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RESEARCH**

***APPLICATION NUMBER:* 21-066**

STATISTICAL REVIEW(S)

550-Rodriguez

Statistical Review and Evaluation

MAY 19 1999

NDA: 21-066
Drug Class: Topical Ophthalmic Anti-allergy Agent
Name of Drug: Ketotifen Fumarate Ophthalmic Solution 0.025%
Applicant: Ciba Vision Corporation, Novartis Company
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Indications: Temporary prevention of ocular itching from allergic conjunctivitis

Controlled Clinical Studies Phase 3 Efficacy: C-08-97-002 and C-08-97-004
Phase 3 Safety: C-08-97-003

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I. Background Page 2
II. Reviewer's Conclusions Page 3
III. Phase 3 Efficacy Study - C-08-97-002 Page 6
IV. Phase 3 Efficacy Study - C-08-97-004 Page 9
V. Phase 3 Safety Study - C-08-97-003 Page 11

Attachments

1 Description: Phase 2 and Phase 3 Studies Page 15
2 Reviewer's Results: Efficacy Study C-08-97-002 Page 16
3 Reviewer's Results: Efficacy Study C-08-97-004 Page 18
4 Reviewer's Results: Safety Study C-08-97-003 Page 20

I. Background [Attachment # 1 - Page 15]

Ketotifen fumarate is a new molecular entity under FDA review as a topical ophthalmic anti-allergy agent. This statistical review is an evaluation of the performance of Ketotifen Fumarate 0.025% Ophthalmic Solution as studied for the temporary prevention of ocular itching associated with seasonal allergic conjunctivitis. In that the time necessary to demonstrate unqualified relief is currently being considered by FDA as 6 weeks to 3 months, the word, "temporary" must be included to qualify the indication. The indication is labeled as "prevention" if only conjunctival provocation test (CPT) trials are conducted, however, this could be changed to "relief" if both CPT and environmental studies are conducted, including the replication of results necessary to support this new claim. The sponsor is currently conducting environmental studies internationally.

A minimum of 8 hours must be shown for duration of effect in order to label the product as having a B.I.D. dosing regimen. And a minimum of 300 patients are required for approval. Additionally, to gain pediatric approval, a minimum of 5 patients per age in years should be included in trials, with labeling based on the lowest age not having difficulty with study medication. Products not used chronically are not required to demonstrate safety from carcinogenic potential.

The sponsor reports, "Ketotifen fumarate is a second-generation histamine receptor antagonist. Oral Ketotifen, in both immediate and sustained release tablets, has been available for the treatment of asthma throughout Europe, Canada, and Japan. Ketotifen prevents anaphylaxis and allergic reactions by inhibiting the release of chemical mediators such as histamine and leukotrienes from sensitized mast cells and by inhibiting the interaction between histamine and the H₁-receptor." [Vol 16-0026]

In 1997, the sponsor began a clinical development program in Europe and the United States to investigate the efficacy of Ketotifen fumarate ophthalmic solution as compared to vehicle placebo and positive control topical ophthalmic agents (demethindene maleate 0.05%; levocabastine 0.05%; olopatadine 0.1%), to determine the impact of concentration and dose regimen, and to evaluate ocular tolerance and safety. The NDA was filed January 04, 1999.

Phase 2 Studies: One Phase 2 study of Ketotifen Fumarate 0.05% used the conjunctival provocation test (CPT) or allergen challenge model to expose healthy patients to a sensitizing antigen in creating a quantifiable and reproducible reaction. After deliberately provoking an allergen challenge, the post-treatment response was assessed. In this Phase 2 Pilot Study, the sponsor concluded that Ketotifen fumarate 0.05% and demethindene maleate 0.05% were as effective as levocabastine 0.05% in inhibiting signs and symptoms of allergic conjunctivitis. A second Phase 2 study evaluated the efficacy and safety in dose response of 4 concentrations (0.025%, 0.05%, 0.1%, 0.15%) of Ketotifen Fumarate Ophthalmic Solution. In this dose response study, the sponsor determined that Ketotifen in all 4 concentrations was safe and effective from 15 minutes to 12 hours after a single dose in relieving the signs and symptoms of induced allergic conjunctivitis in sensitive individuals. The efficacy of Ketotifen in relieving itching and redness was comparable to that of olopatadine 0.1% (Patanol).

Phase 3 Studies: In 1998, the sponsor conducted 2 Phase 3 studies, C-08-97-002 and C-08-97-004, to compare the safety and efficacy of Ketotifen fumarate 0.025% with vehicle in

preventing symptoms of allergic conjunctivitis. Allergen challenges were performed at 15 minutes, 6 hours, and 8 hours after treatment. The sponsor concluded that Ketotifen fumarate 0.025% ophthalmic solution had an anti-itching effect that lasted for up to 8 hours. Phase 3 safety Study C-08-97-003 investigated continuous, multiple daily dosing in healthy volunteers whose eyes were instilled 4 times daily for 6 weeks. The sponsor concluded Ketotifen fumarate 0.025% was safe and well-tolerated.

II. Reviewer's Conclusions

1. **Reviewer Comments:** Dr. Mark Abelson [redacted] was the Principal Investigator for Efficacy Study 002. Even though the protocol for the second Efficacy Study 004 does not identify him as an investigator, it lists [redacted] for this Study 004. [Vol 24-0116]. This may represent a conflict of interest and disallow this submission from having 2 independent, adequate, well-controlled studies. The sponsor does list Abelson as an investigator for both studies in Vol 17-0171.

To gain pediatric approval, a minimum of 5 patients per age in years should be included in trials, with labeling based on the lowest age not having difficulty with study medication. Safety Study C-08-97-003 enrolled 41 pediatric subjects under 12 years of age who were randomized to receive Ketotifen fumarate and 17 randomized to Vehicle placebo. The distribution by age in years for all pediatric subjects in this trial meets the minimum of 5 patients per age.

