CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **21-066**

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 21-066

NDA 21-066
Original

Submission Date: 12/31/98
Receive Date: 01/05/99
Review Date: 05/26/99

Drug name:	Ketotifen fumarate ophthalmic solution, 0.025% topical
Generic name:	Ketotifen fumarate ophthalmic solution
Chemical name:	4-(1-Methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta [1,2-b]thiophen-10(9H)-one hydrogen fumarate
Sponsor:	CIBA Vision – A Novartis Company 11450 Johns Creek Parkway Duluth, Georgia 30097
Pharmacologic Category:	anti-histamine
Proposed Indication(s):	For the prevention of itching of the eye due to allergic conjunctivitis
Dosage Form and Route of Administration:	Ophthalmic solution, Topical
NDA Drug Classification:	1P
Related Drugs:	Levocabastine
Submission:	Initial Submission
Related Reviews:	None

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3 **Material Reviewed**

NDA 21-066: Volumes 1.1, 1.16-1.49

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

Raw Material	Quantity mg/mL
Ketotifen	0.25
Glycerin USP	
Benzalkonium chloride NF	
Sodium hydroxide NF, 1N and/or Hydrochloric acid	
Purified Water	

Additional Specifications:

pH	
Osmolality	
Particle size	
Sterility	USP
Preservative efficacy	USP

Reviewer Comments:

Acceptable. No additional Chemistry Manufacturing Control issues identified from a clinical perspective.

5 Animal Pharmacology/Toxicology-See Pharmacology & Toxicology Review

Reviewer Comments:

Acceptable. No additional Pharmacology/Toxicology issues identified from a clinical perspective.

6 Clinical Background

6.2 Important information from related INDs and NDAs

[redacted]

6.3 Foreign experience

[redacted]

Country	Tradename	Date of Approval	Date of Launch	1998 Units Until 12-1-98	License Holder
Japan			1991	[redacted]	[redacted]
Argentina			12/1/97	[redacted]	CIBA Vision
Mexico			9/10/98	[redacted]	CIBA Vision
Ecuador			Planned Q1 1999	N/A	CIBA Vision
Colombia			Planned Q1 1999	N/A	CIBA Vision

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

A request was submitted to the FDA by CIBA that the requirement for a pharmacokinetic study after ophthalmic administration of the drug product be waived. In the pre-NDA meeting held September 9, 1998, the FDA stated that an investigation of the systemic exposure after ophthalmic administration of ketotifen fumarate ophthalmic solution is required. It was agreed that this study can be performed as a separate phase 4 study after the drug is approved.

Reviewer Comments:

The company must keep this Phase 4 commitment to perform a human PK study after ocular administration of Ketotifen. No additional Human Pharmacokinetic issues identified.

7 Description of Clinical Data Sources

All completed trials conducted by or on behalf of CIBA Vision.

Review #	Protocol	Indication	Design	Treatment	# in each arm	Age Range	%(M/F) B/W/O	Duration of treatment	Country
—	96-18	Allergic conjunctivitis	Paired eye Double-masked Randomized Allergen Challenge	KE 0.05% Levocabastine 0.05% Dimethindine maleate Vehicle Placebo	DI/KE: 35 LE/DI: 36 LE/KE: 36	19-67	(54/46) 3/100/4	4 days nonsequential (15 min, 4 hr, 6 hr, 8 hr before challenge) 4 drops total over 49 days	USA Single Center
1	C-08-97-001	Allergic conjunctivitis	Paired eye Double-masked Randomized Allergen Challenge Dose Ranging	KE 0.025% KE 0.05% KE 0.10% KE 0.15% Olapatadine 0.10% Vehicle Placebo	26 26 26 26 25	19-68	(46/54) 4/91/5	3 days non-sequential (15 min, 8 hr, 12 hr before challenge) 3 drops total over 28 days	USA Single Center
2	C-08-97-002	Allergic conjunctivitis	Paired eye Double-masked Randomized Allergen Challenge	KE 0.025% Vehicle Placebo	89	19 to68	(54/46) 2/83/4	3 days non-sequential	USA Single Center
3	C-08-97-003	Allergic conjunctivitis	Paired eye, Double-masked, Randomized Allergen Challenge	KE 0.025% Vehicle Placebo	330/165	3 to 77	(42/58) 3/56/41	43 days	USA Muti Center
4	C-08-97-004	Allergic conjunctivitis	Paired eye Double-masked Randomized Allergen Challenge	KE 0.025% Vehicle Placebo	87	19 to 68	(36/64) 66/16/6	3 days non-sequential	USA Muti Center
5	UK/DR 42000-97 1	Allergic conjunctivitis	Paired eye Double-masked Randomized Dose Ranging	KE 0.05% KE 0.10% KE 0.15% KE 0.20% Vehicle Placebo	82	18 to 60	(56/44) 80/2	8 days	UK Single Center

This page of the document contains confidential information that will not be included in the redacted portion of the document for the public to obtain.

Uncontrolled trials performed using ketotifen fumarate ophthalmic solution in support of registration of the 0.05% strength product[redacted]

Review #	Protocol	Indication	Design	Treatment	# in each arm	Age Range	%(M/F) B/W/O	Duration of treatment	Country
—	A3 Mikuni, I Jap. Journal of Clin. Ophth. 35(5): 753-759, 1981	Allergic Conjunctivitis	Open label	KE 0.1%	11	7 to 38	(73/27)	2 weeks	Japan
—	G2 Mikuni I, et al Jap. Clin. Ther. And Medicines 4(12): 2371-2383, 1988	Allergic Conjunctivitis	Open label	KE 0.05%	196	4 to 80	(40.9/59.1)	4 weeks	Japan
—	G3 Fujita Y, et al jap. Clin. Ther. And medicines 5(4): 709-721, 1989	Allergic Conjunctivitis	Open label	KE 0.05% KE 0.025%	14 15	5 to 72	(37.9/62.1)	4 weeks	Japan
—	G5 Kogure M I, et al Progress in Medicine	Allergic Conjunctivitis	Open label	KE 0.05%	25	7 to 54	(36/74)	14 weeks to 78 weeks	Japan

Controlled trials performed using ketotifen fumarate ophthalmic solution in support of registration of the 0.05% strength product [redacted]

Review #	Protocol	Indication	Design	Treatment	# in each arm	Age Range	%(M/F) B/W/O	Duration of treatment	Country
—	A4 Mikuni I, Jap. J. Clin. Ophth 36(6): 573-576 1982	Allergic Conjunctivitis	Paired Eye Not Masked Not Randomized Allergen Challenge	KE 0.06% Vehicle Control	10	Age 8 - 49	(70/30)	1 day	Japan Single Center
—	G1 Nakayasu K, et al Jap. Clin. Ther. & Medicines 4(12): 2357-2369	Allergic Conjunctivitis	Parallel Group Double masked Not Randomized Tolerability & Safety Study	KE 0.05% KE 0.1% Disodium cromoglycate 2% Vehicle Control	3 x 6 arms	Age 23-54	(100/0)	Part 1: 1 day QID Part 2: 7 day QID	Japan Single Center
—	Mikuni I, et al Clinical Evaluation 17(2): 275-297, 1989	Allergic Conjunctivitis	Parallel Group Double masked Randomized	KE 0.5% Disodium cromoglycate 2%	KE 138 Disodium cromoglycate 141	Age 9-60	(28/72)	4 weeks	Japan Multi Center

[redacted]

[redacted]

8.1 Indication #1

For the prevention of itching of the eye due to allergic conjunctivitis

8.1.1 Study #1 Protocol #C-08-97-001

Title: A Dose-Response Evaluation of Ketotifen Fumarate Ophthalmic Solution in Varying Concentrations Against Placebo Control in the Allergen Challenge Model

Objectives:

To compare the efficacy and safety, onset and duration of action, and to determine the optimal concentration of ketotifen fumarate ophthalmic solution (0.025%, 0.05%, 0.1%, and 0.15%) versus placebo in the prevention of ocular itching and conjunctival injection (redness) induced by the allergen challenge model. A secondary objective was to determine the onset and duration of action for the active control, olopatadine 0.1%.

Study design:

A prospective, double-masked, randomized, single-center,, fellow-eye comparison, active and placebo-vehicle control, antigen-challenge dose-ranging ocular tolerance, safety and efficacy trial.

Drug Schedule:

Dosing was a single drop in the eye as randomized, at three visits.

Investigators:

	Number of Subjects	Number Completed
Mark B. Abelson, M.D. Ophthalmic Research Associates, 863 Turnpike St., North Andover, MA 01845, USA	130	129

Study Plan:

Subjects were randomized to receive one of the four different concentrations of ketotifen fumarate ophthalmic solution or olopatadine 0.1% solution in one eye and placebo in the other eye beginning at Visit 3. At Visit 3, subjects received assigned treatment to each eye fifteen minutes before receiving the allergen challenge which consisted of ragweed pollen, tree pollen, or cat dander. Effectiveness was measured for subjective itching at 3, 7, 10, 15, and 20 minutes after allergen challenge. Subjects then underwent a two-week washout period between Visits 3-5.

At Visit 4, subjects received treatment approximately 8 hours before allergen challenge. Effectiveness was measured for subjective itching ratings at 3, 7, 10, 15, and 20 minutes after allergen challenge, and by the investigator's examination of conjunctival injection and secondary efficacy parameters at 3, 10, and 20 minutes after allergen challenge. At Visit 5, subjects received treatment approximately 12 hours prior to allergen challenge. Efficacy measurements were made at the same time intervals used at Visits 3 and 4.

Number of subjects (planned and analyzed):

Approximately 130 planned; 129 analyzed for safety and efficacy.

Study Flow Chart

Procedure	*Visit 1 Day -21*	*Visit 2 Day -14*	*Visit 3 Day 0*	*Visit 4 Day 14*	*Visit 5 Day 28*
Informed Consent	X				
Inclusion/Exclusion	X	X	X	X	X
Demographics	X				
Medication History	X	X	X	X	X
Ocular Signs and Symptoms	X	X	X	X	X
Visual Acuity[1]	X	X	X	X	X
Slit-lamp[2]	X	X	X	X	X
Ophthalmoscopy[3]	X				
Adverse Events	X	X	X	X	X
Instill Allergen/Allergic Assessments	X	X	X	X	X
Instill Medication (-15 min)			X		
Instill Medication (-8 hours)				X	
Instill Medication (-12 hours)					X
Photographs[4]			X	X	X
Exit Form[5]					X

[1] Visual acuity was measured using an ETDRS chart.
[2] Synonymous with biomicroscopy.
[3] Called funduscopy in the protocol.
[4] Photographs taken immediately after 10-minute assessments
[5] Complete at Visit 5 or whenever subject discontinued from the trial.

Study Schedule

	Screening	Initial CPT	15 min Tx	8 hr Tx	12 hr Tx
Visit	1	2	3	4	5
	(Day -21)	(Day -14)	(Day 0)	(Day 14)	(Day 28)

Subject Population:

Subjects were recruited who had a history of allergic hypersensitivity to animal dander, or to pollen not currently in season in the site's geographic area. The inclusion/exclusion criteria were designed to reproducibly elicit allergic response to the sensitizing allergen in the study population.

Inclusion Criteria

Subjects were required to meet the following criteria:

- Male or female of any race between the ages of 18 and 70, inclusive.
- IOP of ≤ 21 millimeters of mercury (mm Hg) in both eyes.
- Best-corrected distance visual acuity of 20/40 or better in both eyes.
- A positive diagnostic test (skin or RAST) for allergic disease, or a positive conjunctival allergen challenge on file (within prior 24 months).
- In order to receive study treatment, subjects must have had a successful antigen challenge reaction, inducing at least 2+ itching and 2+ conjunctival redness in both eyes within 10 minutes at Visits 1 and 2.
- An allergic history to animal dander and/or seasonal airborne antigens such as ragweed, mountain cedar, etc. (perennial allergens such as molds were not acceptable).
- Willing to avoid the disallowed medications and/or the wearing of contact lenses for three days prior to and during the trial period (mast cell stabilizers were to be discontinued two weeks prior to trial entry).
- Able and willing to give written informed consent.
- Able and willing to comply with the requirements of the trial protocol including following instructions and making the required trial visits.

Exclusion Criteria

Subjects with any of the following conditions were to be excluded from the study:

- Subjects with a known history of retinal detachment, diabetic retinopathy, or any retinal disease which could progress during the time course of the trial.
- Contraindications to the use of the trial medication(s).
- Known hypersensitivity to any component of the trial medications including the preservative(s).
- Presence of an active bacterial or viral ocular infection or positive history of ocular herpes.
- Positive diagnosis of dry eye.
- Manifests signs and symptoms of clinically active allergic conjunctivitis in either eye at the start of each trial visit (presence of any itching or greater than 1+ conjunctival redness).
- Requirement for regular use of any topical ophthalmic solutions during the trial, including tear substitutes, except those allowed by the protocol at the end of each visit or use of any topical

medication less than one week before the trial initiation. Use of ophthalmic medications which require longer than a one-week washout will result in exclusion from the study.

- Females of child-bearing potential who are pregnant or nursing or females who have a positive urine pregnancy test or do not agree to use a reliable means of birth control during the conduct of the trial.
- Participation in an investigational drug or device trial within 30 days prior to the initiation of this trial.

Criteria for evaluation

Efficacy:
Efficacy was determined from the subject's rating of itching and the investigator's evaluation of conjunctival injection. Secondary efficacy parameters measured were the investigator's examination of ciliary and episcleral injection, chemosis, lid edema, and mucous discharge. For both primary and secondary efficacy variables, the difference between treated and untreated eyes was used as the efficacy parameter.

Safety:
Safety was determined from comprehensive ophthalmic examinations including slit-lamp biomicroscopy and distance visual acuity using an ETDRS chart, and from adverse event reports.

Disposition:

n = 129 Randomized	0.025% KE	0.05% KE	0.10% KE	0.15% KE	Olapatadine	Total
Number Enrolled	26	26	26	26	25	129
# not Completing	3	5	7	4	5	24

APPEARS THIS WAY
ON ORIGINAL

Individual Subject Early Termination Data:

Drug	Subject #	Age	Gender	Race	Visit	Reason	Comment
KE 0.025%	139	36	M	White	3	Lost to F/U	Subject did not come in for visit 4
	222	50	F	White	3	Other	Pt d/c by sponsor's request
	225	40	M	Hispanic	3	Other	Pt d/c by sponsor's request
KE 0.05%	146	24	M	White	4	S/Sx of Allergy	Baseline hyperemia >1.0 Left Eye at visit 4
	176	26	F	White	3	Lost to F/U	Subject did not come in for visit 4
	220	44	M	White	3	Other	no comment given
	223	56	F	White	3	Other	Pt d/c by sponsor's request
	226	24	M	Hispanic	3	Other	Pt d/c by sponsor's request
KE 0.10%	108	47	M	White	4	S/Sx of Allergy	Subject had baseline redness OU which was >1 unit. His scores were not recorded in the source document
	137	32	F	White	4	Lost to F/U	Subject did not come in for visit 5
	177	42	F	Asian	4	Lost to F/U	Subject did not come in for visit 5
	212	34	M	White	4	Lost to F/U	Subject did not come in for visit 5
	218	50	M	White	4	Lost to F/U	Drug instilled at visit 4, but due to family emergency subject had to leave and did not return for the 8 hr rechallenge
	227	34	F	White	3	Other	Pt d/c by sponsor's request
	230	31	M	White	3	Other	Pt d/c by sponsor's request
KE 0.15%	101	45	M	White	4	S/Sx of Allergy	Subject had baseline redness OU which was >1 unit at visit 4.
	207	26	M	White	3	Lost to F/U	Subject did not come in for visit 4
	224	29	F	White	3	Other	Pt d/c by sponsor's request
	229	27	M	Hispanic	3	Other	Pt d/c by sponsor's request
OL 0.10%	103	40	F	White	4	Voluntary d/c	Pt chose not to participate in study because shecould not stay for the 8 hr visit
	156	41	F	White	4	S/Sx of Allergy	Subject had baseline redness OU which was >1 unit at baseline exam-values were not recorded on source document.
	217	38	M	White	3	Lost to F/U	Subject did not come in for visit 4
	219	35	F	White	3	Other	Pt d/c by sponsor's request
	221	40	F	White	3	Other	Pt d/c by sponsor's request

Reviewer Comment:

Ten patients were discontinued at the sponsor's request with no information given regarding why. This may confound the reporting of adverse events.

Demographics:

The mean age of the study population was 39 years (range: 19 to 68).

Reviewer Comment:

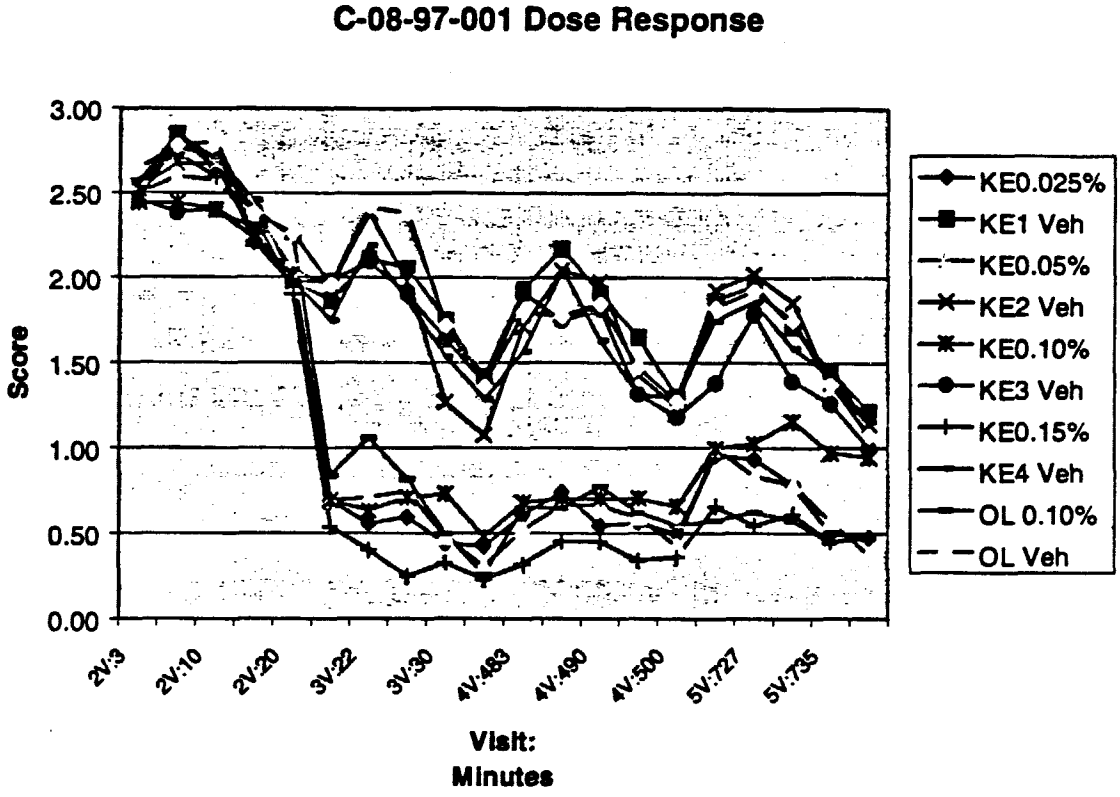
Acceptable.

