject with any of the 3 study medications. No nonocular adverse events were reported.

### 7.4.2 Laboratory Findings

Clinical laboratory evaluations were not performed for any of the studies.

### 7.4.3 Vital Signs

In the phase 3 studies, blood pressure and heart rate were measured at screening and on postoperative day 14. In the phase 1 study, blood pressure and heart rate were measured at screening, pre-dose, and at hour 4.5.

Mean and median changes in blood pressure and pulse rate from baseline to day 14/exit were small and were clinically unimportant in both treatment groups in both phase 3 studies. Similarly, mean and median changes in blood pressure and pulse rate from baseline to hour 4.5 were small and had no discernible pattern.

### 7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed in any of the studies.

### 7.4.5 Special Safety Studies/Clinical Trials

A 120-Day Safety Update was submitted on January 29, 2009.

The Phase 3 studies in support of the original NDA, 191578-005 and 191578-006, were completed and the final study reports were submitted in the original NDA. There are no additional safety data from these studies, and Allergan is not conducting any other clinical studies at this time related to the proposed indication for this NDA with Acuvail (ketorolac tromethamine ophthalmic solution) 0.45%.

### 7.4.6 Immunogenicity

Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% is not expected to be immunogenic.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

No drug dose relationship to adverse effects was assessed; a single dose and regimen of ketorolac tromethamine ophthalmic solution 0.45% (1 drop twice daily on the day before surgery and for 14 days after surgery, 6 drops on the day of surgery) was evaluated in the phase 3 studies that form the basis of this application.

### 7.5.2 Time Dependency for Adverse Events

A review of time to onset of adverse events did not identify any safety concerns. Some of the adverse events reported may be the consequence of the cataract surgical procedure.

### 7.5.3 Drug-Demographic Interactions

An analysis of adverse events by age category (adults and elderly), gender, race, and iris color did not identify any safety concerns for any demographic subpopulation.

### 7.5.4 Drug-Disease Interactions

Consistent with the class labeling for topical ophthalmic NSAIDs:

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk for the occurrence and severity of corneal adverse events.

### 7.5.5 Drug-Drug Interactions

Consistent with the class labeling for topical ophthalmic NSAIDs:

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some NSAIDs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that Acuvail be used with caution in patients with known bleeding tendencies or who are receiving other medications, which may prolong bleeding time.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

The safety profile of ketorolac tromethamine ophthalmic formulations at concentrations up to 0.5% via a topical ocular drop four times per day in humans have been established by the other topical ophthalmic marketed products. A favorable safety profile has been demonstrated by previously conducted non-clinical ocular toxicity studies in support of the marketed products and additional studies evaluating this reformulated ketorolac tromethamine; both set of studies support the clinical use of the reformulated ketorolac tromethamine.

Per the proposed labeling:

Ketorolac tromethamine was not carcinogenic in either rats given up to 5 mg/kg/day orally for 24 months or in mice given 2 mg/kg/day orally for 18 months. These doses are approximately 900 times and 300 times higher respectively than the typical human topical ophthalmic daily dose given as BID to an affected eye on a mg/kg basis.

Ketorolac tromethamine was not mutagenic in vitro in the Ames assay or in forward mutation assays. Similarly, it did not result in an in vitro increase in unscheduled DNA synthesis or an in vivo increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 9 mg/kg/day and 16 mg/kg/day, respectively. These doses are respectively 1500 and 2700 times higher than the typical human topical ophthalmic daily dose.

### 7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women. Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of Acuvail during late pregnancy should be avoided.

Per the proposed labeling:

**Pregnancy Category C:** Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits and rats at oral doses of 3.6 mg/kg/day and 10 mg/kg/day, respectively. These doses are approximately 600 times and 1700 times higher respectively than the typical human topical ophthalmic daily dose of 0.35 mg (4.5 mg/mL x 0.04 mL/drop, BID) to an affected eye on a mg/kg basis. Additionally, when administered to rats after Day 17 of gestation at oral doses up to 1.5 mg/kg/day (approximately 300 times the typical human topical ophthalmic daily dose), ketorolac tromethamine resulted in dystocia and increased pup mortality.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. In accordance with CFR 314.55(c)(2)(i), Allergan, Inc. requested a waiver for Pediatric Studies in all patients (neonates, infants, children, and adolescents) from birth to 16 years of age.

Pediatric cataracts most often result from abnormal lens development during gestation. Lens malformations that occur in conjunction with other findings are often the result of a genetic or metabolic abnormality.

In patients less than 6 months of age, the cataract is most often removed under anesthesia. The preferred procedure is lensectomy with vitrectomy, with or without IOL placement. Postoperative inflammation in the absence of IOL implantation is generally mild, and medical management usually includes topical mydriatic, anti-infective, and steroid medications.

Allergan previously submitted a Pediatric Study Report to the Agency on 18 June 2001 for NDA 19-700 and NDA 20-811 which was done with the same active ingredient, ketorolac tromethamine, formulated at 0.5% in pediatric patients between 3 and 12 years of age. This pediatric study was subsequently accepted by the Agency on 8 February 2002 and pediatric exclusivity was granted to the abovementioned NDAs. The current application for ketorolac tromethamine ophthalmic solution 0.45% uses the same active ingredient, at a lower concentration and lower dosing frequency (BID compared to QID) as that of the 0.5% formulation for which a pediatric clinical trial has been completed.

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#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Acuvail (ketorolac tromethamine ophthalmic solution) 0.45% is intended for topical ophthalmic use only. No pharmacological evidence of any potential for drug abuse with ketorolac tromethamine ophthalmic solution exists. No studies related to overdosage in humans have been conducted.

#### 7.7 Additional Submissions / Safety Issues

No additional submissions are expected or required.

### 8 Postmarketing Experience

Ketorolac tromethamine ophthalmic solution 0.45% is not presently marketed. Therefore, there are no postmarketing reports.

Since initial marketing approval in 1989 for Acular, 1997 for Acular PF, and 2003 for Acular LS, a combined maximum exposure estimate for the Acular product family is nearly (b) (4) patients.

## **9 Appendices**

### **9.1 Literature Review/References**

There is no additional contributory information available from the literature.

### **9.2 Advisory Committee Meeting**

No Advisory Committee was necessary or convened for this drug product.

### **9.3 Labeling Recommendations**

It is recommended that NDA 22-427 be approved with the revised package insert labeling which follows.

6 Pages Withheld as b(4) Draft Labeling

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/s/

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William Boyd  
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MEDICAL OFFICER

Wiley Chambers  
7/22/2009 11:36:23 AM  
MEDICAL OFFICER