Distribution of Pediatric Subjects

	Safety Study C-08-97-003								
Age (Years)	3.3 to 3.9	4.2 to 4.9	5.1 to 5.9	6.0 to 6.9	7.1 to 7.9	8.1 to 8.9	9.3 to 9.9	10.3 to 10.9	11.2 to 11.8
# Ketotifen Subjects	6	3	5	5	4	4	5	5	4
# Vehicle Subjects	2	2	3	2	1	3	1	2	1
Total # Subjects	8	5	8	7	5	7	6	7	5

2. **Efficacy Summary:** This Statistical Review is in agreement with the sponsor's conclusions. In both efficacy CPT studies, Ketotifen fumarate was statistically superior to vehicle-placebo in reducing ocular itching in challenged eyes at all 3 post-challenge time points ($p < 0.001$). Onset of action was established as 15 minutes since the overall mean unadjusted between-treatment difference in ocular itching for all time points after the 15-minute allergen challenge was > 1.4 units in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution. Duration of effect was confirmed by the 6 hour and 8 hour allergen challenges. The 1.4 unit difference in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution after the 15-minute and 6-hour allergen challenge, and 1.2 unit difference, again in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution, after the 8-hour allergen challenge were all greater than the 1.0 unit difference

[redacted]

necessary for clinical significance. Itching for Ketotifen-treated eyes was scored as mild, whereas that of vehicle-treated eyes was mild to moderate in severity. There were no remarkable differences among sex, race, and age groups.

Although the secondary efficacy measures demonstrated a statistically significant difference in the performance of Ketotifen fumarate over Vehicle placebo, the differences were not greater than the 1.0 unit improvement necessary for clinical significance. In both efficacy studies (-002 and -004), the mean unadjusted difference in ciliary injection ranged from 0.34 to 0.89 for the three allergen challenge time points of 15 minutes, 6 hours, and 8 hours. The mean unadjusted difference in episcleral injection was 0.24 to 0.61 units, and the mean unadjusted difference in conjunctival injection was 0.24 to 0.57 units. The scores for each of these secondary efficacy measures showed an improvement of mild to moderate rating for eyes treated with Ketotifen fumarate as compared that with Vehicle placebo scored moderate to severe.

3. Safety Summary: This Statistical Review summarized the safety profile of Ketotifen fumarate 0.025% solution as studied in patient discontinuations and adverse experiences reported for three Phase 3 studies (C-08-97-002; C-08-97-004; and C-08-97-003). Ocular safety results investigated by visual acuity, slit lamp findings, and dilated ophthalmoscopy are reported in the Medical Review.

All Phase 3 Trials [Efficacy Studies -002 and -004 and Safety Study -003]

Reviewer's Results	Ketotifen	Vehicle	Total
# Enrolled (Safety Evaluable)	506 (75%)	165 (25%)	671
# Completed Study	466 (92%)	158 (96%)	624
# Discontinued Due to Adverse Event	03 (<1%)	03 (<2%)	06
# Disc - Treatment Failure	0	0	0
# Disc - Protocol Violation	10 (02%)	0(<1%)	11
# Disc - Lost-to-Follow up	12 (02%)	01 (<1%)	13
# Disc - Voluntary Reasons	10 (02%)	01 (<1%)	11

Patient Disposition: Six hundred seventy-one (671) subjects were randomized in the three Phase 3 studies. Twenty-five percent (165/671) were randomized to receive Vehicle placebo in both eyes for 6 weeks duration, and 75% instilled Ketotifen fumarate 0.025% (49% or 330/671 in both eyes for 6 weeks and 26% or 176/671 in one eye for 3 nonconsecutive days). Sixty-two percent (62% or 416/671) of the subjects were Caucasian; 29% (194/671) were Hispanic; and the remaining 9% (61/671) were of Black, Asian, and other racial origins. More females than males participated (59% or 393/671 were female and 41% or 278/671 were male).

Patient Discontinuations: Ninety-three percent (93% or 624/671) of the subjects completed study. More Ketotifen fumarate subjects discontinued for protocol violations, lost-to-follow-up, and voluntary reasons (7% or 36/506) as compared to Vehicle placebo (2% or 4/165). However, fewer Ketotifen fumarate subjects (< 1% or 3/506) discontinued due to adverse events as compared to Vehicle placebo subjects (< 2% or 3/165). Three Ketotifen fumarate

subjects discontinued due to adverse events that were related to study drug. In Efficacy Study C-08-97-004, Subject # 519 discontinued at Visit 3 due to adverse events reported as ear discharge, headache, and rhinitis, all of moderate intensity and possibly related to study drug. In 6-week Safety Study C-08-97-003, 2 Ketotifen fumarate subjects discontinued due to adverse events: at Visits 3 and 4, Subject # 4005 developed moderate injection and lid discharge in both eyes that were determined related to study drug. He also reported mild headache that was not considered related to drug. At Visit 2, Subject # 5115 developed possibly related, matting and crusting discharge of mild severity.

Duration of 3 Nonconsecutive Days: In Efficacy Studies C-08-97-002 and C-08-97-004, 176 subjects were randomized to receive Ketotifen fumarate 0.025% instilled in one eye for three nonconsecutive days (Days 0, 14, and 28). Nineteen percent (19% or 34/176) of these subjects reported 44 adverse events. Six percent (6% or 10/176) reported events that were related or possibly related to study drug. Nine percent (9% or 16/176) reported 19 adverse events of mild severity, and 6% (10/176) reported 25 events of moderate severity. No serious events were reported. The moderate events included B/S UDI; bronchitis; dyspepsia; ear discharge; flu syndrome; headache; migraine; pain; pain abdominal; rhinitis; and stomatitis. The highest incidence of events reported was headache (7% or 12/176 subjects) and rhinitis (7% or 13/176).

Duration of 6 Weeks: Of the 495 subjects randomized to receive treatment for 6 consecutive weeks in Safety Study C-08-97-003, 330 instilled Ketotifen fumarate and 165 instilled Vehicle placebo in both eyes. [Attachment # 4 - Page 20]

Related: Twenty percent (20% or 65/330) Ketotifen fumarate subjects reported 90 events and 17% (28/165) Vehicle placebo subjects reported 36 events that were related or possibly related to study drug.

Treatment-related events reported by the Ketotifen subjects included asthenia; B/S; B/S UDI; conjunctivitis; discharge; dry eye; eye discharge; FBS; headache; injection; irritation; itching; keratitis; lacrimation discharge; lid discharge; pain eye; rhinitis; somnolence; tachycardia; and vision abnormal.

Serious: One percent (1% or 3/330) Ketotifen fumarate subjects reported 3 events and 2% (3/165) Vehicle placebo subjects also reported 3 events that were deemed serious. In the Ketotifen fumarate group, these events included neoplasm of the breast; pain; and pain abdomen.

Moderate and Severe: Eighteen percent (18% or 60/330) Ketotifen fumarate subjects reported 88 events and 17% (28/165) Vehicle placebo subjects reported 36 events that were of moderate severity; 3% (11/330) Ketotifen fumarate subjects reported 13 events and 4% (7/165) Vehicle placebo subjects reported 8 events of severe intensity.