Demographics by Treatment Group:

# Subjects		KE 0.025% Placebo	KE 0.05% Placebo	KE 0.10% Placebo	KE 0.15% Placebo	OL 0.10% Placebo	P-Value*
Gender							
	Female	13 (50%)	15 (58%)	12 (46%)	13 (50%)	17 (68%)	0.558
	Male	13 (50%)	11 (42%)	14 (54%)	13 (50%)	8 (32%)	
Race							
	White	24 (92%)	24 (92%)	23 (88%)	24 (92%)	23 (92%)	0.806
	Black	0 (0%)	1 (4%)	1 (4%)	1 (4%)	1 (4%)	
	Asian	0 (0%)	0 (0%)	2 (8%)	0 (0%)	0 (0%)	
	Hispanic	1 (4%)	1 (4%)	0 (0%)	1 (4%)	0 (0%)	
	Native American	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Iris Color							
	Black	0 (0%)	0 (0%)	2 (8%)	0 (0%)	0 (0%)	0.612
	Brown	10 (38%)	10 (38%)	6 (23%)	9 (35%)	13 (52%)	
	Hazel	8 (31%)	10 (38%)	5 (19%)	4 (15%)	5 (20%)	
	Green	0 (0%)	2 (8%)	0 (0%)	3 (12%)	2 (8%)	
	Blue	8 (31%)	4 (15%)	13 (50%)	10 (38%)	5 (20%)	
Age (Years)							
	18-19	0 (0%)	1 (4%)	2 (8%)	0 (0%)	0 (0%)	
	20-29	7 (27%)	8 (31%)	1 (4%)	7 (27%)	3 (12%)	
	30-39	10 (38%)	7 (27%)	11 (42%)	4 (15%)	10 (40%)	
	40-49	5 (19%)	5 (19%)	8 (31%)	9 (35%)	6 (24%)	
	50-59	4 (15%)	3 (12%)	3 (12%)	3 (12%)	6 (24%)	
	60-65	0 (0%)	2 (8%)	1 (4%)	3 (12%)	0 (0%)	

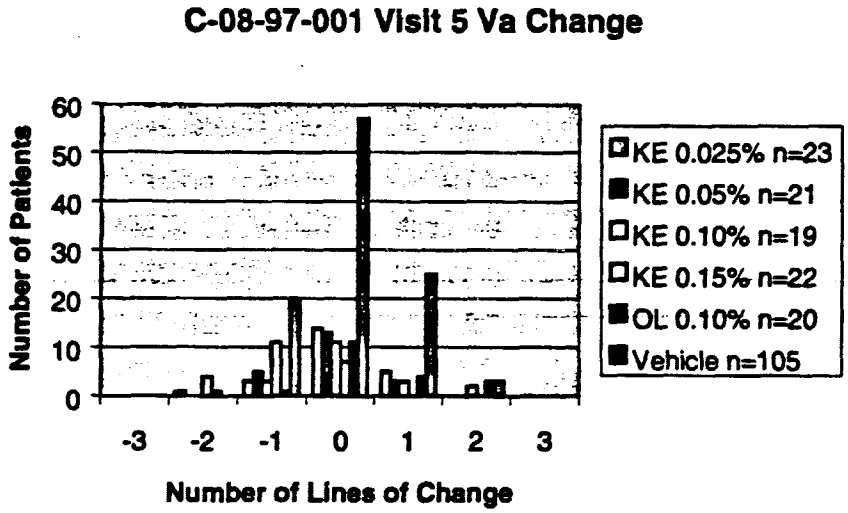
*Supplied by sponsor.

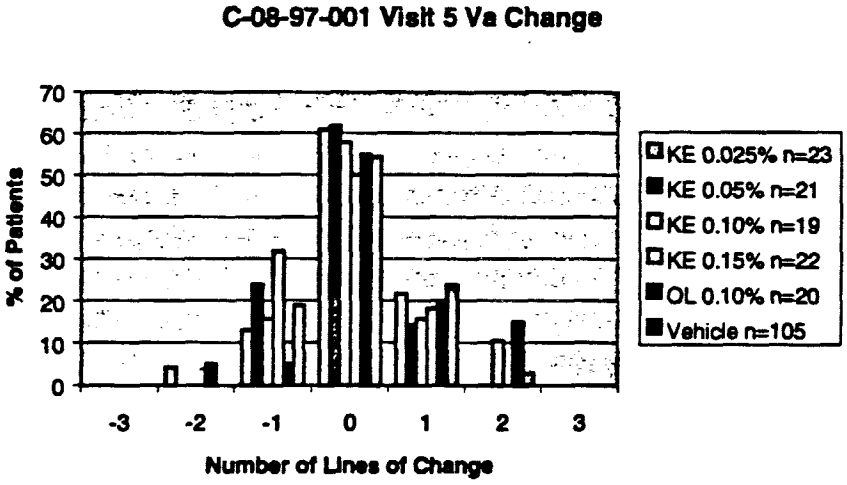
Results:



Reviewer Comment:

A dose-response relationship in the efficacy of reducing itching was not observed in the range of Ketotifen concentrations given. There was a separation between active drug and vehicle control. The efficacy of Ketotifen and the active control was similar. The efficacy analysis of the dose-ranging study supports the choice of the 0.025% Ketotifen as the study drug because it is the lowest concentration that is efficacious.





Reviewer Comment:

The number of lines of vision change did not differ significantly between the groups.

Adverse Events:

Summary of Non-Ocular Treatment Emergent Adverse Events:

Body System	Preferred Term	KE 0.025% Vehicle	KE 0.05% Vehicle	KE 0.10% Vehicle	KE 0.15% Vehicle	OL 0.10% Vehicle
		N	N	N	N	N
Totals	Total Subjects Exposed to Tx	26	26	26	26	25
Body as a Whole						
	Headache	5	5	1	6	3
	Back Pain	1	0	0	0	0
	Pain	0	0	1	0	0
Digestive System		0	0	0	0	1
	Dyspepsia	0	0	0	0	1
Musculoskeletal						
	Myalgia	0	0	0	0	2
Respiratory						
	Pharyngitis	1	0	0	0	0
	Rhinitis	1	0	1	0	2

Reviewer Comment:

The treatment-emergent non-ocular adverse events appear similarly distributed between the various treatment and vehicle placebo groups. The sponsor did not separate adverse events from treatment and vehicle placebo groups.

Summary of Ocular Treatment Emergent Adverse Events:

Body System	Preferred Term	KE 0.025%	KE 0.05%	KE 0.10%	KE 0.15%	OL 0.10%	Vehicle
		N	N	N	N	N	N
Totals	Total Subjects Exposed to Tx	26	26	26	26	25	129
Special Senses							
	Burning/Stinging	0	0	0	1	0	0
	Itching	0	1	0	0	0	1

Reviewer Comment:

The incidence of treatment-emergent ocular adverse events appear similarly distributed between the various treatment and vehicle placebo groups.

8.1.2 Study #2 Protocol #C-08-97-002

Title: Safety and Efficacy of Ketotifen Fumarate 0.025% Ophthalmic Solution Compared with Vehicle Placebo Control in the Allergen Challenge Model of Allergic Conjunctivitis

Objective/Rationale:

To compare the safety and efficacy of ketotifen fumarate 0.025% ophthalmic solution with placebo in the prevention of symptoms of allergic conjunctivitis.

Study design:

This was a double-masked, randomized, placebo-controlled study.

Drug Schedule:

Each eye received one drop of either placebo or ketotifen fumarate 0.025% ophthalmic solution as randomized, at three visits.

Investigator:	**Number of Subjects**	**Number Completed**
Mark B. Abelson, M.D. Ophthalmic Research Associates 863 Turnpike Street North Andover, Massachusetts 01845, USA	89	72

Study Plan:

Efficacy and safety of ketotifen fumarate 0.025% ophthalmic solution were tested in the allergen challenge model of allergic conjunctivitis. This was a prospective, double-masked, randomized, placebo-controlled single-center study. Subjects had a history of ocular and/or systemic allergies to known substances (including cat dander, grass, tree pollen, and ragweed). At Visit 1, a provocation dose reaction was established for each subject resulting in a moderately severe hypersensitivity (scores between 2-3 on a scale of 4). The provocation dose was confirmed at Visit 2.

At Visit 3 (Day 0), subjects received a drop of placebo in one eye and a drop of ketotifen fumarate 0.025% ophthalmic solution in the fellow eye. Fifteen minutes after treatment, both eyes were challenged with the appropriate allergen and evaluated for itching 3, 7 and 10 minutes after challenge. Conjunctival, ciliary and episcleral injection were evaluated at 7, 10, and 15 minutes after the allergen challenge. These evaluations were repeated at Visits 4 and 5 in eyes pre-treated with ketotifen fumarate 0.025% in one eye and a drop of vehicle in the fellow eye 6 and 8 hours before the allergen challenge, respectively. Subsequent to Visit 2, there was a 14-day recovery period between visits.

Number of subjects (planned and analyzed):

Approximately 100 planned for randomization; 167 were screened, 89 were analyzed for safety and efficacy, 72 completed the study.

Flow Chart:

Schedule of Assessments

PROCEDURE	Visit 1 Day –21	Visit 2 Day -14	Visit 3 Day 0	Visit 4 Day 14	Visit 5 Day 28
Informed Consent	X				
Inclusion/Exclusion	X	X	X	X	X
Demographics	X				
Urine Pregnancy Test (all females)	X				
Medical and Ocular History	X	X			
Medication History	X	X	X	X	X
Ophthalmic examination*: corrected visual acuity slit lamp biomicroscopy	X	X	X	X	X
Dilated Ophthalmoscopy	X				X
IOP	X				
Conjunctival Provocation Test (CPT)	X	X			
Instill Medication (-15 min)			X		
Instill Medication (-6 hours)				X	
Instill Medication (-8 hours)					X
Allergen Challenge			X	X	X
Evaluations**		X	X	X	X
Adverse Events			X	X	X
Safety Follow-Up Exam		X	X	X	X
Exit Form***					X

* Ophthalmic examinations were performed before the CPT, and before and after the allergen challenge.
** Gradings made by the subject at 3, 7, and 10 minutes after allergen challenge. Investigator gradings were made at 7, 10, and 15 minutes.
*** Complete at Visit 5 or whenever subject discontinued from the trial.

Subject Population:

Subjects were recruited who had a history of allergic hypersensitivity to animal dander, or to pollen not currently in season in the site's geographic area. The inclusion/exclusion criteria were designed to reproducibly elicit allergic response to the sensitizing allergen in the study population.

Inclusion Criteria:

The following requirements had to be met in order for a subject to be enrolled into the trial. Subjects of either gender and any race had to:

- be greater than 17 years of age.
- have an IOP of less than or equal to 21 mm Hg in both eyes.
- have a corrected distance visual acuity of 20/40 or better in both eyes.
- have a positive diagnostic test (skin or RAST) for allergic disease, or a positive conjunctival allergen challenge on file (within 24 months).
- manifest a successful conjunctival provocation test (CPT) reaction, inducing at least 2+ itching and 2+ conjunctival redness bilaterally at Visits 1 and 2.
- have an allergic history to animal dander and/or seasonal airborne antigens such as ragweed, mountain cedar, etc. (perennial allergens such as molds are not acceptable).
- be able to give written informed consent.

Exclusion Criteria

A subject could not participate if any of the following criteria were met:

- a known history of retinal detachment, diabetic retinopathy, or any retinal disease.
- contraindications to the use of the trial medication(s).
- known hypersensitivity to any component of the trial medications including the preservative(s).
- presence of an active bacterial or viral ocular infection or positive history of ocular herpes.
- sign or symptom of clinically active allergic conjunctivitis in either eye at the start of any trial visit (presence of any itching or greater than 1+ conjunctival redness).
- any illness that could interfere with the trial parameters e.g., any autoimmune disease such as rheumatoid arthritis, severe cardiovascular disease including arrhythmias, uncontrolled hypertension, or uncontrolled diabetes.
- subject required regular use of any topical ophthalmic solutions during the trial, including tear substitutes, except those allowed by the protocol at the end of each visit or use of any topical ophthalmic medication less than one week before Visit 2.
- females who were pregnant or nursing. All females of childbearing potential who had a positive urine pregnancy test or did not agree to use a reliable means of birth control during the conduct of the trial will be excluded.
- participated in an investigational drug or device trial within 30 days prior to the initiation of this trial.

Reviewer Comment:
Acceptable

8 Criteria for evaluation

Efficacy: Primary efficacy was determined from the subject's rating of itching on a 0 to 4 scale. Secondary efficacy was determined by the investigator's examination of conjunctival, ciliary and episcleral injection on a 0 to 4 scale. For both primary and secondary efficacy assessments the difference between treated and untreated eyes was used as the efficacy variable.

Safety: Safety was determined from comprehensive ophthalmic examinations including slit lamp biomicroscopy, ophthalmoscopy and distance visual acuity using an ETDRS chart, and from adverse event reports.

Disposition

	# Receiving Double-Masked Medication
Randomized	89
Number Enrolled	
Visit 3	89
Visit 4	83
Visit 5	73
Number Completing	72

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Individual Subject Early Termination Data:

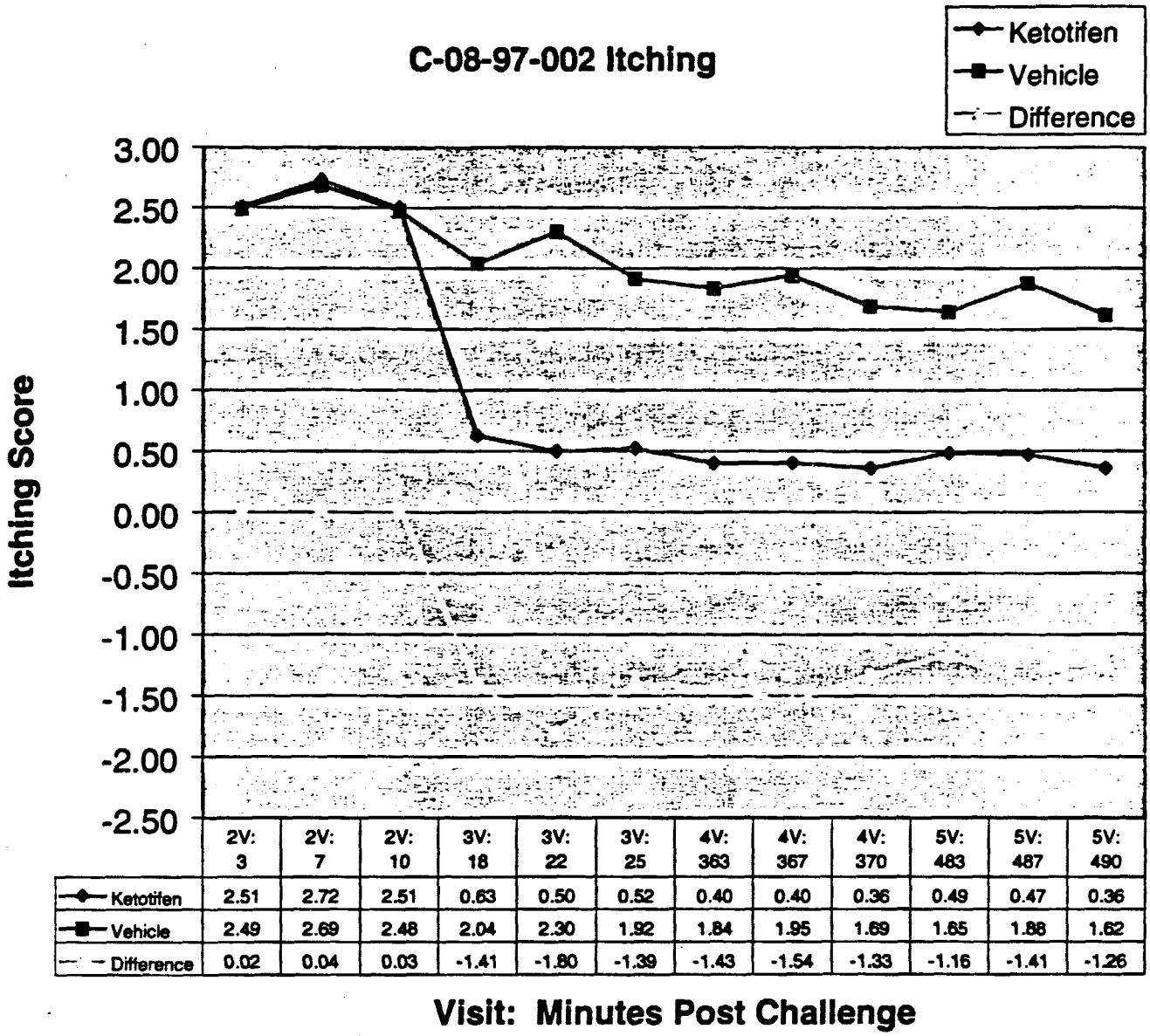
Subject #	Age	Gender	Race	Visit	Reason
102	39	F	White	4	Protocol violation: Disallowed Medication
108	49	F	White	4	Lost to Follow-up
109	30	F	Hispanic	3	Lost to Follow-up
121	57	M	White	4	Protocol violation: Disallowed Medication
124	45	F	White	4	Lost to Follow-up
141	35	F	White	5	Voluntary discontinuation: unable to stay for full 8 hr
142	35	M	White	3	Lost to Follow-up
151	29	M	White	3	Lost to Follow-up
155	37	F	White	4	Lost to Follow-up
156	47	F	White	4	Protocol violation: Disallowed Medication
157	37	F	Hispanic	4	Protocol violation: Disallowed Medication
160	29	M	White	4	Lost to Follow-up
165	43	F	Hispanic	3	Protocol violation: Disallowed Medication
173	28	M	Black	3	Lost to Follow-up
178	32	M	White	4	Voluntary discontinuation: unable to come for visit 5
187	38	F	White	4	Voluntary discontinuation: pt decided to leave study at visit 4
189	32	M	White	4	Other: arrived for visit at wrong time & unable to reschedule

Demographics:

The mean age was 39 years (range: 19-68).