In the Ketotifen fumarate group, these moderate and severe events included arthralgia; B/S; bone fracture spontaneous; cough inclusion; diarrhea; cholecystitis; dry eye; dysmenorrhea; dyspepsia; ear discharge; fever; flu syndrome; headache; hypertension; hypertonia; infection; injection; injury accidental; itching; lid discharge; nausea; neoplasm of the breast; pain; pain abdomen; pain back; pharyngitis; rhinitis; sinusitis; syncope; tachycardia; and ulcer of the mouth.

Highest Incidence of Events Reported: B/S (2% Ketotifen and <1% Vehicle); B/S UDI (3% Ketotifen and <1% Vehicle); Discharge (2% Ketotifen and 0% Vehicle); Headache (19% Ketotifen and 25% Vehicle); Injection (11% Ketotifen and 11% Vehicle); Itching (4% Ketotifen and 3% Vehicle); Lid discharge (3% Ketotifen and 1% Vehicle); and Rhinitis (14% Ketotifen and 13% Vehicle).

III. Phase 3 Efficacy Study C-08-97-002 [Attachment # 2 - Pages 16-17]

1. **Study Design:** Study C-08-97-002 was a Phase 3, double-masked, fellow-eye, placebo-controlled, parallel group, randomized, single-center investigation in the allergen challenge model [using the conjunctival provocation test or CPT] of allergic conjunctivitis. The study was conducted to compare the safety and efficacy of Ketotifen Fumarate 0.025% Ophthalmic Solution versus vehicle placebo in the prevention of symptoms of allergic conjunctivitis. The study was conducted at one center by Principal Investigator, Mark Abelson, MD of [redacted]

The study began January 24, 1998. The protocol date is December 16, 1997. Amendment #1, dated January 23, 1998, changed the telephone number on the Informed Consent Form. The clinical database was prepared by [redacted]

Subjects included those over 17 years of age who had a positive diagnostic test for allergic disease, (or a positive conjunctival allergen challenge on file within 24 months of study) and who manifested a successful conjunctival provocation test (CPT) reaction that induced at least 2+ itching and 2+ conjunctival redness bilaterally at Visit 1 (screening) and Visit 2 (confirmation). During 3 subsequent visits (Visits 3, 4, and 5) on 3 nonsequential days of treatment, masked study drops was instilled in one eye and vehicle placebo in the fellow eye of each subject. Allergen challenge was then administered bilaterally at 15 minutes, 6 hours, and 8 hours for Visits 3, 4, and 5 respectively. Subjects made primary efficacy assessments on a graded scale at 3, 7, and 10 minutes after the allergen challenge. The investigator evaluated secondary efficacy assessments on a graded scale at 7, 10, and 15 minutes after the allergen challenge. Vehicle placebo drops had the same ingredients as Ketotifen fumarate 0.025% ophthalmic solution, minus the active ingredient, i.e. vehicle contained glycerol, benzalkonium chloride, purified water, hydrochloric acid, and/or sodium hydroxide (to adjust pH).

Visit Schedule

Visit 1	Day -21	Screening, determination of allergen challenge concentration
Visit 2	Day -14	Confirmation of allergen challenge concentration
Visit 3	Day 0	Inclusion assessments, randomization, drug instillation #1, allergen challenge given 15 minutes after drug instillation, efficacy assessments at 3, 7, and 10 minutes (onset of action) following allergen challenge
Visit 4	Day 14	Drug instillation #2, allergen challenge given 6 hours after drug instillation, efficacy assessments at 3, 7, and 10 minutes (duration of effect) following allergen challenge
Visit 5	Day 28	Drug instillation #3, allergen challenge given 8 hours after drug instillation, efficacy assessments at 3, 7, and 10 minutes (duration of effect) following allergen challenge

At least 100 subjects were to be enrolled and randomized at Visit 3 to ensure that a minimum of 80 subjects would complete all visits and allergen challenges. The basis of the 80-subject sample size determination assumed a standard deviation of 1.07 for itching assessments for 98% power to detect a between-treatment difference (in means) of 0.50, assuming a 0.05 two-sided alpha significance level.

The Primary efficacy measure was Ocular itching on a 5-point scale assessed 3, 7, and 10 minutes after allergen challenge at Visits 3, 4, and 5. The ocular itching scale was 0=none; 1=intermittent tickle; 2=mild continuous itch; 3=severe itch; and 4=incapacitating itch. The secondary efficacy measures were conjunctival, ciliary, and episcleral injection assessed 7, 10, and 15 minutes after allergen challenge on a 5-point scale of 0=none; 1=mild; 2=moderate; 3=severe; 4=unusually severe. Baseline efficacy measures were assessments made at Visit 2 (confirmatory visit).

Clinical Significance was defined as a mean difference of at least 1 unit favoring Ketotifen over vehicle. A demonstration of statistical significance was required for at least 2 of 3 time points, with 2 of the 3 time points preferably overlapping. Significance was required at both Visit 3 (onset of action) and Visit 4 (duration of effect). Statistical significance was tested under 2 approaches for comparisons between treatment groups made within subjects:

- 1) Unadjusted scores method used the difference between post-treatment study drug eye and post-treatment vehicle (fellow eye)
- 2) Baseline-adjusted scores method used the difference between change from baseline in post-treatment study drug eye and change from baseline in post-treatment vehicle (fellow eye).

2. Patient Disposition: Of the 167 subjects who enrolled in Screening Visit 1, 89 were randomized into the study. Each randomized subject had Ketotifen fumarate 0.025% instilled in one eye and vehicle placebo in the fellow eye. Fifty-four percent (54% or 48) were male and 46% (or 41/89) were female. Ninety-three percent (93% or 83/49) were Caucasian; 3% Hispanic; 2% Black, and 1% Asian racial origin. The iris color was 41% dark irides (39% brown and 2% black) and 59% light irides (26% hazel and 33% blue).

Nineteen percent (19% or 17/89) of subjects did not complete study: 9% (8/89) lost-to-follow up; 3% (3/89) discontinued; 6% (5/89) protocol violations; and 1% for other reasons. No terminations were due to lack of efficacy or adverse events.

Two subjects were protocol deviations (Subject #134 and #112) in that for one visit only, they received allergen challenge 1 hour earlier than indicated by the protocol. They were included in the intent-to-treat (ITT) analysis.

3. Sponsor's Evaluation: The sponsor reports that Ketotifen fumarate was statistically superior to vehicle-placebo in reducing ocular itching in challenged eyes at all 3 post-challenge time points ($p < 0.001$). The mean unadjusted between-treatment difference in ocular itching was 1.4 units in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution at 3, 7, and 10 minutes after the 15-minute allergen challenge (onset of action). Even though the magnitude of mean itching scores for all treated eyes was slightly smaller than at Visit 3, there was a 1.4 unit difference in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution at 3, 7, and 10 minutes after the 6-hour

allergen challenge (duration of effect), and a 1.2 unit difference, again in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution, at 3, 7, and 10 minutes after the 8-hour allergen challenge (duration of effect). This difference in itching scores exceeded the 1.0 unit necessary for clinical significance. Itching for Ketotifen-treated eyes was scored as mild, whereas that of vehicle-treated eyes was mild to moderate in severity. There was no statistically significant differences in the degree of ocular itching between eyes at baseline ($p>=0.36$). [Vol 20-0036]

**Mean Unadjusted Differences in Itching Scores
Ketotifen-treated minus Vehicle-treated Eyes**

Assessment Time after Challenge	Time of Challenge after Treatment			
	Baseline	15 minutes	6 hours	8 hours
3 minutes	0.02	-1.41	-1.43	-1.16
7 minutes	0.04	-1.80	-1.54	-1.41
10 minutes	0.03	-1.39	-1.33	-1.26

Furthermore, the between-treatment differences in the percentage of eyes with no itching indicated that more Ketotifen-treated eyes (52% to 61%) reported no itching than placebo-treated eyes after all allergen challenge times of 15 minutes, 6 hours, and 8 hours. Ketotifen fumarate was statistically superior to vehicle-placebo in the percentage of subjects reporting no itching in their challenged eyes at all 3 post-challenge time points ($p<0.001$). [Vol 20-0036] test for matched pairs was used to test the association, or marginal homogeneity, of the proportion of subjects with no itching in their active treatment eye and the proportion of subjects with no itching in their placebo-treated eye. The same procedure was used in the analysis of the proportion of subjects with mild (or less) conjunctival injection.

**Between-treatment Differences in Percentages of Eyes with No Itching
Ketotifen-treated versus Vehicle-treated Eyes**

Assessment Time after Challenge	Time of Challenge after Treatment		
	15 minutes	6 hours	8 hours
3 minutes	51.7%	53.0%	54.2%
7 minutes	60.7%	57.8%	61.1%
10 minutes	55.1%	60.2%	61.1%

4. Reviewer's Evaluation: This Statistical Review is in agreement with the sponsor's results. Ketotifen fumarate was statistically superior to vehicle-placebo in reducing ocular itching in challenged eyes at all 3 post-challenge time points ($p<0.001$). The overall mean unadjusted

between-treatment difference in ocular itching for all time points was 1.41 units in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution at 3, 7, and 10 minutes after the 15-minute allergen challenge (onset of action). There was also a 1.4 unit difference in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution at 3, 7, and 10 minutes after the 6-hour allergen challenge (duration of effect), and a 1.2 unit difference, again in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution, at 3, 7, and 10 minutes after the 8-hour allergen challenge (duration of effect). This difference in itching scores exceeded the 1.0 unit necessary for clinical significance. Itching for Ketotifen-treated eyes was scored as mild, whereas that of vehicle-treated eyes was mild to moderate in severity. There was no statistically significant differences in the degree of ocular itching between eyes at baseline ($p > 0.36$).

The intent-to-treat (ITT) or primary efficacy analysis was on all subjects according to randomized treatment group, including any who were protocol violations. Because both eyes within a subject were treated, comparisons between treatments were made within subject. The data points collected within a subject could not be considered independent, and the analysis took this correlation into account. Paired t-tests on the unadjusted and baseline-adjusted score differences between the eyes were used to assess differences between treatments at each visit.

In the protocol, the sponsor indicated that to ensure that the subject sample used a representative sample of the U.S. population, approximately 20% of the subjects enrolled must be composed of several minority ethnic groups. In this study, 93% of the subjects were Caucasian and only 7% were of Hispanic, Black and other racial origins. No measures were taken in the protocol to ensure the 20% minority enrollment.

IV. Phase 3 Efficacy Study C-08-97-004 [Attachment # 3 - Pages 18-19]

1. Study Design: Study C-08-97-004 was a Phase 3, double-masked, fellow-eye, placebo-controlled, parallel group, randomized, multi-center investigation in the allergen challenge model [using the conjunctival provocation test (CPT)] of allergic conjunctivitis. The study was conducted to compare the safety and efficacy of Ketotifen Fumarate 0.025% Ophthalmic Solution versus vehicle placebo in the prevention of symptoms of allergic conjunctivitis. The study design was identical to that of Efficacy Study C-08-97-002, and included the same primary efficacy measure of Ocular itching and secondary measures of conjunctival, ciliary, and episcleral injection.

The study was conducted at 4 centers by Principal Investigators, Thomas Mundorf, MD [redacted] John Lonsdale, MD [redacted] Richard Casey, MD [redacted] and Leonard Parver, MD [redacted]. The Site Management Organization was Ophthalmic Research Associated, [redacted]. The study began January 30, 1998. The protocol date is December 19, 1997.

2. Patient Disposition: Of the 189 subjects enrolled in Screening Visit 1, 87 were randomized into study. Each randomized subject had Ketotifen fumarate 0.025% instilled in one eye and vehicle placebo in the fellow eye. Thirty-six percent (36% or 31/87) were male and 64% (56/87) were female. Seventy-six percent (76% or 66/87) were Caucasian; 5% Hispanic; 18% Black, and 1% other racial origin. The iris color was 44% dark irides (43% brown and 1% black) and 56% light irides (20% hazel, 23% blue, 4% green, and 2% grey).

Ten percent (10% or 11/87) of subjects did not complete study: 3% (3/87) protocol violations; 4% (5/87) discontinued; 1% (1/87) lost-to-follow up; 1% (1/87) due to adverse events; and 1% (1/87) due to signs and symptoms of allergy.

Three subjects were protocol violations (Subject # 513, # 606, and # 718). Subject # 513 took disallowed medication (Ibuprofen) following a car accident; subject # 606 took prohibited medications, Sinulin and Naldecon; and Subject # 718 had co-enrolled in another clinical trial. Subject #519 discontinued due to adverse events reported as ear discharge, headache, and rhinitis, all of moderate intensity and possibly related to study drug. At baseline, Subject #609 discontinued due to signs and symptoms of allergy. Four subjects discontinued voluntarily for family emergencies or scheduling conflicts.