Gender		Number	Percent
	Female	41	46
	Male	48	54
Race			
	White	83	93
	Black	2	2
	Asian	1	1
	Hispanic	3	3
Iris Color			
	Black	2	2
	Brown	35	39
	Hazel	23	26
	Blue	29	33

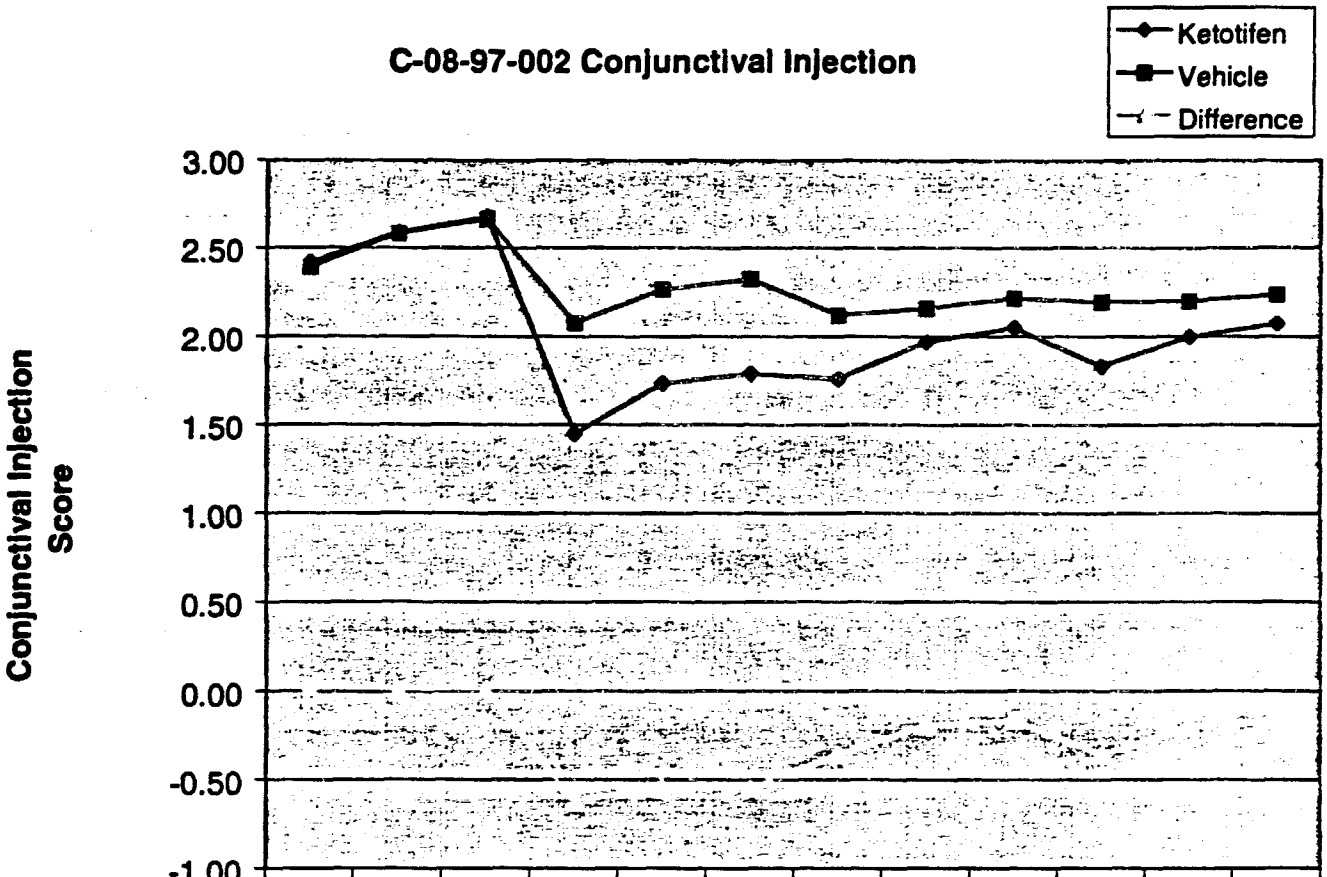
Results:



	2V: 3	2V: 7	2V: 10	3V: 18	3V: 22	3V: 25	4V: 363	4V: 367	4V: 370	5V: 483	5V: 487	5V: 490
Ketotifen	2.51	2.72	2.51	0.63	0.50	0.52	0.40	0.40	0.36	0.49	0.47	0.36
Vehicle	2.49	2.69	2.48	2.04	2.30	1.92	1.84	1.95	1.69	1.65	1.88	1.62
Difference	0.02	0.04	0.03	-1.41	-1.80	-1.39	-1.43	-1.54	-1.33	-1.16	-1.41	-1.26

Reviewer Comment:

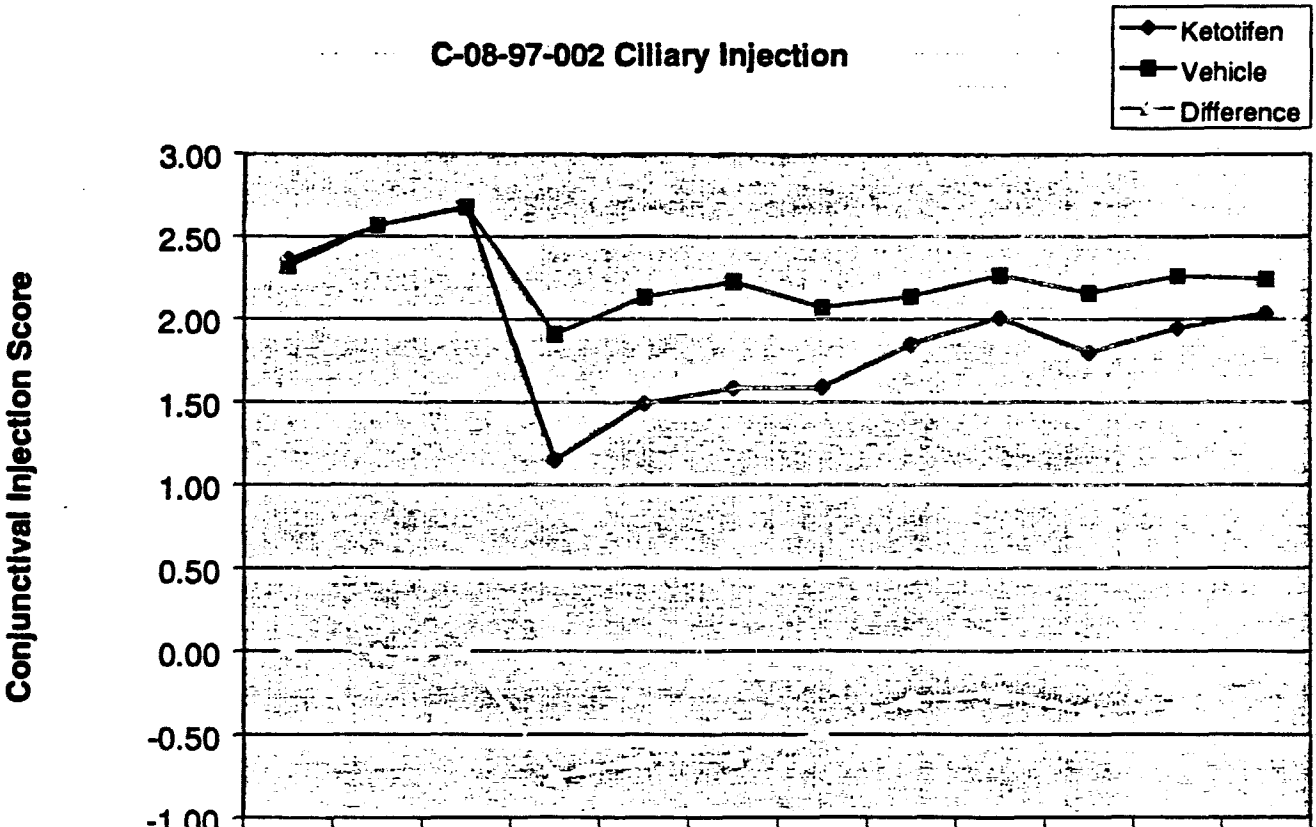
Ketotifen shows at least one point reduction in the severity of itching score over vehicle. The effect remained durable over the eight-hour period studied. Acceptable.



	2V: 7	2V: 10	2V: 15	3V: 22	3V: 25	3V: 30	4V: 367	4V: 370	4V: 375	5V: 487	5V: 490	5V: 495
Ketotifen	2.42	2.59	2.68	1.45	1.74	1.79	1.76	1.97	2.05	1.83	2.00	2.07
Vehicle	2.39	2.58	2.67	2.08	2.26	2.33	2.12	2.16	2.22	2.19	2.20	2.24
Difference	0.03	0.01	0.01	-0.63	-0.53	-0.54	-0.36	-0.19	-0.17	-0.36	-0.20	-0.17

Reviewer Comment:

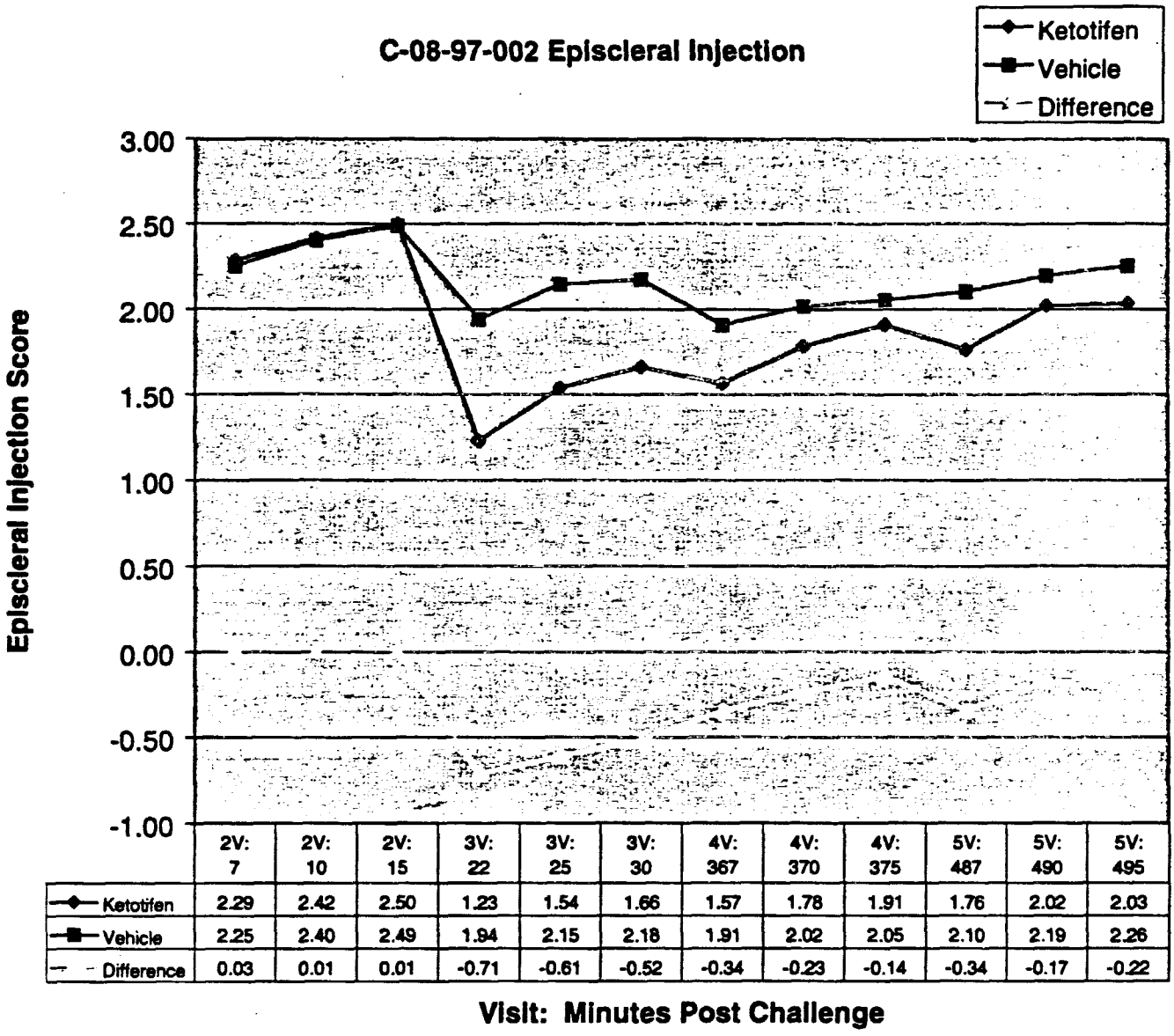
Ketotifen fails to show at least one point reduction in the severity of conjunctival injection score over vehicle. Ketotifen fails to demonstrate efficacy in conjunctival injection reduction.



	2V: 7	2V: 10	2V: 15	3V: 22	3V: 25	3V: 30	4V: 367	4V: 370	4V: 375	5V: 487	5V: 490	5V: 495
Ketotifen	2.36	2.56	2.67	1.15	1.49	1.58	1.59	1.85	2.01	1.80	1.94	2.03
Vehicle	2.32	2.57	2.68	1.91	2.13	2.23	2.07	2.14	2.27	2.16	2.26	2.24
Difference	0.04	-0.01	-0.01	-0.76	-0.65	-0.64	-0.48	-0.29	-0.26	-0.36	-0.32	-0.21

Reviewer Comment:

Ketotifen fails to show at least one point reduction in the severity of ciliary injection score over vehicle. Ketotifen fails to demonstrate efficacy in ciliary injection reduction.



	2V: 7	2V: 10	2V: 15	3V: 22	3V: 25	3V: 30	4V: 367	4V: 370	4V: 375	5V: 487	5V: 490	5V: 495
Ketotifen	2.29	2.42	2.50	1.23	1.54	1.66	1.57	1.78	1.91	1.76	2.02	2.03
Vehicle	2.25	2.40	2.49	1.94	2.15	2.18	1.91	2.02	2.05	2.10	2.19	2.26
Difference	0.03	0.01	0.01	-0.71	-0.61	-0.52	-0.34	-0.23	-0.14	-0.34	-0.17	-0.22

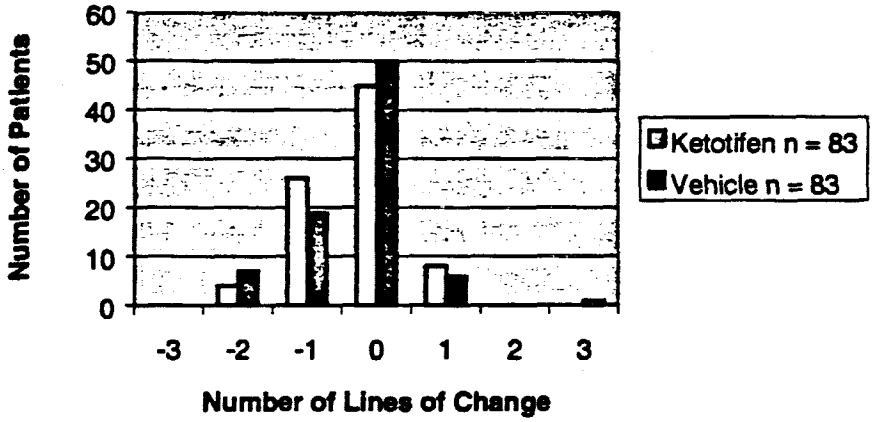
Reviewer Comment:

Ketotifen fails to show at least one point reduction in the severity of episcleral injection score over vehicle. Ketotifen fails to demonstrate efficacy in episcleral injection reduction.

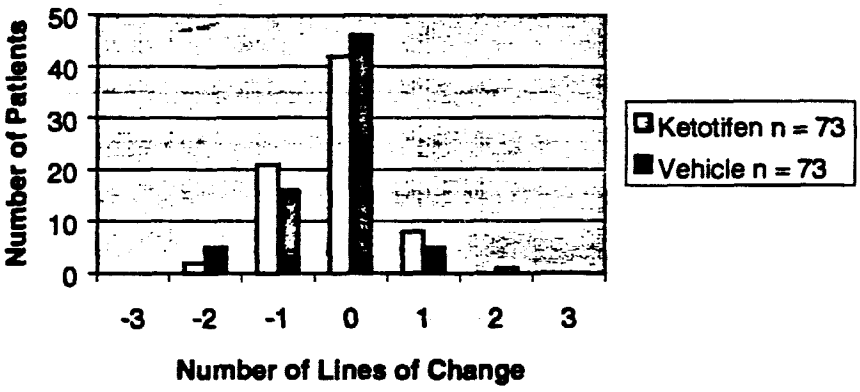
Safety Analysis:

Safety was determined based on Visual Acuity, Slit Lamp examination, dilated retinal examination and determination of adverse events.

C-08-97-002 Visit 4 Va Change



C-08-97-002 Visit 5 Va Change



Reviewer's Comments:
Changes in Visual Acuity were not significantly different between the Ketotifen and Vehicle groups at Visit 4 or Visit 5.

Adverse Events: Study C-08-97-002

Body System	Preferred Term		
		N	%
Totals	Total Subjects Exposed to Tx	89	100%
Body as a Whole			
	Headache	5	6%
	Flu Syndrome	1	1%
Musculoskeletal			
	Myalgia	1	1%
Respiratory			
	Bronchitis	1	1%
	Sinusitis	1	1%
	Rhinitis	3	3%

Summary of All Ocular Treatment-Emergent Adverse Events:

None were reported by the sponsor.

Reviewer's Comment:
Acceptable

8.1.3 Study #3 Protocol #C-08-97-003

Title: **Six-Week Safety Trial of Ketotifen Fumarate 0.025% Ophthalmic Solution in Volunteers with Normal Ocular Health**

Objectives:

To evaluate the ocular tolerance and safety of ketotifen fumarate 0.025% ophthalmic solution when instilled four times daily over a period of six weeks in healthy volunteers, including children as young as 3 years old with normal ocular health and to assess the presence or absence of ocular rebound vasodilation and itching approximately 24-48 hours after the final treatment.

Study design:

A prospective, double-masked, randomized, multi-center, fellow-eye comparison, placebo-controlled ocular tolerance and safety trial.

Drug Schedule:

Dosing was a single drop in each eye four times daily for six weeks.

Investigators:	**Number of Subjects**	**Number Completed**
Mark B. Abelson, M.D. Ophthalmic Research Associates 863 Turnpike Street North Andover, Massachusetts 01845, USA	129	125
Steven Dell, M.D. 1020 West 34th Street Austin, Texas 78705, USA	66	63
George Lowry, M.D. Vision Care, 8123 Broadway San Antonio, Texas 78209, USA	181	172
David G. Shulman, M.D. 999 Basse Road, #116 San Antonio, Texas 78209, USA	83	80
Francis J. Wapner, M.D. Advanced Eye Care 1250 East 3900 South, #310 Salt Lake City, Utah 84124, USA	36	34

Study Plan:

Subjects were randomized in a 2:1 ratio to receive ketotifen fumarate 0.025% ophthalmic solution or vehicle. One drop of the assigned treatment was instilled into each eye four times daily at approximately 4-hour intervals for six weeks. Subjects were evaluated at Visit 1 (baseline, Day 0) to qualify for study participation and returned for evaluation after 7, 14, and 42 days of treatment as well as 24-48 hours after stopping the assigned study treatment. Clinical evaluations at each visit were completed before the first daily dose of study medication was instilled. In addition, clinical evaluations were repeated approximately 30 minutes after the first daily dose at Visit 2 (Day 7).

Number of subjects (planned and analyzed):

Approximately 525 planned; 635 screened; 495 randomized and analyzed for safety (330 ketotifen, 165 placebo); 61 (42 ketotifen, 19 placebo) pediatric subjects (ages 2-11) were recruited at one center only.

Flow Chart

Procedure	Visit 1 Day 0	Visit 2 Day 7	Visit 3 Day 14	Visit 4 Day 42	Visit 5 Day 43
	X				
	X				
	X				
	X				
	X	X	X	X	X
	X	X	X	X	X
	X*				X
	X	X	X	X	X
	X	X			X***
	X	X	X	X	
		X			
	X				X
	X	X	X	X	
			X		
	X	X	X	X	
			X		
	X	X	X	X	X
	X	X+	X+	X+	
	X		X	X	X**
	X	X	X	X	
	X		X		
			X	X	
					X

\+ Urine pregnancy test required for all females at Visit 1. After Visit 1 only required for pre-pubescent females who begin menses since the previous visit.

* Dilated ophthalmoscopy should be the final procedure conducted on Day 0

** Study medication compliance will be considered as taking at least 70% of all doses

*** 24-48 hours post dose

Subject Population

Volunteers with normal ocular health, age 3 and older, will be solicited to participate in this trial. To ensure that the subject samples used are a representative sample of the U.S. population, an attempt must be made to enroll approximately 20% of the subjects from minority ethnic groups. The sites will be encouraged to enroll an equal number of light and dark iris subjects.

Inclusion Criteria

The following criteria must be met to be eligible for enrollment into the trial:

a. subject or legal guardian must sign and date an informed consent
b. must be at least 3 years of age
c. must be of either gender and of any race
d. must make the required trial visits
e. must be able to follow instructions
f. must have a best corrected distance visual acuity of 20/40 or better in both eyes (utilizing an ETDRS chart for adolescent and adult subjects, and a picture chart for pediatric subjects)
g. must have an IOP $\leq$ 21 mm Hg in both eyes
h. must have blood pressure and heart rate within the following limits after sitting for 5 minutes: ADULTS (Age 12 and up): BP $\leq$ 150 mm Hg systolic and $\leq$ 90 mm Hg diastolic Heart rate $\leq$ 90/minute PEDIATRIC: See criteria specified in protocol
i. must have a negative urine pregnancy test at Visit 1 for all females except pre-pubescent girls
j. women of childbearing potential must use an adequate form of birth control

Exclusion Criteria

Subjects will be excluded from enrollment if any of the following criteria apply:

a. known hypersensitivity to the trial medication(s) or their components;
b. participation in any investigational medication or device trial within the last 30 days prior to or during the trial period;
c. manifesting signs or symptoms of ocular inflammation, ocular allergy or presence of active bacterial or viral ocular infection;
d. use of contact lenses will not be allowed within three days prior to Visit 1 (Day) and during the trial period;

Reviewer Comment:

Acceptable

Criteria for evaluation

Efficacy:

Efficacy was not evaluated in this study.

Safety:

Safety was determined from comprehensive ophthalmic examinations including slit lamp biomicroscopy, distance visual acuity, pupil size and reactivity, intraocular pressure, and dilated ophthalmoscopy. In addition, safety was determined from ocular signs and symptoms, from sitting blood pressure and heart rate, and from adverse event reports.

Disposition

	Ketotifen	Placebo	Total
Randomized	330	165	495
Number Enrolled			
Visit 1 (Day 0)	330	165	495
Visit 2 (Day 7)	328	161	489
Visit 3 (Day 14)	324	159	483
Visit 4 (Day 42)	321	159	480
Visit 5 (Day 43)	317	158	475
Number Completing	317	158	475

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Early Terminations:

	Ketotifen	Placebo	Total
Terminated Trial Prematurely	13	7	20
Visit 1 (Day 0)	2	4	6
Adverse Event	0	2	2
Protocol Violation	0	1	1
Lost to Follow-up	1	0	1
Voluntary D/C	1	1	2
Visit 2 (Day 7)	4	2	6
Adverse Event	1	0	1
Protocol Violation	1	0	1
Lost to Follow-up	0	1	1
Voluntary D/C	2	0	2
Other	0	1	1
Visit 3 (Day 14)	3	0	3
Lost to Follow-up	1	0	1
Voluntary D/C	2	0	2
Visit 4 (Day 42)	4	1	5
Adverse Event	1	1	2
Protocol Violation	1	0	1
Lost to Follow-up	1	0	1
Voluntary D/C	1	0	1
Visit 5 (Day 43)	0	0	0
Completed all Five Visits Per Protocol	314	157	471

Individual Subject Early Termination Data:

Drug	Subject #	Age	Gender	Race	Visit	Reason
KE	1031	5	F	White	4	Protocol Violation: disallowed medication
KE	1161	23	M	White	2	Protocol Violation: disallowed medication
KE	1163	21	F	Asian	4	Lost to follow-up: no show for visit #5
KE	3059	20	M	White	2	Voluntary D/C: unable to come to remaining visits
KE	4005	27	M	White	4	Adverse event: reaction to gtts which returned with re-challenge
KE	4026	35	M	Hispanic	2	Voluntary D/C: unable to come to remaining visits
KE	5030	35	M	White	3	Voluntary D/C:
KE	5031	23	M	White	4	Voluntary D/C: subject could not come to visit 5 at designated
KE	5062	23	F	Hispanic	1	Lost to follow-up: no show for visit #2
KE	5110	23	M	Hispanic	1	Voluntary D/C: out of town for visit
KE	5115	33	M	Hispanic	2	Adverse event: matting and crusting
KE	5120	25	M	Hispanic	3	Voluntary D/C
KE	5128	18	F	White	3	Lost to Follow-up: no show for visit 4
PL	1168	31	F	White	4	Adverse Event: Cholecystitis Diagnosis from pre-existing abdominal pain with subsequent surgery/hospitalization
PL	2005	24	F	White	1	Voluntary D/C: subject refuses to come in for exit exam
PL	3029	50	M	White	2	Lost to follup-up: no show for visit 3
PL	3061	36	M	White	1	Adverse event: subject hospitalized and refused to give information regarding hospitalization, subject withdrew from study
PL	4021	37	F	Hispanic	1	Protocol Violation: wore contact lenses
PL	5037	51	M	Hispanic	1	Adverse event: subject hospitalized for myocardial infarction
PL	5057	26	F	White	2	Other: noncompliance with 70% taken doses requirement

Reviewer Comment:

Thirteen subjects were terminated early in the Ketotifen group, 7 subjects were terminated early in the Placebo group. No greater proportion of Ketotifen subjects discontinued than Vehicle subjects.

Two adverse events were reported in the Ketotifen group. Both were related to the study medication and were not serious, however, both patients discontinued. Subject 4005 discontinued due to moderate redness and swollen eyelids in both eyes which the investigator considered to be related to masked trial medication. Subject 5115 discontinued due to mild crusting and matting in both eyes which the investigator considered to be possibly related to masked trial medication.

Three adverse events occurred in the Vehicle group. All were serious and involved hospitalization. All three patients were discontinued from the study. Subject 1168 discontinued due to severe cholecystitis. Subject 5037 discontinued after experiencing a severe myocardial. Subject 3061 was hospitalized for an adverse event and discontinued masked trial medication; however, he would not provide any information about the adverse event.

Demographics

The mean age of the study population was 35 years (range: 2 to 77).

Subject Distribution of Gender, Race, and Iris Color

		Ketotifen		Vehicle Placebo		Total		P Value
# Subjects		330		165		495		
Gender								
	Female	192	58%	104	63%	296	60%	0.331
	Male	138	42%	61	37%	199	40%	
Race								
	White	174	53%	93	56%	267	54%	0.717
	Black	18	5%	5	3%	23	5%	
	Asian	8	2%	4	2%	12	2%	
	Hispanic	125	38%	62	38%	187	38%	
	Other	5	2%	1	1%	6	1%	
Iris Color								
	Black	3	1%	1	1%	4	1%	0.496
	Brown	200	61%	95	58%	295	60%	
	Hazel	43	13%	28	17%	71	14%	
	Green	21	6%	15	9%	36	7%	
	Blue	61	18%	22	13%	83	17%	
	Gray	1	0%	4	2%	5	1%	

Reviewer Comment:

Acceptable

Subject Age Distribution

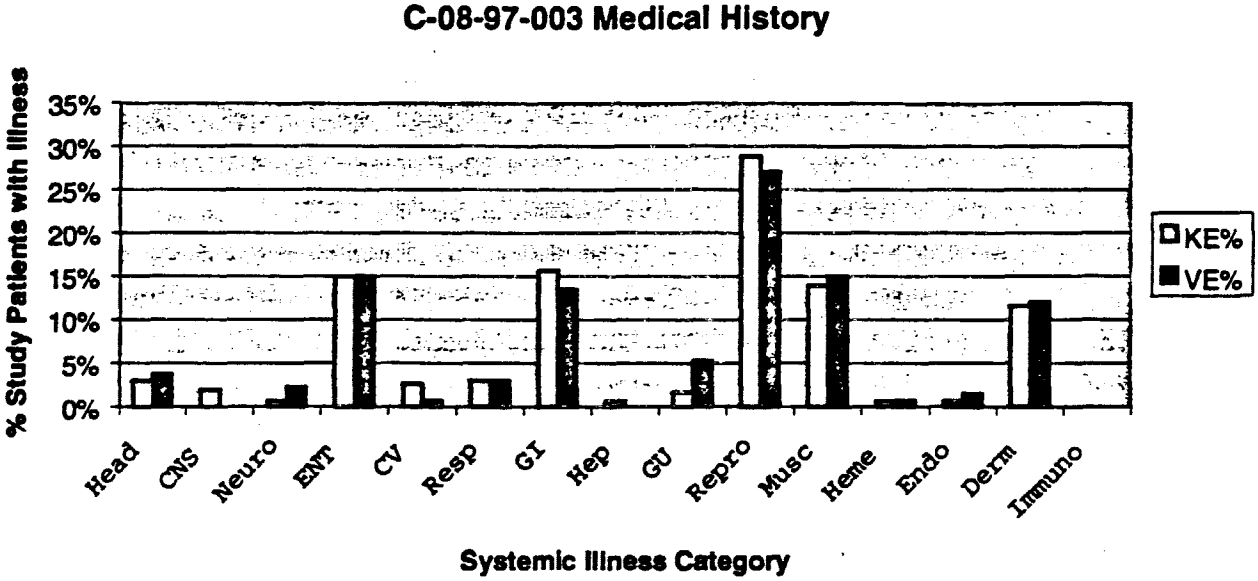
		Ketotifen	Vehicle Placebo	Total
Age (Yrs)				
	≤ 3	6	3	9
	4 to 6	14	7	21
	7 to 11	21	9	30
	12 to 17	10	1	11
	18 to 19	7	2	9
	20 to 29	59	33	92
	30 to 39	74	45	119
	40 to 49	79	42	121
	50 to 59	45	14	59
	60 to 69	12	6	18
	≥ 70	2	3	5
Mean		34.7	35	34.8
S.D.		16	15.2	15.7
Median		36	36	36
Min-Max		2 to 71	3 to 77	2 to 77

Age Distribution of Pediatric Patients Receiving Ketotifen

Age	Ketotifen	Placebo
2	1	0
3	6	3
4	4	1
5	5	4
6	5	2
7	5	1
8	2	2
9	5	1
10	6	2
11	3	3

Reviewer Comment:

The mean age was 35. There was no statistical difference between the two groups. Pediatric subjects were studied. Pediatric subject enrollment goals agreed upon with the agency were met for each pediatric age stratification. The sponsor should reassess the number of patients entered into the pediatric study ages three and under.



Reviewer Comment:
Subjects in the Ketotifen group had slightly higher incidences of systemic illness than those in the Vehicle Placebo group. Nevertheless, the Vehicle Placebo group had a higher incidence of serious adverse events related to systemic illnesses. A high proportion of patients had a reproductive past medical history. Review of the individual line listings revealed multiple patients with surgical sterilization.

Safety Data

Safety assessments included ocular signs and symptoms reported by the patient, physical examination including visual acuity, pupil diameter, slit lamp examination, intraocular pressure, and dilated ophthalmoscopy. Other safety assessments were adverse events, and vital signs, including blood pressure and heart rate.

Signs and Symptoms

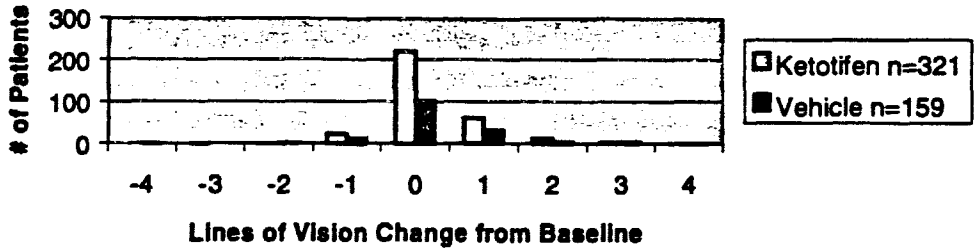
There was no statistically significant difference between the Ketotifen and Vehicle Placebo groups in the ocular signs and symptoms of redness, itching, eyelid swelling, chemosis, tearing, burning/stinging, foreign body sensation, photophobia, or dryness observed both prior to and after receiving the study medications.

Physical Examination

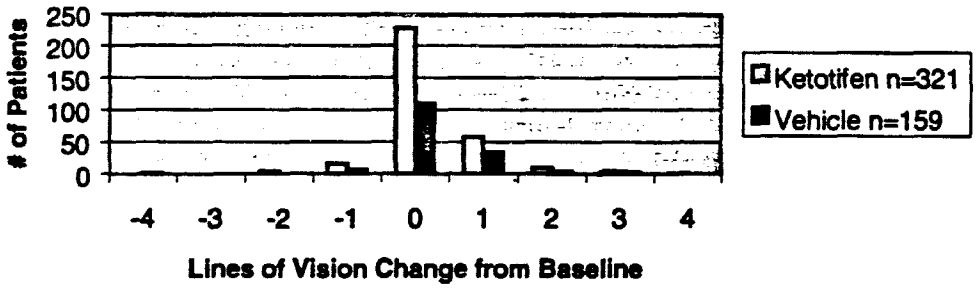
Visual Acuity

There was no statistically significant difference in the mean visual acuities between the two groups at each of the five visits prior to receiving the study medication. The distribution of change in visual acuity from baseline was similar between the two groups at day 42.

C-08-97-003 OD Va Change Day 42



C-08-97-003 OS Va Change Day 42



Pupil Size

There was no statistically significant difference in pupil size assessed prior to dose between the two groups.

Slit Lamp Examination

Changes in slit lamp findings were similar between the two groups. From baseline to Day 42 about 1% had corneal changes from normal to abnormal in both groups.

Intraocular Pressure

There was no statistically significant difference in intraocular pressure between the Ketotifen and Vehicle Placebo groups at either visit one or visit five.

Dilated Fundus Exam

There were no significant differences in abnormalities found on dilated fundus exam between the two groups.

Adverse Events

The number of subjects reporting one or more adverse events regardless of relationship to study medication was 196/330 (59.4%) and 90/165 (54.5%) for the ketotifen and vehicle placebo groups, respectively. Headache was the most frequently reported adverse event with an incidence of 19.4 percent in the Ketotifen group and 24.8 percent in the vehicle placebo group.

Six hundred forty-two treatment-emergent adverse events were reported during the study. Of these 642 events, 192 (30.1%) were ocular, 449 (69.9%) were non-ocular, and 1 was unknown. The number of subjects reporting one or more ocular adverse events in the ketotifen fumarate and vehicle placebo groups was 84/330 (25.5%) and 34/165 (20.6%), respectively, whereas 153/330 (46.6%) ketotifen fumarate-treated subjects and 73/165 (44.2%) vehicle placebo-treated subjects reported one or more non-ocular adverse events.