3. Sponsor's Evaluation: The sponsor reports that Ketotifen fumarate was statistically superior to vehicle-placebo in reducing ocular itching in challenged eyes at all 3 post-challenge time points ($p < 0.001$). The mean unadjusted between-treatment difference in ocular itching was 1.46 to 1.56 units in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution at 3, 7, and 10 minutes after the 15-minute allergen challenge (onset of action). Even though the magnitude of mean itching scores for all treated eyes was slightly smaller than at Visit 3, there was a 1.31 to 1.51 unit difference in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution at 3, 7, and 10 minutes after the 6-hour allergen challenge (duration of effect), and a 0.94 to 0.9 unit difference, again in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution, at 3, 7, and 10 minutes after the 8-hour allergen challenge (duration of effect). This difference in itching scores met or exceeded the 1.0 unit necessary for clinical significance. Ocular itching for Ketotifen-treated eyes was scored as extremely mild, whereas that of vehicle-treated eyes was mild to moderate in severity. There was no statistically significant differences in the degree of ocular itching between eyes at baseline ($p > 0.68$). [Vol 23-0006]

Mean Unadjusted Differences in Itching Scores
Ketotifen-treated minus Vehicle-treated Eyes

Assessment Time after Challenge	Time of Challenge after Treatment			
	Baseline	15 minutes	6 hours	8 hours
3 minutes	0.00	-1.51	-1.31	-0.96
7 minutes	-0.01	-1.56	-1.51	-0.98
10 minutes	0.02	-1.46	-1.34	-0.94

Furthermore, the between-treatment differences in the percentage of eyes with no itching indicated that more Ketotifen-treated eyes (35% to 56%) reported no itching than placebo-treated eyes after all allergen challenge times of 15 minutes, 6 hours, and 8 hours. Ketotifen fumarate was statistically superior to vehicle-placebo in the percentage of subjects reporting no itching in their challenged eyes at all 3 post-challenge time points ($p < 0.001$). [Vol 20-0036]

**Between-treatment Differences in Percentages of Eyes with No Itching
Ketotifen-treated versus Vehicle-treated Eyes**

Assessment Time after Challenge	Time of Challenge after Treatment		
	15 minutes	6 hours	8 hours
3 minutes	54.0%	35.0%	37.7%
7 minutes	48.3%	38.8%	35.1%
10 minutes	56.3%	42.5%	42.9%

4. Reviewer's Evaluation: This Statistical Review is in agreement with the sponsor's results. Ketotifen fumarate was statistically superior to vehicle-placebo in reducing ocular itching in challenged eyes at all 3 post-challenge time points ($p < 0.001$). The mean unadjusted between-treatment difference in ocular itching was 1.46 to 1.56 units in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution at 3, 7, and 10 minutes after the 15-minute allergen challenge (onset of action). Even though the magnitude of mean itching scores for all treated eyes was slightly smaller than at Visit 3, there was a 1.31 to 1.51 unit difference in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution at 3, 7, and 10 minutes after the 6-hour allergen challenge (duration of effect), and a 0.94 to 0.9 unit difference, again in favor of Ketotifen Fumarate 0.025% Ophthalmic Solution, at 3, 7, and 10 minutes after the 8-hour allergen challenge (duration of effect). This difference in itching scores met or exceeded the 1.0 unit necessary for clinical significance. Ocular itching for Ketotifen-treated eyes was scored as extremely mild, whereas that of vehicle-treated eyes was mild to moderate in severity. There was no statistically significant differences in the degree of ocular itching between eyes at baseline ($p > 0.68$).

V. Phase 3 Safety Study C-08-97-003 [Attachment # 4 - Page 20]

1. Study Design: Study C-08-97-003 was a Phase 3, double-masked, placebo-controlled, parallel group, randomized, multi-center investigation of the ocular tolerance and safety of Ketotifen Fumarate 0.025% Ophthalmic Solution. The study was conducted at 5 centers by Principal Investigators, Mark Abelson, MD [redacted], Dell, Lowry, Schullman, and Wapner. The study began January 17, 1998. The protocol is dated December 12, 1997. One amendment, dated January 13, 1998, increased the study enrollment plan from 420 subjects at 5 sites to 525 subjects at 7 sites.

Subjects were randomized to receive Ketotifen fumarate and vehicle placebo in a 2:1 ratio on an outpatient basis. The subjects had normal ocular health and included adults and adolescents over 12 years of age and children of age 3 to 11 years. On an outpatient basis, one drop of masked study medication was to be instilled in each eye four times daily for six weeks. The trial involved 5 clinic visits during which time safety assessments were taken.

Visit Schedule - Safety Study C-08-97-003

Visit 1	Day 0	Measures of blood pressure; heart rate; visual acuity; slit lamp examination; dilated ophthalmoscopy; intraocular pressure determination by applanation tonometry; pupil size and reactivity evaluation; rating of ocular signs and symptoms; assessment of ocular and nonocular adverse events.
Visit 2	Day 7	Blood pressure; heart rate; visual acuity; slit lamp examination; pupil size and reactivity evaluation; rating of ocular signs and symptoms; assessment of ocular and nonocular adverse events; assessment of subject compliance.
Visit 3	Day 14	Blood pressure; heart rate; visual acuity; slit lamp examination; pupil size and reactivity evaluation; rating of ocular signs and symptoms; assessment of ocular and nonocular adverse events; assessment of subject compliance.
Visit 4	Day 42	Blood pressure; heart rate; visual acuity; slit lamp examination; intraocular pressure determination by applanation tonometry; pupil size and reactivity evaluation; rating of ocular signs and symptoms; assessment of ocular and nonocular adverse events; assessment of subject compliance.
Visit 5	Day 43	Blood pressure; heart rate; dilated ophthalmoscopy; assessment of ocular and nonocular adverse events

2. Patient Disposition: Of the planned enrollment of 525 subjects, 495 subjects were randomized into the study. Sixty-seven percent (67% or 330/495) were randomized to the group instilling Ketotifen fumarate 0.025% in both eyes, and 33% (165/495) instilled vehicle placebo in both eyes. Forty-two percent (42% or 138/330) of the Ketotifen fumarate subjects and 37% (61/165) in the Vehicle placebo group were male. There were 58% Ketotifen fumarate and 63% Vehicle placebo female subjects. Fifty-three percent (53% or 174/330) of the Ketotifen fumarate subjects and 56% (93/165) in the Vehicle placebo group were Caucasian; 38% Hispanic in both treatment groups; 3 - 5% Black, and 3 - 4% other racial origin. The iris color of the Ketotifen fumarate subjects was 62% dark and 38% light irides, whereas the Vehicle placebo subjects had 58% dark and 42% light irides. Twelve percent (12% or 41/330) of the Ketotifen fumarate subjects and 10% (17/165) in the Vehicle placebo group were 3 to 11 years of age.

3. Discontinuations: In both treatment groups, there was comparable distribution of subjects who discontinued. Four percent (13/330 and 7/165) of subjects did not complete study: < 1% protocol violations; < 2% voluntary discontinuations; < 1% lost-to-follow up; < 2% due to adverse events; and < 1% for other reasons. The data had only one documented case of noncompliance for placebo subject 5057 who took less than 70% of the required doses and was deemed in violation of protocol.

Two Ketotifen fumarate subjects discontinued for protocol violations because they took disallowed medications (Children's Tylenol Cold and Cimetidine), whereas the Vehicle placebo patient violated protocol by wearing contact lenses for 5 hours. The 6 voluntary discontinuations in the Ketotifen fumarate group and 1 in the Vehicle placebo group, as well as the other reason given by a discontinued Vehicle subject were due to work-related and scheduling conflicts.

Two Ketotifen fumarate subjects discontinued due to adverse events: Subject # 4005 developed moderate injection and lid discharge in both eyes that was determined related to study drug. He also reported mild headache that was not considered related to drug. Subject # 5115 developed possibly related, mild, matting and crusting discharge.

Three Vehicle placebo subjects were reported as discontinuing due to adverse events: Subject 1168 diagnosed with cholecystitis and pre-existing abdominal pain followed by surgery and hospitalization. Subject # 3061 was also hospitalized but refused to provide information. Subject # 5037 was hospitalized for myocardial infarction.

4. Adverse Events

Related: Twenty percent (20% or 65/330) Ketotifen fumarate subjects reported 90 events and 17% (28/165) Vehicle placebo subjects reported 36 events that were related or possibly related to study drug.

Treatment-related events reported by the Ketotifen subjects included asthenia; B/S; B/S UDI; conjunctivitis; discharge; dry eye; eye discharge; FBS; headache; injection; irritation; itching; keratitis; lacrimation discharge; lid discharge; pain eye; rhinitis; somnolence; tachycardia; and vision abnormal.

Serious: One percent (1% or 3/330) Ketotifen fumarate subjects reported 3 events and 2% (3/165) Vehicle placebo subjects also reported 3 events that were deemed serious. In the Ketotifen fumarate group, these events included neoplasm of the breast; pain; and pain abdomen.

Moderate and Severe: Eighteen percent (18% or 60/330) Ketotifen fumarate subjects reported 88 events and 17% (28/165) Vehicle placebo subjects reported 36 events that were of moderate severity; 3% (11/330) Ketotifen fumarate subjects reported 13 events and 4% (7/165) Vehicle placebo subjects reported 8 events of severe intensity.

In the Ketotifen fumarate group, these moderate and severe events included arthralgia; B/S; bone fracture spontaneous; cough inclusion; diarrhea; cholecystitis; dry eye; dysmenorrhea; dyspepsia; ear discharge; fever; flu syndrome; headache; hypertension; hypertonia; infection; injection; injury accidental; itching; lid discharge; nausea; neoplasm of the breast; pain; pain abdomen; pain back; pharyngitis; rhinitis; sinusitis; syncope; tachycardia; and ulcer of the mouth.

Highest Incidence of Events Reported: B/S (2% Ketotifen and <1% Vehicle); B/S UDI (3% Ketotifen and <1% Vehicle); Discharge (2% Ketotifen and 0% Vehicle); Headache (19% Ketotifen and 25% Vehicle); Injection (11% Ketotifen and 11% Vehicle); Itching (4% Ketotifen and 3% Vehicle); Lid discharge (3% Ketotifen and 1% Vehicle); and Rhinitis (14% Ketotifen and 13% Vehicle).

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Lillian Patrician, MS, MBA
Mathematical Statistician

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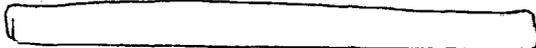
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Concur: Dr. Lin
cc: Orig. NDA 21-066
HFD-550/File
HFD-550/DeLap/Chambers/Dunbar/Rodriguez
HFD-725/File/
HFD-725/Huque/Lin/Patrician
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This review has twenty [20] pages including four [4] attachments.

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Study Description for Phase 2 and Phase 3 Studies

Study	Phase & Design	Study & Treatment Duration	Regimen: Enrollment
96-18	Phase 2 Pilot, Active Control CPT, Double-masked, Fellow-eye Comparison, Placebo-controlled, Parallel Group, Randomized, Single-Center	02/97 - 03/97 4 Days (15 min, 4 hr, 6 hr, 8 hr before allergen challenge)	Dimethindene Maleate 0.05% Ketotifen fumarate 0.05% Levocabastine HCl 0.05% DI/KE: 35 LE/DI: 36 LE/KE: 36
C-08-97-001 Abelson	Phase 2 Dose Response, Active Control CPT, Double-masked, Fellow-eye Comparison, Placebo-controlled, Parallel Group, Randomized, Single-Center	06/97 - 08/97 3 Days (15 min, 8 hr, 12 hr before allergen challenge)	Ketotifen fumarate 0.025% Ketotifen fumarate 0.05% Ketotifen fumarate 0.10% Ketotifen fumarate 0.15% Placebo KE 0.025/PBO: 26 KE 0.05/PBO: 26 KE 0.10/PBO: 26 KE 0.15/PBO: 26 OL 0.10/PBO: 25
C-08-97-002 Abelson	Phase 3 CPT, Double-masked, Fellow-eye Comparison, Placebo-controlled, Parallel Group, Randomized, Single-Center	01/98 - 03/98 3 Days (15 min, 8 hr, 12 hr before allergen challenge)	Ketotifen fumarate 0.025% Placebo KE 0.025/PBO: 89
C-08-97-004 Abelson Casey Lonsdale Mundorf Parver	Phase 3 CPT, Double-masked, Fellow-eye Comparison, Placebo-controlled, Parallel Group, Randomized, Multi-Center	01/98 - 04/98 3 Days (15 min, 8 hr, 12 hr before allergen challenge)	Ketotifen fumarate 0.025% Placebo KE 0.025/PBO: 87
C-08-97-003 Abelson Dell Lowry Shullman Wapner	Phase 3 Safety, Double-masked, Placebo-controlled, Parallel Group, Randomized, Multi-Center	01/98 - 04/98 6 weeks	Ketotifen fumarate 0.025% Placebo KE 0.025: 330 PBO: 165

Demographic Summary for Efficacy Study C-08-97-002

Ketotifen Fumarate 0.025% / Vehicle Placebo (Fellow Eye)