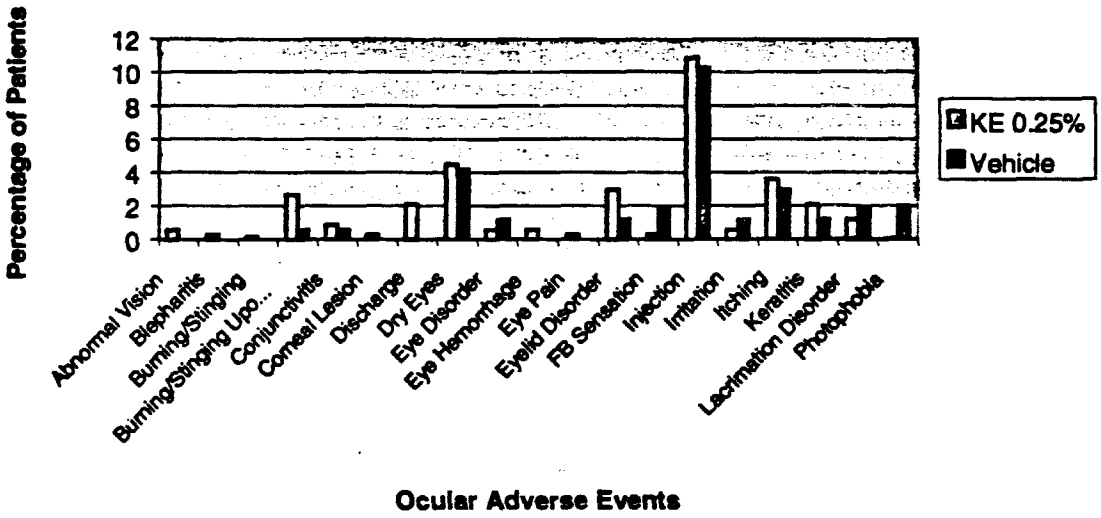
The most frequently occurring treatment-emergent adverse events reported by 10% or more of the subjects in either treatment group were headache, rhinitis, and injection. Twenty-four of the 642 (3.7%) adverse events reported were severe in intensity, and included headache in 7 subjects, flu syndrome in 5 subjects, pain and abdominal pain in 2 subjects each, and cholecystitis, dyspepsia, fever, myocardial infarction, accidental injury, itching, breast neoplasm and syncope, each in 1 subject. There were 5 subjects who discontinued prematurely due to adverse events (injection, eyelid disorder, discharge, cholecystitis, myocardial infarction and 1 unknown event).

Body System	KE 0.025%		Vehicle	
Body as a Whole	**N**	**%**	**N**	**%**
Total exposed to Treatment	330		165	100
Abdominal Pain	1	0%	1	1%
Accidental Injury	3	1%	1	1%
Allergic Reaction	2	1%	0	0%
Asthenia	2	1%	0	0%
Back Pain	6	2%	2	1%
Fever	6	2%	2	1%
Flu Syndrome	11	3%	4	2%
Headache	64	19%	41	25%
Infection	4	1%	0	0%
Neck Rigidity	1	0%	0	0%
Pain	9	3%	6	4%
Cardiovascular				
Hypertension	1	0%	1	1%
Migraine	1	0%	0	0%
Myocardial Infarction	0	0%	1	1%
Syncope	1	0%	0	0%
Tachycardia	1	0%	0	0%
Digestive				
Cholecystitis	0	0%	1	1%
Constipation	1	0%	1	1%
Diarrhea	3	1%	2	1%
Dyspepsia	12	4%	7	4%
Gingivitis	0	0%	1	1%
Mouth Ulceration	1	0%	0	0%
Nausea	3	1%	0	0%
Tooth Disorder	3	1%	1	1%
Metabolic & Nutritional				
Hypercholesteremia	1	0%	0	0%
Hypokalemia	1	0%	0	0%
Musculoskeletal				
Arthralgia	1	0%	0	0%
Myalgia	6	2%	1	1%
Pathological Fx	1	0%	0	0%
Nervous				
Dizziness	1	0%	1	1%
Hypertonia	1	0%	0	0%
Insomnia	1	0%	0	0%
Neuropathy	0	0%	2	1%
Somnolence	1	0%	0	0%
Respiratory				
Cough Increased	5	2%	2	1%
Epistaxis	0	0%	1	1%
Lung Disorder	2	1%	0	0%
Pharyngitis	10	3%	8	5%
Rhinitis	47	14%	21	13%
Sinusitis	4	1%	3	2%
Skin & Appendages				
Acne	0	0%	1	1%
Herpes Simplex	1	0%	0	0%
Rash	1	0%	0	0%
Urogenital				
Breast Neoplasm	1	0%	0	0%
Cystitis	1	0%	0	0%
Dysmenorrhea	12	4%	3	2%
Metrorrhagia	0	0%	1	1%
UTI	1	0%	0	0%

Ocular Adverse Events

The most frequently reported treatment-emergent adverse event occurring in more than 1% of the subjects in either treatment group included burning/stinging, discharge, dry eyes, eyelid disorder, injection, lacrimation disorder, and photophobia. For each of these adverse events, the incidence was similar for ketotifen fumarate and vehicle placebo, except for burning and stinging, which was worse in the ketotifen group.

C-08-97-003



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ON ORIGINAL

Table of Ocular Adverse Events

	KE 0.25%	Vehicle Placebo
Abnormal Vision	0.6	0
Blepharitis	0.3	0
Burning/Stinging	0.15	0
Burning/Stinging Upon Drug Insti	2.7	0.6
Conjunctivitis	0.9	0.6
Corneal Lesion	0.3	0
Discharge	2.1	0
Dry Eyes	4.5	4.2
Eye Disorder	0.6	1.2
Eye Hemorrhage	0.6	0
Eye Pain	0.3	0
Eyelid Disorder	3	1.2
FB Sensation	0.3	1.8
Injection	10.9	10.3
Irritation	0.6	1.2
Itching	3.6	3
Keratitis	2.1	1.2
Lacrimation Disorder	1.2	1.8
Photophobia	0	2

Reviewer Comment:

Ocular adverse events occurring at a rate of 1% or more will be described in the labeling.

Serious Adverse Events

Three ketotifen subjects and three placebo subjects experienced serious adverse events. Five of the serious adverse events were judged to be severe. Serious adverse events reported for ketotifen subjects included abdominal pain secondary to gall stones, surgical removal of a breast tumor, and arthroscopic knee surgery. Serious adverse events reported by placebo subjects included cholecystitis and myocardial infarction. The adverse event experienced by Subject 3061 was considered to be serious; however, more specific information was not available. The subject stated that his serious adverse event was not related to study medication.

In pediatric subjects, a total of 69 treatment-emergent adverse events were reported, with 28/42 (66.7%) of the ketotifen fumarate-treated subjects and 8/19 (47.4%) of the placebo-treated subjects reporting at least one adverse event. The most frequently reported adverse events occurring in more than 10% of the pediatric subjects in either treatment group were rhinitis, fever, flu syndrome, and headache. None of the pediatric subjects discontinued prematurely due to adverse events, and none of the adverse events reported for pediatric subjects was considered serious.

Adverse events reported for pediatric subjects were symptoms typically associated with the common cold, flu syndrome, and ear infections. The frequency of reporting was slightly higher for pediatric subjects than for the overall study population for all adverse events listed above except headaches, although this may reflect the same number of patients studied.

Vital Signs

For the entire study population, mean values for systolic blood pressure, diastolic blood pressure, and heart rate were within normal limits for each treatment group at each visit. There were no statistically significant differences between treatments in means for any of these variables at any visit. No clinically significant changes in mean values were observed during the study treatment period.

For pediatric subjects, mean values for systolic blood pressure, diastolic blood pressure, and heart rate were within normal limits for each age category in each treatment group. No abnormal values were observed at any visit, and no clinically significant changes in mean values were observed during the study treatment period.

Reviewer Comment:

Acceptable

8.1.4 Study #4 **Protocol #C-08-97-004**

Title: **Safety and Efficacy of Ketotifen Fumarate 0.025% Ophthalmic Solution Compared with Vehicle Placebo Control in the Allergen Challenge Model of Allergic Conjunctivitis**

Objective/Rationale:

To compare the safety and efficacy of ketotifen fumarate 0.025% ophthalmic solution with placebo in the prevention of symptoms of allergic conjunctivitis

Study Design:

A prospective, double-masked, randomized, multi-center, fellow-eye comparison, placebo-controlled allergen challenge trial.

Test Drug Schedule:

All subjects received one drop of ketotifen fumarate 0.025% ophthalmic solution in one eye and one drop of vehicle placebo in the other eye three times over a seven-week period. A total of three drops of ketotifen was given.

Investigators:	# Subjects Enrolled:	# Subjects Completed:
Tomas Mundorf, M.D. (#138) Presbyterian Medical Tower 1718 E. 4th Street, suite 902 Charlotte, NC 28204	19	16
John Lonsdale, M.D. (#151) 181 Russell Street Lewiston, ME 04240	32	29
Richard Casey, M.D. (#130) Jules Stein Eye Institute 100 Stein Plaza UCLA, Los Angeles, CA 90024-7004	15	14
Leonard Parver, M.D. (#152) 1145 19th Street, N.W. Washington D.C., 20036-3701	21	18

Study Plan:

This was a prospective, double masked, placebo controlled, multi center (4), allergen challenge study in patients with a history of ocular and or systemic allergies to known substances (including cat dander, grass, tree pollen, and ragweed). At Visit 1, a provocation dose reaction was established for each subject resulting in a moderately severe hypersensitivity reaction for each subject prior to inclusion in the trial (scores between 2-3 on a scale of 4). The provocation dose was confirmed on Visit 2. At Visit 3 (Day 0) subjects received a drop of placebo (PL) in one eye and a drop of ketotifen fumarate (KE) ophthalmic solution 0.025% in the fellow eye; 15 minutes after treatment both eyes were challenged with the appropriate allergen. Itching was evaluated at 3, 7, and 10 minutes after challenge. Conjunctival, ciliary and episcleral injection were evaluated at 7, 10, and 15 minutes after the allergen challenge. These evaluations were repeated at Visits 4 and 5 in eyes pre-treated with KE 0.025% in one eye and a drop of PL in the fellow eye 6 and 8 hours before allergen challenge, respectively. After Visit 2, there was a 14-day recovery period between visits.

Of 189 patients screened, 87 were analyzed for safety and efficacy. Ten subjects did not complete the study.

Procedure	Visit 1 Day -21	Visit 2 Day -14	Visit 3 Day 0	Visit 4 Day 14	Visit 5 Day 28
	X				
	X	X	X	X	X
	X				
	X				
	X	X			
	X	X	X	X	X
			X	X	X
	X	X	X	X	X
	X	X			
			X	X	X
	X				
	X				X
			X		
				X	
					X
		X	X	X	X
		X	X	X	X
					X

*Ophthalmic examination is performed before the CPT and the Allergen Challenge.
**Evaluations are subjective gradings made by the subject at 3, 7 and 10 minutes and investigator gradings to be completed at 7, 10, and 15 minutes.
*** Complete at visit 5 or whenever subject discontinues from the trial.

Inclusion Criteria

- Subjects of either gender and any race 18 years of age or older
- IOP of $\leq$ 21 mm Hg in both eyes with no more than a 4 mm difference between each eye
- Corrected distance visual acuity of 20/40 or better in both eyes
- Positive diagnostic test (skin or RAST) for allergic disease, or a positive conjunctival allergen challenge on file (within 24 months).
- Successful conjunctival provocation test (CPT) reaction, inducing at least 2+ itching and 2+ conjunctival redness in both eyes (OU) at visits 1 and 2.
- Allergic history to animal dander and/or seasonal airborne antigens such as ragweed, mountain cedar, etc. (perennial allergens such as molds are not acceptable).
- Able to give written consent

Exclusion Criteria

- Presence of any ocular condition that could affect trial parameters (particularly narrow angle glaucoma, blepharitis, follicular conjunctivitis, iritis, or preauricular lymphadenopathy or mucous discharge, excess lacrimation or the diagnosis of dry eye).
- Ocular surgical intervention within two months before or during the trial.
- A known history of retinal detachment, diabetic retinopathy, or any retinal disease.
- Contraindications to the use of the trial medications
- Known hypersensitivity to any component of the trial medications including the preservative(s).
- Presence of an active bacterial or viral ocular infection or positive history of ocular herpes.
- Sign or symptom of clinically active allergic conjunctivitis in either eye at the start of any trial visit (presence of any itching or greater than 1+ conjunctival redness).
- Subject is taking any systemic medication that may interfere with the trial, such as monoamine oxidase (MAO) inhibitors, nonsteroidal anti-inflammatory agents (e.g. aspirin, ibuprofen), antihistamine, decongestant (except for pseudoephedrine) or newly instituted immunotherapeutic agent within 72 hours of visit 1 or any time during the trial. **Mast cell stabilizer treatment and steroid use are not permitted during the trial nor within 30 days of visit 1.**
- Any illness that could interfere with the trial parameters e.g., any autoimmune disease such as rheumatoid arthritis, severe cardiovascular disease including arrhythmias, uncontrolled hypertension, or uncontrolled diabetes.
- Subject requires regular use of any topical ophthalmic solutions during the trial, **including tear substitutes**, except those allowed by the protocol at the end of each visit or use of any topical ophthalmic medication less than one week before visit 2.
- Females who are pregnant or nursing. All females of childbearing potential who have a positive urine pregnancy test or do not agree to use a reliable means of birth control during the conduct of the trial will be excluded. A reliable means of birth control includes:
  - Oral contraceptives
  - Implants
  - IUD
  - Barrier method (spermacide with barrier)
  - Depo-provera

This reliable means of birth control must have been used consistently for at least 30 days prior to visit 1. Females not of childbearing potential is defined as those females who have had a hysterectomy, tubal ligation or those who have not had a menses in the past 24 months.

- Participated in an investigational drug or device trial within 30 days prior to the initiation of this trial.
- Is an immediate family member of the investigative study staff, or employee of the participating investigator.
- Has a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions (e.g., inability to read, comprehend and write) which will limit the validity of informed consent to participate in this study.
- Agree to avoid the disallowed medications during the trial period and the wearing of contact lenses for three days prior to visit 1 and during the trial period.

Safety Criteria:

Safety was determined from comprehensive ophthalmic examinations including slit lamp biomicropscopy, dilated ophthalmoscopy and distance visual acuity using an ETDRS chart, and from adverse event reports.

Efficacy Criteria:

Primary efficacy was determined from the subject's rating of itching (symptom) on a 0 to 4 scale. The scoring system used to measure the symptoms of allergic conjunctivitis asks the subject to grade itching as follows:

0 = None
1 = an intermittent tickle sensation involving more than just the corner of the eye
2 = a mild continuous itch (can be localized) not requiring rubbing
3 = a severe itch; you would like to be able to rub
4= an incapacitating itch which would require significant eye rubbing

Secondary efficacy was determined by the investigator's examination of conjunctival, ciliary and episcleral injection (sign) on a 0 to 4 scale. These were graded separately by the investigator as follows:

0 = None
1 = Mild
2 = Moderate
3 = Severe
4 = Unusually severe

For both primary and secondary efficacy assessments the difference between treated and untreated eyes was used as the efficacy variable in the initial assessment, however, the unaltered values were used for the final analysis.

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Patient Disposition

Reasons for Patients discontinuing study:

Age	Gender	Race	Visit	Drug	Subject #	Reason
33	F	Black	3	KE	407	Did not show up for visit 4
20	F	White	4	KE	606	Prohibited med use: sinulin and naldecon
37	F	White	4	KE	608	Pt unable to stay for entire 4
27	F	White	4	KE	609	Signs/Sx of allergy at beginning of visits 1,2,3,4,5
35	M	White	5	KE	502	Family emergency, unable to attend visit 5
38	M	White	3	KE	513	Protocol violation: Pt took disallowed medication because of car accident
47	F	White	3	KE	519	Adverse event: sinus congestion, ear
46	M	Hispanic	4	KE	711	Schedule conflict, subject unable to attend visit 5
28	F	White	4	KE	714	Family emergency, unable to attend visit 5
38	M	White	3	KE	718	Subject enrolled in another clinical trial

Subject Trial Disposition

	Screened	Randomized	Visit 3 (Day 0)	Visit 4 (Day 14)	Visit 5 (Day 28)	Total
	189	87	87	80	77	
Terminated Early			4	5	1	10
Adverse event			1			1
Protocol Violation			2	1		3
Voluntary D/C				3	1	4
Lost to F/U			1			1
S/Sx				1		1

Protocol Deviations

Eight noteworthy deviations occurred during the conduct of the study:

- Subject #'s 603, 607, 619, 513, and 515 all failed to respond adequately to the allergen challenge at Visit 5.
- Subject #712 failed to show a successful CPT reaction of at least 2+ itching and 2+ redness. AT Visit 2, after 10 minutes her OD itching score was 1.5 and OS itching score was also 1.5
- Subject #609 presented with hyperemia at Visit 4. Her OD conjunctival injection score was 2.0, and her OS conjunctival injection score was 2.5.
- Subject #603 received study medication intended for subject #617 at Visit 4.

Although these deviations were noted, it was decided by the sponsor that they were too few to warrant a per-protocol analysis.

Study C-08-97-004 Demographic Data

Gender		
	Female	56/87 (64%)
	Male	31/87 (36%)
Race		
	Caucasian	66/87 (76%)
	Black	16/87 (18%)
	Hispanic	4/87 (5%)
	Other	1/87 (1%)
Iris Color		
	Black	1 (1%)
	Brown	37 (43%)
	Hazel	20 (23%)
	Green	4 (5%)
	Blue	23 (26%)
	Gray	2 (2%)

Reviewer's Comments:

The patient demographic data shows balance for gender, race, and iris color. As each patient was used as their own control, the treatment and placebo groups appear comparable.