Reviewer's Results	Ketotifen / Vehicle	Vehicle / Ketotifen	Total
Study C-08-97-002	OD / OS	OD / OS	
# Enrolled (Safety Evaluable)	45	44	89 (100%)
# Efficacy Evaluable - ITT (%)	45	44	89 (100%)
# Completed Study (%)	37	35	72 (81%)
# Terminations (%)	08	09	17 (19%)
- Due to Lost-to-follow-up	04	04	08 (09%)
- Due to Protocol Violation	01	04	05 (06%)
- Due to Voluntary Discontinuation	02	01	03 (03%)
- Due to Scheduling Problem	01	0	01 (01%)
- Due to Trt Fail/Resc Med	0	0	0
- Due to Adverse Reaction	0	0	0
# Patients with Any AE (%)	07	07	14 (16%)
- # Adverse Events	07	07	14
# Patients with Trt-rel AE (%)	03	01	04 (04%)
- # Trt-rel Adverse Events	03	01	04
# Males (%)	24	24	48 (54%)
# Females (%)	21	20	41 (46%)
# Caucasian (%)	43	40	83 (93%)
# Hispanic (%)	01	02	03 (03%)
# Other (%)	01	0	01 (01%)
Age Range in Years	19 - 64	19 - 68	19 - 68
# Blue/Green Hazel Irides	29	23	52 (59%)
# Brown/Black Irides	16	21	37 (41%)

**Mean Treatment Scores and Mean Treatment Differences
Unadjusted and Adjusted for Baseline Scores**

[Ketotifen Fumarate 0.025% - Vehicle Placebo (Fellow Eye)]

Reviewer's Results Study C-08-97-002	n	Ketotifen Eye		Vehicle Eye		Mean Difference [KE - VEH]	Significance KE vs VEH	Baseline-Adj Mean Diff [KE - VEH]	Significance Adj Mean KE vs VEH
		mean	sd	mean	sd				
OCULAR ITCHING									
- Visit 2 - 3 min.	89	2.51	0.8	2.49	0.8	0.02	p = 0.66	.	.
- Visit 2 - 7 min.	89	2.72	0.7	2.69	0.7	0.04	p = 0.36	.	.
- Visit 2 - 10 min.	89	2.51	0.8	2.48	0.8	0.03	p = 0.45	.	.
- Visit 3 - 3 min.	89	0.63	0.9	2.04	0.9	-1.41	p < 0.0001	-1.43	p < 0.0001
- Visit 3 - 7 min.	89	0.50	0.8	2.30	0.9	-1.80	p < 0.0001	-1.84	p < 0.0001
- Visit 3 - 10 min.	89	0.52	0.8	1.92	1.0	-1.39	p < 0.0001	-1.42	p < 0.0001
- Visit 4 - 3 min.	83	0.40	0.6	1.84	0.9	-1.43	p < 0.0001	-1.46	p < 0.0001
- Visit 4 - 7 min.	83	0.40	0.6	1.95	0.9	-1.54	p < 0.0001	-1.59	p < 0.0001
- Visit 4 - 10 min.	83	0.36	0.7	1.69	0.9	-1.33	p < 0.0001	-1.36	p < 0.0001
- Visit 5 - 3 min.	72	0.49	0.8	1.65	0.9	-1.16	p < 0.0001	-1.22	p < 0.0001
- Visit 5 - 7 min.	72	0.47	0.8	1.88	0.9	-1.41	p < 0.0001	-1.47	p < 0.0001
- Visit 5 - 10 min.	72	0.36	0.7	1.62	0.9	-1.26	p < 0.0001	-1.28	p < 0.0001
Ciliary Injection									
- Visit 2 - 7 min.	89	2.36	0.6	2.32	0.7	0.04	p = 0.40	.	.
- Visit 2 - 10 min.	89	2.56	0.6	2.57	0.6	-0.01	p = 0.89	.	.
- Visit 2 - 15 min.	89	2.67	0.6	2.68	0.6	-0.01	p = 0.88	.	.
- Visit 3 - 7 min.	89	1.15	1.0	1.91	1.0	-0.76	p < 0.0001	-0.80	p < 0.01
- Visit 3 - 10 min.	89	1.49	1.0	2.13	1.0	-0.65	p < 0.0001	-0.64	p < 0.01
- Visit 3 - 15 min.	89	1.60	1.1	2.25	1.0	-0.65	p < 0.0001	-0.65	p < 0.01
- Visit 4 - 7 min.	83	1.59	0.8	2.07	0.8	-0.48	p < 0.0001	-0.54	p < 0.01
- Visit 4 - 10 min.	83	1.85	0.8	2.14	0.8	-0.29	p < 0.001	-0.28	p < 0.01
- Visit 4 - 15 min.	83	2.01	0.8	2.27	0.8	-0.26	p < 0.001	-0.25	p < 0.01
- Visit 5 - 7 min.	72	1.80	0.8	2.16	0.7	-0.36	p < 0.0001	-0.42	p < 0.01
- Visit 5 - 10 min.	72	1.94	0.8	2.26	0.8	-0.32	p < 0.0001	-0.32	p < 0.01
- Visit 5 - 15 min.	72	2.03	0.9	2.24	0.7	-0.21	p < 0.01	-0.23	p < 0.01

Ocular Itching: 0=none 1=intermittent tickle 2=mild continuous itch 3=severe itch 4=incapacitating itch

Conjunctival Injection: 0=none 1=mild 2=moderate 3=severe 4=unusually severe

Demographic Summary for Efficacy Study C-08-97-004

Ketotifen Fumarate 0.025% / Vehicle Placebo (Fellow Eye)

Reviewer's Results Study C-08-97-004	Ketotifen / Vehicle OD / OS	Vehicle / Ketotifen OD / OS	Total
# Enrolled (Safety Evaluable)	44	43	87 (100%)
# Efficacy Evaluable - ITT	44	43	87 (100%)
# Completed Study	38	39	77 (89%)
# Terminations	06	04	10 (11%)
- Due to Lost-to-followup	01	0	01 (01%)
- Due to Trt Fail/Resc Med	0	0	0
- Due to Adverse Reaction	01	0	01 (01%)
# Patients with Any AE (%)	08	14	22 (25%)
- # Adverse Events	11	19	30
# Patients with Trt-rel AE (%)	02	04	06 (07%)
- # Trt-rel Adverse Events	04	04	08
# Males (%)	16	15	31 (36%)
# Females (%)	28	28	56 (64%)
# Caucasian (%)	35	31	66 (76%)
# Hispanic (%)	03	01	04 (05%)
# Other (%)	01	0	01 (01%)
Age Range in Years	21 - 57	20 - 65	20 - 65
# Blue/Green/ Hazel Irides	26	23	49 (56%)
# Brown/Black Irides	18	20	38 (44%)