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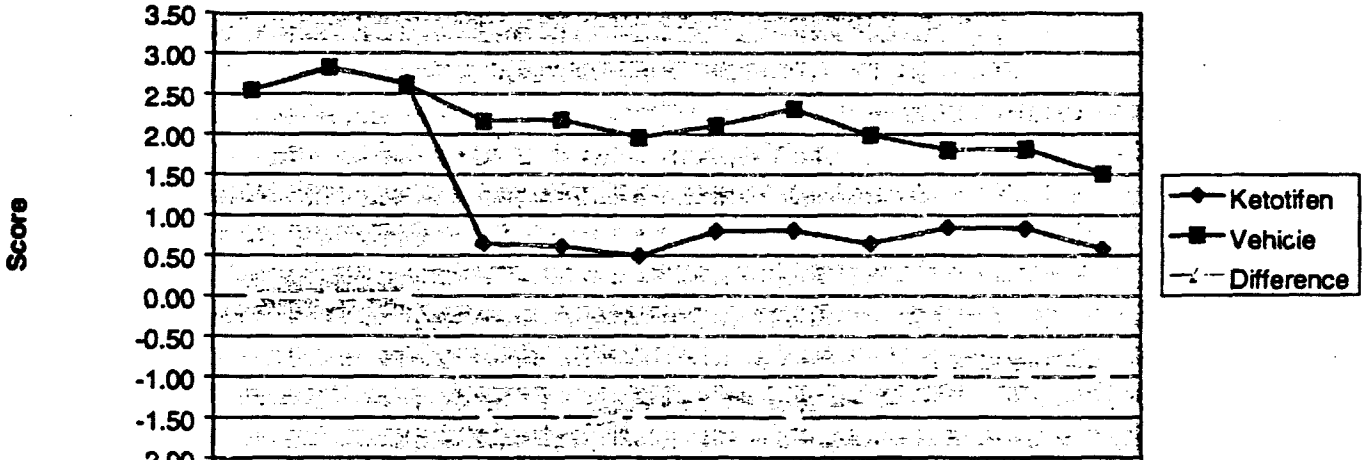
Itching C-08-97-004



	2V: 3	2V: 7	2V: 10	3V: 18	3V: 22	3V: 25	4V: 363	4V: 367	4V: 370	5V: 483	5V: 487	5V: 490
Ketotifen	2.55	2.82	2.64	0.65	0.61	0.50	0.80	0.81	0.65	0.85	0.84	0.58
Vehicle	2.55	2.83	2.62	2.16	2.18	1.97	2.11	2.32	1.99	1.81	1.82	1.52
Difference	0.00	-0.01	0.02	-1.51	-1.56	-1.47	-1.31	-1.51	-1.34	-0.96	-0.98	-0.94

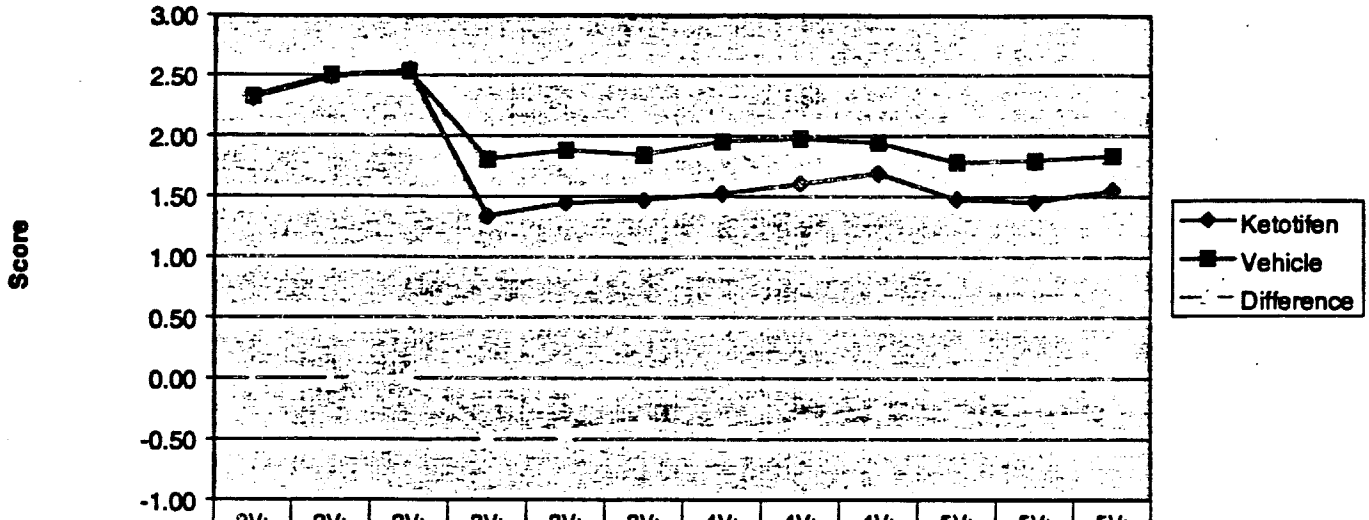
Visit: Minutes Post Challenge

Reviewer Comment:

Eyes receiving Ketotifen had average itching scores one point less than those receiving vehicle placebo. This effect extended through the eight-hour duration of effectiveness visit (483, 487, and 490 minutes). These results were durable when subgroup analysis was applied to groupings based on investigator, gender, iris color, and race.

APPEARS THIS WAY
ON ORIGINAL

Redness C-08-97-004



	2V: 7	2V: 10	2V: 15	3V: 22	3V: 25	3V: 30	4V: 367	4V: 370	4V: 375	5V: 487	5V: 490	5V: 495
Ketotifen	2.31	2.49	2.55	1.34	1.45	1.47	1.53	1.61	1.69	1.48	1.45	1.55
Vehicle	2.33	2.51	2.53	1.81	1.89	1.85	1.96	1.98	1.95	1.79	1.80	1.84
Difference	-0.02	-0.02	0.01	-0.47	-0.44	-0.38	-0.43	-0.38	-0.26	-0.31	-0.34	-0.29

Minutes

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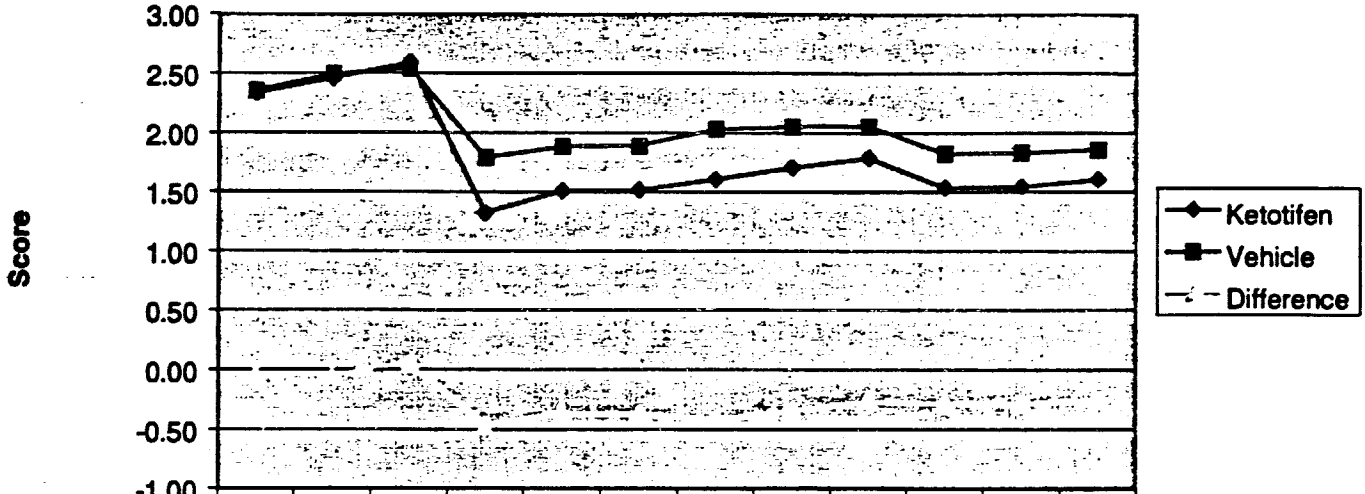
APPEARS THIS WAY
ON ORIGINAL

Episcleral Injection C-08-97-004



	2V: 7	2V: 10	2V: 15	3V: 22	3V: 25	3V: 30	4V: 367	4V: 370	4V: 375	5V: 487	5V: 490	5V: 495
Ketotifen	2.33	2.45	2.59	1.33	1.51	1.52	1.61	1.71	1.79	1.54	1.55	1.60
Vehicle	2.36	2.49	2.54	1.79	1.89	1.89	2.03	2.05	2.06	1.82	1.83	1.86
Difference	-0.02	-0.04	0.05	-0.47	-0.37	-0.38	-0.43	-0.34	-0.27	-0.29	-0.29	-0.25

Minutes

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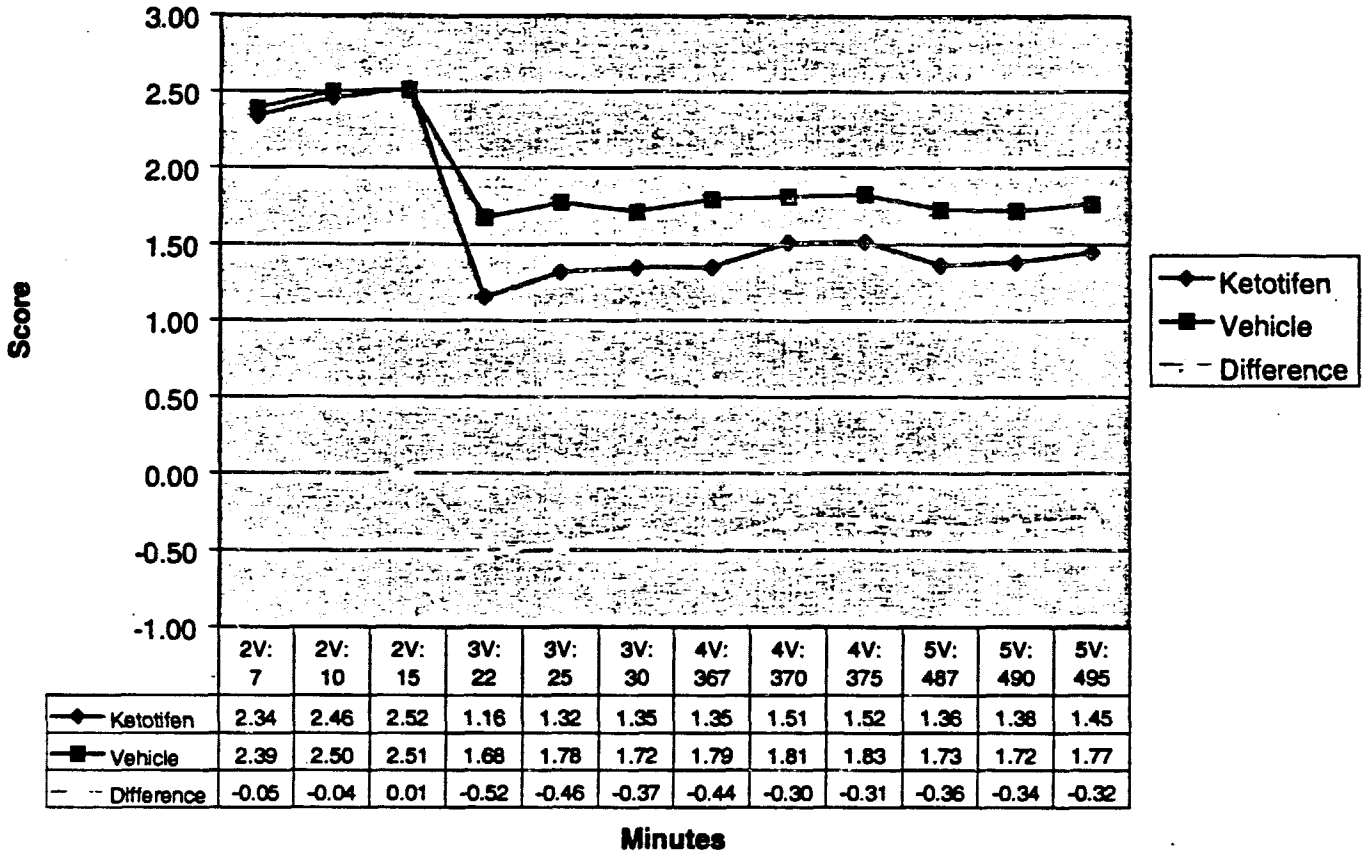
APPEARS THIS WAY
ON ORIGINAL

Ciliary Injection C-08-97-004



	2V: 7	2V: 10	2V: 15	3V: 22	3V: 25	3V: 30	4V: 367	4V: 370	4V: 375	5V: 487	5V: 490	5V: 495
Ketotifen	2.34	2.46	2.52	1.16	1.32	1.35	1.35	1.51	1.52	1.36	1.38	1.45
Vehicle	2.39	2.50	2.51	1.68	1.78	1.72	1.79	1.81	1.83	1.73	1.72	1.77
Difference	-0.05	-0.04	0.01	-0.52	-0.46	-0.37	-0.44	-0.30	-0.31	-0.36	-0.34	-0.32

Minutes

Reviewer Comment:

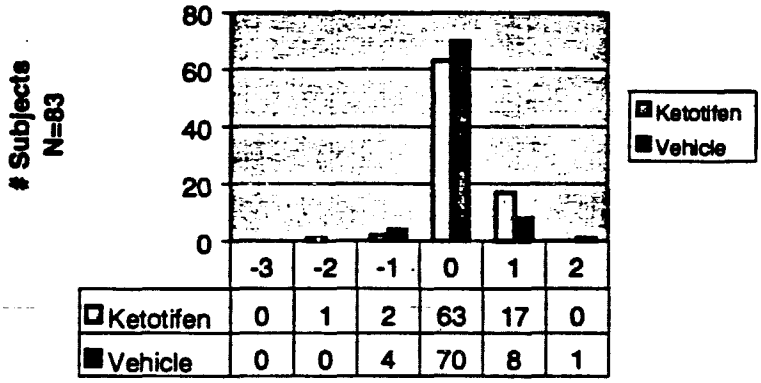
Eyes receiving Ketotifen had average redness scores < 0.5 points less than eye receiving vehicle placebo. This does not represent a clinically significant difference between the two groups. This was true of all three types of redness evaluated, including Conjunctival Redness, Episcleral Injection, and Ciliary Injection.

APPEARS THIS WAY
ON ORIGINAL

Safety Analysis:

Safety was determined based on Visual Acuity, Slit Lamp examination, dilated retinal examination and determination of adverse events.

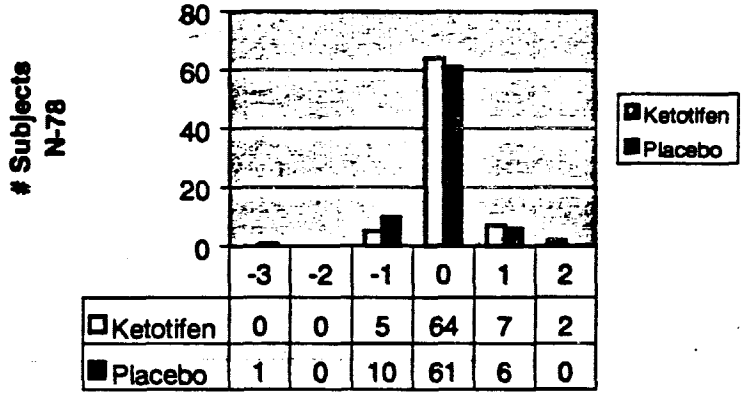
C-08-97-004 Visit 4 Va Change



	-3	-2	-1	0	1	2
Ketotifen	0	1	2	63	17	0
Vehicle	0	0	4	70	8	1

Number of Lines Va Change

C-08-97-004 Visit 5 Va Change



	-3	-2	-1	0	1	2
Ketotifen	0	0	5	64	7	2
Placebo	1	0	10	61	6	0

Number of Lines Change Va

Reviewer's Comments:
Changes in Visual Acuity were not significantly different between the Ketotifen and Vehicle Placebo groups at Visit 4 or Visit 5.

APPEARS THIS WAY
ON ORIGINAL

Adverse Events:

Body System	Preferred Term		
		N	%
Totals	Total Subjects Exposed to Tx	87	100%
Body as a Whole			
	Abdominal Pain	1	1%
	Fever	2	2%
	Headache	7	8%
	Pain	1	1%
Digestive			
	Dyspepsia	1	1%
	Nausea	1	1%
	Stomatitis	1	1%
Musculoskeletal			
	Myalgia	1	1%
Respiratory			
	Bronchitis	1	1%
	Pharyngitis	2	2%
	Rhinitis	9	10%
Special Senses			
	Ear disorder	1	1%

Summary of All Ocular Treatment-Emergent Adverse Events:

Of 87 total subjects at risk, 1 patient reported burning and stinging.

Reviewer's Comment:
Acceptable.

APPEARS THIS WAY
ON ORIGINAL

8.1.5 Study #5 Protocol UK/DR 42000-97-001

Title: **Double Masked Clinical Trial Between Different Concentrations of Ketotifen Fumarate Ophthalmic Solution and its Vehicle in Healthy Subjects to Assess and Compare the Local Tolerance and Safety after Multiple Dosing**

Objective/Rationale:

To assess and compare the local ocular tolerance and safety of 4 different concentrations (0.05%, 0.10%. 0.15% and 0.20% ketotifen base) of ketotifen fumarate ophthalmic solution versus vehicle placebo after b.i.d. and q.i.d administration to 40 healthy subjects each regimen, for one week.

Study Design:

A Single-center, double-masked, parallel-group, multiple-dose, prospective, randomized comparison of four different concentrations of ketotifen fumarate ophthalmic solution using a fellow-eye vehicle control.

Test Drug Schedule:

A first set of 40 subjects (10 each test drug concentration) receiving the trial medication twice a day (b.i.d.) for one week, a second set of 40 subjects (10 each test drug concentration) receiving the trial medication four times a day (q.i.d.) for one week.

Investigators: Number of Patients Enrolled:

Mark MacMahon M.D. 82
Chiltern House
Bells Hill
Stoke Poges, U.K.