**Mean Treatment Scores and Mean Treatment Differences
Unadjusted and Adjusted for Baseline Scores**

[Ketotifen Fumarate 0.025% - Vehicle Placebo (Fellow Eye)]

Reviewer's Results Study C-08-97-004	n	Ketotifen Eye		Vehicle Eye		Mean Difference [KE - VEH]	Significance KE vs VEH	Baseline-Adj Mean Diff [KE - VEH]	Significance Adj Means KE vs VEH
		mean	sd	mean	sd				
OCULAR ITCHING									
- Visit 2 - 3 min.	87	2.55	0.9	2.55	0.9	0.00	p = 1.00	.	.
- Visit 2 - 7 min.	87	2.82	0.8	2.83	0.8	-0.01	p = 0.78	.	.
- Visit 2 - 10 min.	87	2.64	0.9	2.62	0.9	0.02	p = 0.68	.	.
- Visit 3 - 3 min.	87	0.65	1.0	2.16	1.0	-1.51	p < 0.0001	-1.51	p < 0.0001
- Visit 3 - 7 min.	87	0.62	0.9	2.18	1.1	-1.56	p < 0.0001	-1.55	p < 0.0001
- Visit 3 - 10 min.	87	0.51	0.8	1.97	1.1	-1.46	p < 0.0001	-1.48	p < 0.0001
- Visit 4 - 3 min.	80	0.80	1.0	2.11	1.0	-1.31	p < 0.0001	-1.29	p < 0.0001
- Visit 4 - 7 min.	80	0.81	0.9	2.32	1.0	-1.51	p < 0.0001	-1.48	p < 0.0001
- Visit 4 - 10 min.	80	0.65	0.9	1.99	1.1	-1.34	p < 0.0001	-1.36	p < 0.0001
- Visit 5 - 3 min.	77	0.85	1.0	1.81	1.0	-0.96	p < 0.0001	-0.95	p < 0.0001
- Visit 5 - 7 min.	77	0.84	0.9	1.82	1.0	-0.98	p < 0.0001	-0.94	p < 0.0001
- Visit 5 - 10 min.	77	0.58	0.8	1.52	1.0	-0.94	p < 0.0001	-0.95	p < 0.0001
Ciliary Injection									
- Visit 2 - 7 min.	87	2.34	0.7	2.39	0.7	-0.05	p = 0.23	.	.
- Visit 2 - 10 min.	87	2.46	0.6	2.50	0.6	-0.04	p = 0.37	.	.
- Visit 2 - 15 min.	87	2.52	0.5	2.51	0.5	0.01	p = 0.88	.	.
- Visit 3 - 7 min.	87	1.16	0.7	1.68	0.8	-0.52	p < 0.0001	-0.47	p < 0.01
- Visit 3 - 10 min.	87	1.32	0.8	1.78	0.9	-0.46	p < 0.0001	-0.42	p < 0.01
- Visit 3 - 15 min.	87	1.35	0.9	1.71	0.9	-0.36	p < 0.0001	-0.37	p < 0.01
- Visit 4 - 7 min.	80	1.35	0.8	1.79	0.9	-0.44	p < 0.0001	-0.40	p < 0.01
- Visit 4 - 10 min.	80	1.51	0.8	1.81	0.9	-0.30	p < 0.0001	-0.26	p < 0.01
- Visit 4 - 15 min.	80	1.52	0.9	1.83	0.9	-0.31	p < 0.0001	-0.30	p < 0.01
- Visit 5 - 7 min.	77	1.36	0.8	1.73	0.8	-0.36	p < 0.0001	-0.32	p < 0.01
- Visit 5 - 10 min.	77	1.38	0.8	1.72	0.9	-0.34	p < 0.0001	-0.30	p < 0.01
- Visit 5 - 15 min.	77	1.45	0.9	1.77	0.9	-0.32	p < 0.0001	-0.31	p < 0.01

Ocular Itching: 0=none 1=intermittent tickle 2=mild continuous itch 3=severe itch 4=incapacitating itch

Conjunctival Injection: 0=none 1=mild 2=moderate 3=severe 4=unusually severe

Ketotifen Fumarate 0.025% versus Vehicle Placebo

Reviewer's Results - Study C-08-97-003	Ketotifen	Vehicle Placebo	Total
# Enrolled (Safety Evaluable)	330 (100%)	165 (100%)	495
# Completed Study	317 (96%)	158 (96%)	475
# Terminations	13 (04%)	07 (04%)	20
# Discontinued - Lost-to-follow-up	03 (01%)	01 (<1%)	04
# Discontinued - Adverse Reaction	02 (<1%)	03 (<2%)	05
# Males	138 (42%)	61 (37%)	199
# Females	192 (58%)	104 (63%)	296
# Caucasian	174 (53%)	93 (56%)	267
# Hispanic	125 (38%)	62 (38%)	187
# Other	13 (04%)	05 (03%)	18
Age Range in Years (All Subjects)	3 - 72	4 - 78	3 - 78
# Pediatric Subjects (Age 3 - 11 years)	41 (12%)	17 (10%)	58
# Blue/Green/ Hazel Irides	127 (38%)	69 (42%)	196
# Brown/Black Irides	203 (62%)	96 (58%)	299
# Patients with Any Adverse Events	196	92	288
- # Adverse Events	359	173	532
# Patients with Serious Adverse Events	03 (<1%)	03 (<2%)	06
- # Serious Adverse Events	03	03	06
# Patients with Rel/Poss Rel Adverse Events	65 (20%)	28 (17%)	93
- # Rel/Poss Rel Adverse Events	90	36	126
# Patients with Severe Adverse Events	11 (3%)	07 (4%)	18
- # Severe Adverse Events	13	08	21
# Patients with Moderate Adverse Events	60 (18%)	28 (17%)	88
- # Moderate Adverse Events	88	42	130
Incidence - B/S	05 (2%)	01 (<1%)	06
Incidence - B/S UDI	09 (3%)	01 (<1%)	10
Incidence - Discharge	07 (2%)	0	07
Incidence - Headache	64 (19%)	41 (25%)	105
Incidence - Injection	36 (11%)	18 (11%)	54
Incidence - Ocular Itching	12 (4%)	05 (3%)	17
Incidence - Lid Discharge	10 (3%)	02 (1%)	12
Incidence - Rhinitis	47 (14%)	21 (13%)	68