Study Plan:

This was a single-center, double-masked, parallel-group, multiple-dose, prospective, balanced, randomized comparison of 4 different concentrations (0.05%, 0.10%, 0.15% and 0.20% ketotifen base) of ketotifen fumarate ophthalmic solution using a fellow-eye vehicle control. The study was designed to include 80 evaluable healthy volunteers treated for one week. A first set of 40 subjects (10 each test drug concentration) received the trial medication twice a day (b.i.d.). A second set of 40 subjects (10 each test drug concentration) received the trial medication four times a day (q.i.d).

Of 102 subjects screened, 82 were randomized. Seventy-nine subjects completed the study.

Inclusion Criteria:

Subjects who fulfilled all of the following criteria were included in the trial:

- Male or female of any race.
- Age from 18 to 60 years.
- Intraocular pressure ≤ 21 mmHg.
- Best-corrected distance visual acuity > 0.8 (20/25) in both eyes (Snellen chart).
- Normal aspects of all corneal layers by slit-lamp examination.
- Negative pregnancy test for women of childbearing age.
- Use of a reliable hormonal (for at least 1 month prior to the study) or mechanical method of contraception for women of childbearing age.
- Written informed consent given.
- Able and willing to comply with the requirements of the study protocol.

Exclusion Criteria:

Subjects who had one of the following conditions, were receiving one of the following treatments, or who fulfilled one or more of the following criteria were excluded from the trial:

- Systemic/ophthalmic conditions:
  Ocular/lid disease or ocular/lid malformations
  Ocular subjective symptoms
  Ocular surgical intervention within six months prior to the study
  Presence of any significant condition which might interfere with the trial measurements
  Hypersensitivity to any component of the trial medication
- Previous treatment with any local ocular or systemic medication within seven days prior to the start of treatment, except for contraceptives for women of childbearing potential
- Concomitant treatments/non-product therapies:
  Any local ocular treatments
  Any systemic medication except hormonal contraceptives
  Any eye make-up or any skin care product around the eyes during the study treatment period and on the day before the start of treatment
- Others:
  Non-compliant subjects (e.g., not willing to attend the follow-up visits).
  Positive pregnancy test of females of childbearing age
  Contact lens wearing 3 days prior to and during the study treatment period
  Product abuse (including alcoholism)
  Participation in another clinical drug trial within one month prior to treatment start

Number of Subjects (planned and analyzed):

The study was designed to include 80 evaluable healthy volunteers treated for one week: a first set of 40 subjects (10 each test drug concentration) receiving the trial medication twice a day (b.i.d.), a second set of 40 subjects (10 each test drug concentration) receiving the trial medication four times a day (q.i.d.).

One hundred two subjects were screened. Eighty two subjects were randomized, 41 on the b.i.d. regimen and 41 on the q.i.d. regimen.

Seventy nine subjects completed the trial: 40 on the b.i.d. regimen and 39 on the q.i.d. regimen. Replacement subjects were used in both groups: Subject numbers 1-40 and replacement numbers 41-48 received the b.i.d. regimen, subjects numbers 49-88 and replacement numbers 89-96 received the q.i.d. regimen.

Flow Chart:

Study Period	Screen	Baseline	Treatment		
Study day	Day -15 to day -1	Day 1		Day 2	Day 8
Visit	Visit 1	Visit 2 Pre-Tx	Visit 2 Post-Tx	Visit 3	Visit 4
Written informed consent	X				
Check inclusion/exclusion criteria	X	X			
Demographics	X				
Pregnancy test (If applicable)	X				
Medical history	X	X			
Medication history	X	X			
Drug instillation 1			X----------		----------X
Subjective "global" local tolerance			X2	X2	X2
Symptoms of ocular drug intolerance		X	X		X3
Signs of ocular drug intolerance		X	X4	X4	X4
Slit-lamp examination, funduscopy	X	X			X
VA, Schirmer's test, BUT, tonomet	X				X
Adverse events			X	X	X
Vital signs (blood pressure, heart rate)		X			X
Concomitant medication			X	X	X

1. Subjects returned to the study center on a daily basis for drug instillation: subjects 1 to 40: 2x1 drop daily in each eye at an interval of 9 hours (± 30 minutes); subjects 49 to 88: 4x1 drop daily in each eye at an interval of 3 hours (± 30 minutes) from first instillation.
2. Subjective "global" local tolerance was assessed by the subject in each eye 5 minutes after first drug instillation of the day.
3. Symptoms of ocular drug intolerance were assessed by the subject in each eye immediately after each drug instillation.
4. Signs of ocular drug intolerance were assessed by the investigator in each eye 5 minutes after first drug instillation of the day.

APPEARS THIS WAY
ON ORIGINAL

Subject Population:

Method of Assigning Subjects to Treatment Groups:

Random assignment to masked trial medication to the four different dose groups was accomplished by the prepackaging of masked medication for each eye. Equal numbers of right and left eyes were assigned to active drug and placebo treatment.

- One group to receive 0.05% ketotifen in one eye and the vehicle placebo in the contralateral eye
- One group to receive 0.10% ketotifen in one eye and the vehicle placebo in the contralateral eye
- One group to receive 0.15% ketotifen in one eye and the vehicle placebo in the contralateral eye
- One group to receive 0.20% ketotifen in one eye and the vehicle placebo in the contralateral eye

The bottles were randomized in balanced blocks of 8 and continuously numbered from 1 to 96 (including reserve material for 16 subjects). Within each regimen (b.i.d. and q.i.d.), the allocation of the trial material to the subjects was done according to the next available consecutive serial number, which was recorded in the CRF. B.i.d. regimen: Subject numbers 1 to 40. Q.i.d. regimen: Subject numbers 49 to 88.

In order to guarantee that the different treatment groups would include approximately equal numbers of subjects, the CSLU advised the clinical monitor – without unmasking the subject- on how to replace the discontinued subjects, when appropriate.

Reviewer comment:
Not acceptable. Replacing discontinued subjects confounds statistical analysis of adverse events.

Efficacy:

No efficacy variables were assessed.

Ocular Tolerability:

Ocular tolerability was assessed by recording the subjective "global" local tolerance. The symptoms and signs of ocular drug intolerance were assessed by the subjects and investigator respectively.

Safety: Safety was determined from comprehensive ophthalmic examinations at visits 1 (pre-dose) and 4 (post-dose) including:

- Slit lamp examination
- Best-corrected distance visual acuity (Va) (Snellen chart)
- Schirmer's test
- Tear film break-up time
- Tonometry (contact aplanometer)
- Funduscopy (inspection of retina with ophthalmoscope-undilated pupil)

Disposition:

A total of 102 subjects were screened for eligibility. Of those screened, 20 subjects were not randomized to treatment for the following primary reasons: eleven (11) did not fulfil the selection criteria, three (3) had intercurrent illnesses, two (2) failed to attend the randomization visit, one (1) decided not to take part for personal reasons, and three (3) were not enrolled for other reasons.

Of the 82 subjects randomized, three (3) dropped out of the study. One dropped out due to an adverse event (urticarial rash, Subject No. 77), one was lost to follow-up (Subject No. 59) and one violated protocol (Subject No. 21). Subject No. 52 temporarily withdrew consent after one day of treatment (not able to adhere to visit schedule) and then rejoined at a later stage for a complete treatment period, i.e., from day 1 to day 8. This meant having two different CRF code numbers (CRF Nos. 95 and 100). Only data collected after restart were used for tolerability analyses.

A total of 79 subjects completed the study. Of these, 40 were on the b.i.d. regimen and 39 on the q.i.d. regimen.

	Total	0.05%	0.10%	0.15%	0.20%
Screened	102				
Randomised	82	21	21	20	20
b.i.d.	41	11	10	10	10
q.i.d	41	10	11	10	10
Completing trial	79	19	20	20	20
b.i.d.	40	10	10	10	10
q.i.d.	39	9	10	10	10
Prematurely D/C	3	2	1	0	0
Product-related AE	1	1	0	0	0
b.i.d.	0	0	0	0	0
q.i.d.	1	1	0	0	0
Lost to follow-up	1	0	1	0	0
b.i.d.	0	0	0	0	0
q.i.d.	1	0	1	0	0
Protocol violation	1	1	0	0	0
b.i.d.	1	1	0	0	0
q.i.d	0	0	0	0	0

Protocol Deviations:

Subject No. 21 was given the first dose of study medication when corneal abnormalities were present. No further treatment was given and the subject was withdrawn from the study.

Ten subjects (Nos. 4,9,10,11,12,35,36,53,65,68) were randomized although the best-corrected visual acuity in at least one eye was recorded as 6/9, and therefore worse than 0.8. This arose because the Snellen chart used had test types for 6/6 and 6/9, with no intermediate steps; the resolution of the method was insufficient to allow for minor defects in visual acuity. The ocular examination for these subjects was in all other respects normal, and they were included in the trial on the decision of the investigator.

Demographic and other Baseline Characteristics:

A total of 82 subjects (46 male and 36 female) were randomized to treatment. The average age was 29.9 years (range 18 to 59 years). Average weight was 75.5 kg and average height was 172.1 cm. Eighty subjects were of White, two of Asian origin. There were 19 subjects with brown, 7 with hazel, 16 with green 35 with blue and 5 with gray iris color.

There were no significant differences between treatment groups in age, weight, height, race, gender, iris color or measures of general health including medical history and history of ocular disease or injury.

Measurements of Treatment Compliance:

There were no specific measure of treatment compliance; all medication was applied directly to the subjects' eyes by investigative staff. Due to an oversight by the center's staff, subject No. 73 missed the 3rd drug administration and the following assessment of symptoms of ocular drug intolerance on day 6. No other deviation from the planned time schedule was observed.

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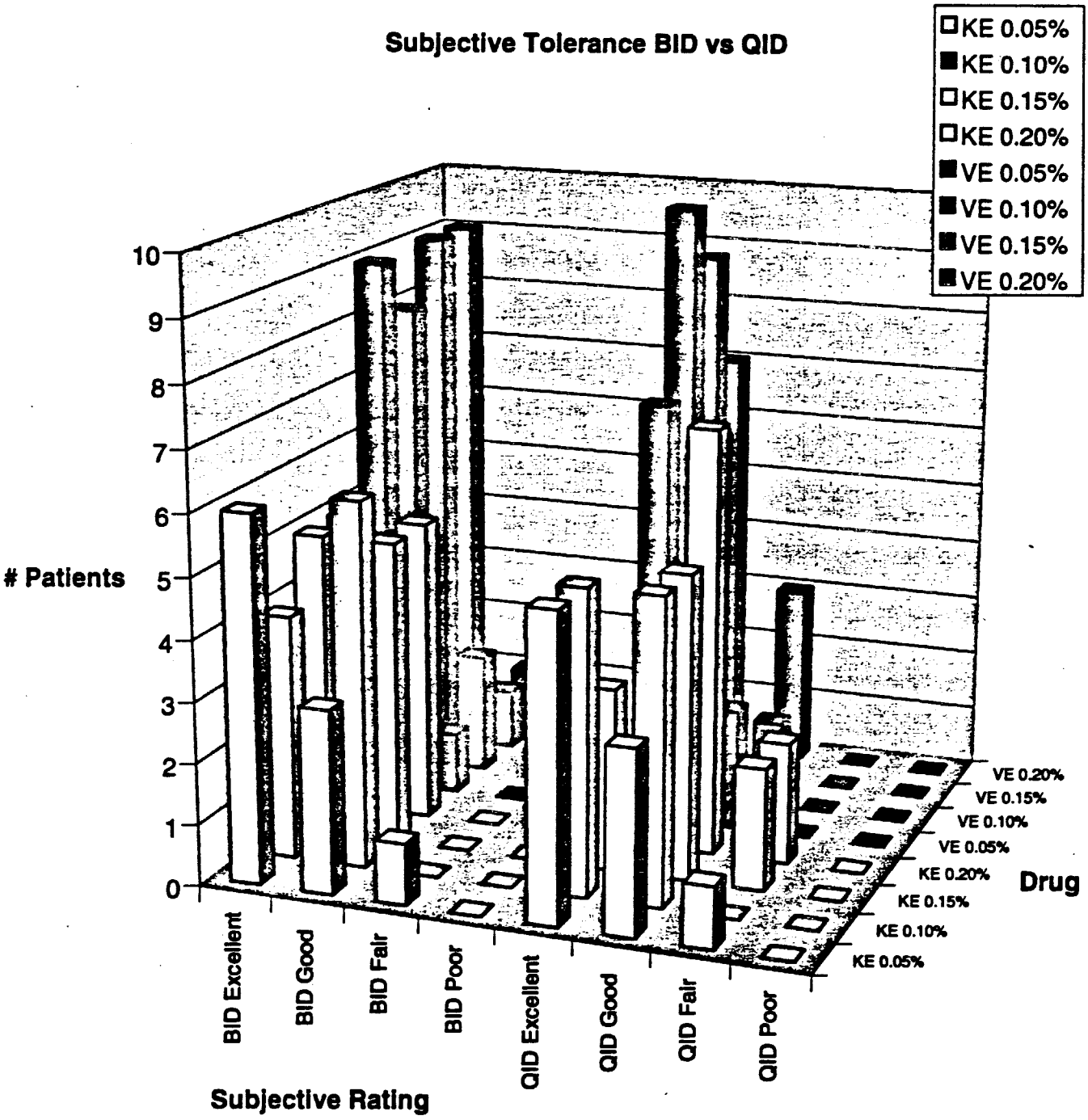
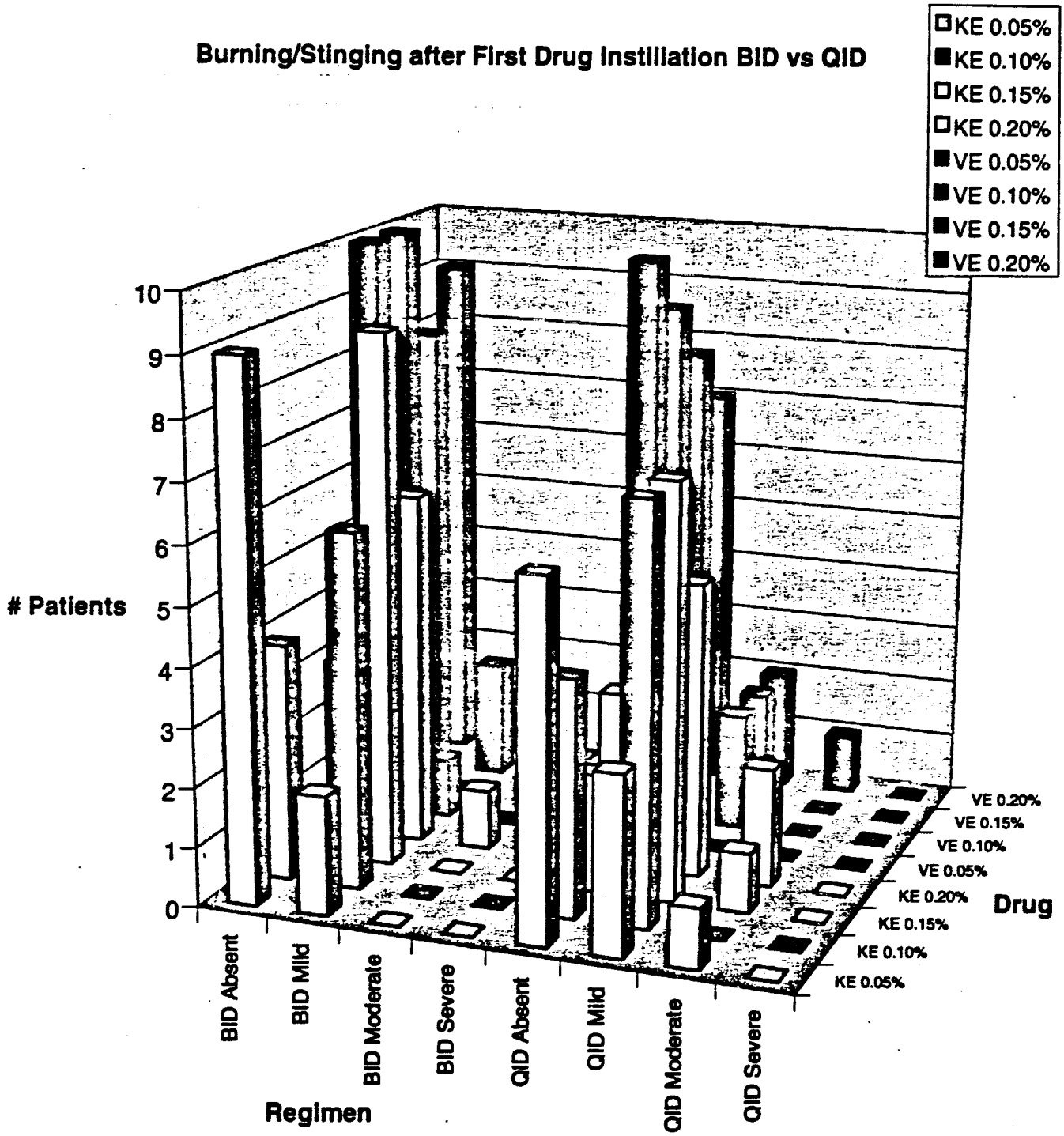
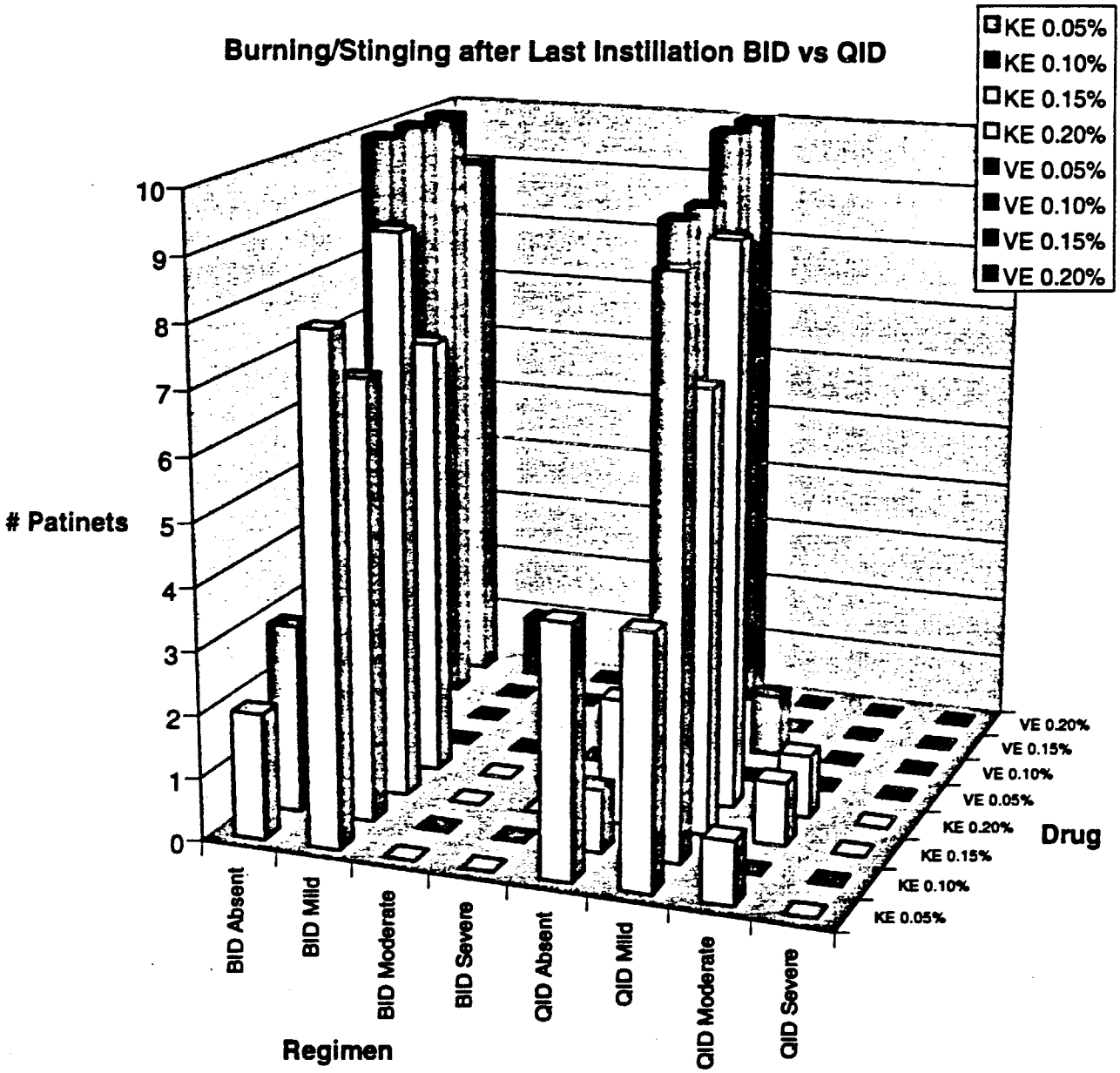
ON ORIGINAL

Results:

Primary assessment focused on the subjective "global" tolerance at the end of treatment.




Burning/Stinging after First Drug Instillation BID vs QID
KE 0.05%
KE 0.10%
KE 0.15%
KE 0.20%
VE 0.05%
VE 0.10%
VE 0.15%
VE 0.20%
Patients
0
1
2
3
4
5
6
7
8
9
10
BID Absent
BID Mild
BID Moderate
BID Severe
QID Absent
QID Mild
QID Moderate
QID Severe
Regimen
Drug



Tolerability Conclusions:

No clinically significant differences were found between treatment groups in the primary tolerability variable. Almost all subjects recorded "good" or "excellent" global tolerance for both eyes throughout the study. A consistent finding among the secondary tolerability variables was an increased incidence of burning or stinging sensation in the eyes receiving active drug. This symptom was almost always "mild", and was always transient. It never led to failure of compliance or a request to discontinue medication.

Adverse Events:

Mydriasis was reported is three patients (2 cases with 0.10% ketotifen q.i.d.; 1 case with 0.20% ketotifen q.i.d.).

One event represented a probable systemic reaction to the study drug: Subject no.77 receiving 0.05% ketotifen q.i.d. developed an itchy urticarial rash of moderate intensity on his forearms on day 1 of the trial, and he was withdrawn from the study. He recovered without sequelae and without being treated for the adverse event.

Treatment-Emergent Adverse Events:

Organ System	Preferred Term	# of Events	Original Term	Severity	Subject #
Body as a Whole					
	Headache	6	Headache	mild	27
			Headache	mild	27
			Headache	mild	28
			Headache	mild	29
			Headache	severe	50
			Headache	moderate	69
Skin					
	Rash	3	Heat rash	mild	26
			Heat rash	mild	26
			Uriticarial rash	moderate	77
Special Senses (Ocular AE)					
	Burning/Stinging	1	Burning	moderate	80
	Eyelid Disorder	1	Feeling of puffiness	mild	35
	Eye Pain	5	Throbbing in OD	mild	73
			Pain/Throbbing Pressure	mild	73
			Pain/Throbbing Pressure	moderate	73
			Sore around OS	mild	86
	Foreign Body Sensation	1	Sensation of FB	mild	9
	Injection	2	Red Eye	mild	25
			Red Eye	mild	27
	Irritation	1	Heavy eyes	mild	74
	Itching	4	Itching in OS	mild	2
			Itching OU	mild	68
			Itching	mild	68
			Itching OD	mild	69
	Mydriasis	3	Dilated OS	mild	60
			Dilated Pupil	mild	61
			Dilated OD	mild	67
	Photophobia	2	Light sensitivity	mild	27
			Light sensitivity	mild	27
Urogenital System	Dysmenorrhea	1	Dysmenorrhea	moderate	22

Treatment-Emergent Adverse Events – b.i.d. Regimen:

Ketotifen conc.	0.05%	0.10%	0.15%	0.20%	Total
Subjects treated	11	10	10	10	41
Ocular	3	0	1	0	4
Non-ocular	1	0	2	1	4
Ocular & non-ocular	0	1	0	0	1
Total number of AE	4	5	4	1	14
Number of ocular AE	3	3	1	0	7
Special Senses	3	3	1	0	7
Eyelid Disorder			1*		1
FB sensation	1*				1
Injection	1**	1*			2
Itching	1**				1
Photophobia		2***			2
Number of non-ocular AE	1	2	3	1	7
Body as a whole	0	2	1	1	4
Headache	0	2	1	1	4
Skin	0	0	2	0	2
Rash	0	0	2	0	2
Uorgenital system	1	0	0	0	1
Dysmenorrhea	1				1

***Eye receiving active drug**
****Eye receiving placebo vehicle**
*****Both eyes**

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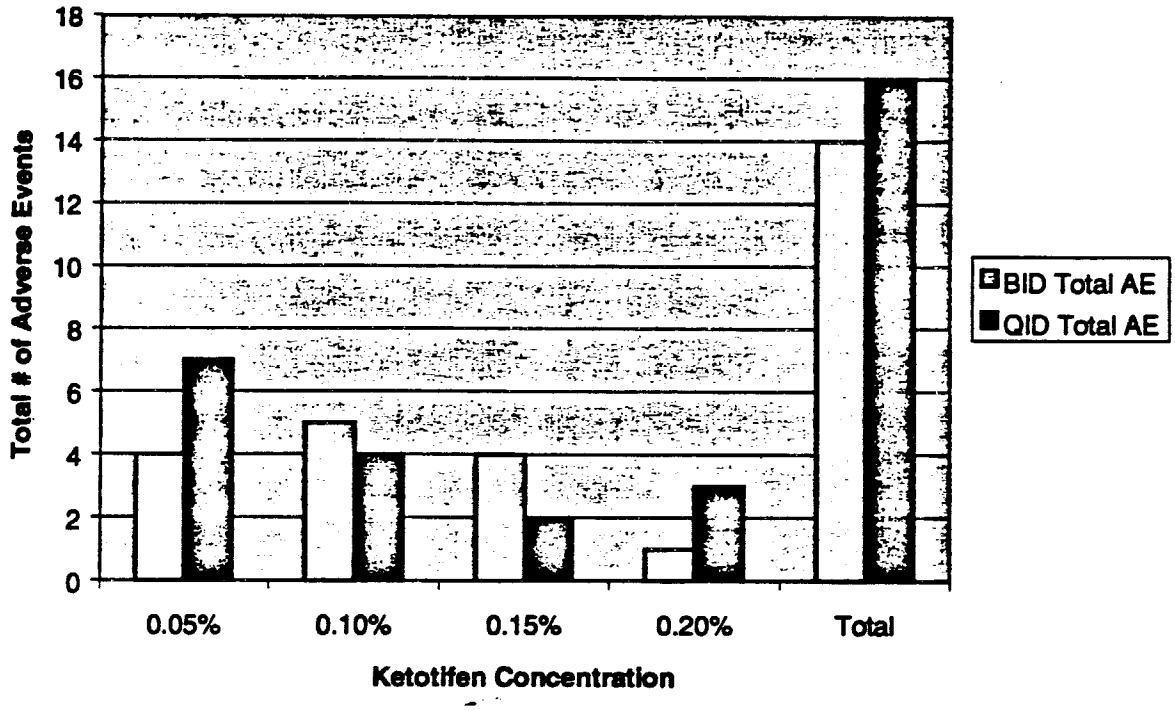
Treatment-Emergent Adverse Events – Q.I.D. Regimen:

Ketotifen conc.	0.05%	0.10%	0.15%	0.20%	Total	
Subjects treated	10	11	10	10	41	
Subjects with at least 1 AE	3	4	1	3	11	
Ocular	2	4	0	2	8	
Non-ocular	1	0	0	1	2	
Ocular & non-ocular	0	0	1	0	1	
Total number of AE	7	4	2	3	16	
Number of ocular AE	6	4	1	2	13	
Special Senses	6	4	1	2	13	
Burning/Stinging	0	1*	0	0	1	
Eye pain	4*	1*	0	0	5	
Irritation	0	0	0	1***	1	
Itching	2***	0	1	0	3	
Mydriasis	0	2*	0	1*	3	
Number of non-ocular AE	1	0	1	1	3	
Body as a whole	0	0	1	1	2	
Headache	0	0	1	1	2	
Skin	1	0	0	0	1	
Rash	1	0	0	0	1	

***Eye receiving active drug**
****Eye receiving placebo vehicle**
*****Both eyes**

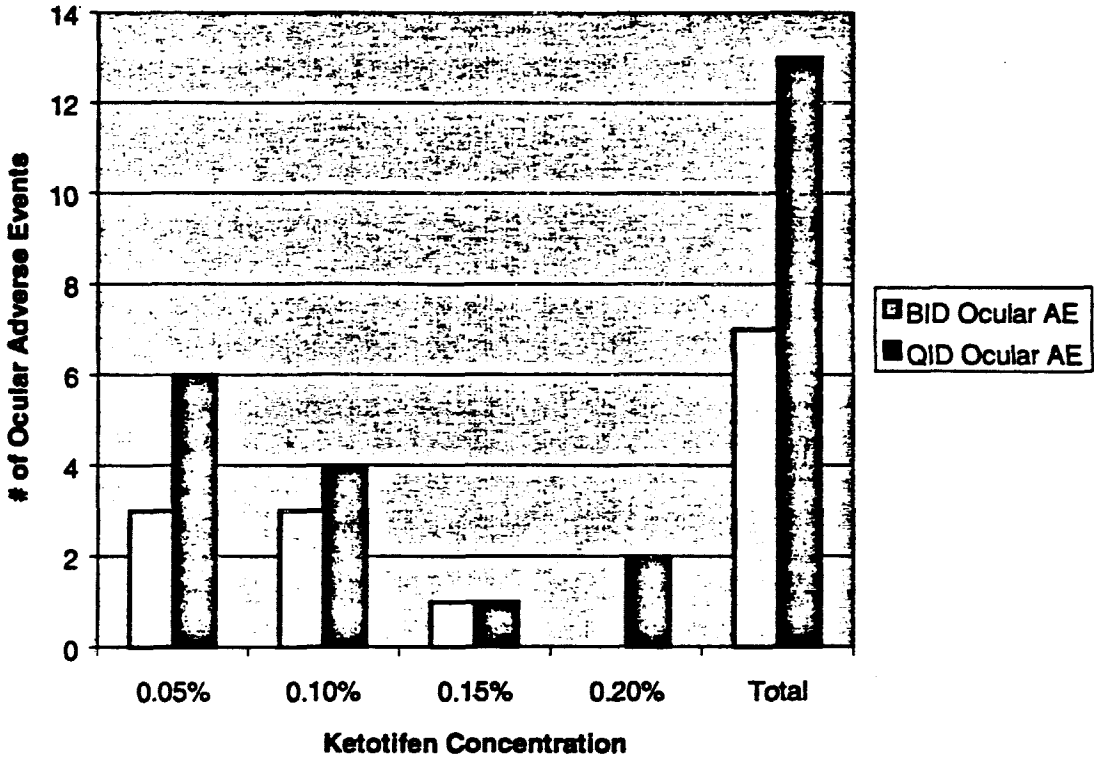
Comparison of Total AE BID vs QID Ketotifen Regimen
Dose Ranging Study UK/DR 42000-97-1



Reviewer Comment:

The total number of adverse events recorded is slightly higher in the q.i.d. regimen over the b.i.d. regimen. The small numbers of patients studied precludes statistical analysis. The number of events within the b.i.d. and q.i.d. regimens does not appear to follow a dose-response relationship.

Comparison of Ocular AE BID vs QID Ketotifen Regimen
Dose Ranging Study UK/DR 42000-97-1



Reviewer Comment:

The total number of ocular adverse events is almost two times higher in the q.i.d. regimen than the b.i.d. regimen. The number of adverse events within each regimen does not appear to follow a dose-response relationship, however. The small number of patients studied precludes further statistical analysis. Mydriasis was reported in three patients on the q.i.d. regimen.

9 Reviewer's Overview of Efficacy

Adequate efficacy for the prevention of itching has been demonstrated in study C-08-97-002 and reproduced in study C-08-97-004. Efficacy for the prevention of redness has not been demonstrated.

10 Reviewer's Overview of Safety

Adequate safety has been established for use of Ketotifen 0.025% in the prevention of itching associated with allergic conjunctivitis. Adverse experiences in the studies were generally confined to mild to moderate ocular events.

4 pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.

11 Conclusions

The submitted studies in NDA 21-066 demonstrate safety and efficacy for the prevention of itching associated with allergic conjunctivitis.

12 Recommendations

1. Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 21-066 is recommended for approval for the prevention of itching associated with allergic conjunctivitis.
2. The applicant should submit revised labeling consistent with the recommendation in this review.
3. The proposed tradename should be specified.
4. The sponsor must commit to a Phase 4 pharmakokinetic study to confirm the lack of detectable in vivo plasma levels following ophthalmologic dosing. The sponsor should submit their protocol for the Phase 4 study to the agency for comment prior to initiation.

APPEARS THIS WAY
ON ORIGINAL

/S/

Jennifer A. Dunbar MD
Medical Officer, Ophthalmology

Cc: NDA 21-066
HFD-550
HFD-340
HFD-550/PM/Rodriguez
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Hughes
HFD-550/PHARM TL/Weir
HFD-550/PHARM/ZChen
HFD-550/MO/Dunbar
HFD-550/SMO/Chambers WHC 5/3/99

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-066

NDA 21-066
Minor Chemistry Amendment

Submission Date: 6/21/99 & 6/30/99
Receive Date: 6/23/99 & 7/1/99
Review Date: 7/1/99

Drug name: Ketotifen fumarate ophthalmic solution, 0.025% topical

Generic name: Ketotifen fumarate ophthalmic solution

Sponsor: CIBA Vision – A Novartis Company
11450 Johns Creek Parkway
Duluth, Georgia 30097

Pharmacologic Category: anti-histamine

Proposed Indication(s): For the prevention of itching of the eye due to allergic conjunctivitis

Submitted: 6/21/99 Amendment with CIBA Vision's response to the outstanding labeling, pharmacokinetics, and chemistry issues.

Issue 1: The systemic absorption of ketotifen following ophthalmic dosing is currently unknown. Please provide a commitment to perform a clinical study designed to measure the systemic absorption of ketotifen. The company provided the following commitment:

"CIBA Vision will perform a clinical study to determine the systemic absorption of ketotifen after dosing with ketotifen fumarate ophthalmic solution 0.025%. A final study report will be provided to the Division for this study during 4th Quarter 1999."

Reviewer Comment: Acceptable

Issue 2: The proposed labeling is not adequately supported by the application. Please submit revised labeling consistent with the attached draft package insert. The company-provided revised labeling making changes in the clinical pharmacology, pregnancy, adverse reactions, and storage sections of the package insert.

Reviewer Comment: The company commits to the package insert provided below. The company submits in writing a commitment to modify the established name on the carton and immediate label to be at least one half the size of the trade name and to be in a font of equal prominence. The acceptable draft package insert copied below responding to these revisions was sent via facsimile and hardcopy by the company on 7/1/99.

Issue Three: The submitted stability data does not currently support an 18 month expiration period.

Reviewer Comment: *CIBA Vision U.S. Ophthalmics submits a stability commitment as part of this amendment. See chemistry review.*

Issue Four: The stability protocol is not adequate.

Reviewer Comment: *The company agrees to the regulatory specifications submitted by the Chemistry division. See chemistry review.*

Issue Five: The submitted sample manufacturing batch record was incomplete.

Reviewer Comment: *The company agrees to submit in writing the batch records for the two most recent commercial lots including fill and package portions. See chemistry review.*

Issue Six: The proposal to use preservative effectiveness testing as a "fall-back" test in the event that the results of chemical testing fail to meet the acceptance criterion is not acceptable.

Reviewer Comment: *CIBA Vision withdrew the proposal in this amendment. See chemistry review.*

Issue Seven: The company lists the drug substance as a "white finely crystalline powder" in the label, but drug substance and drug product specifications list the drug substance and drug product solution as a variety of colors from white to yellowish to brownish. The label and the documentation of color should be consistent.

Reviewer Comment: *The company agrees to submit in writing a commitment to investigating the color change of the original drug substance and the discoloration of the drug product solution during stability. See chemistry review.*

APPEARS THIS WAY
ON ORIGINAL

3 ***pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.***

/S/

Jennifer A. Dunbar MD
Medical Officer, Ophthalmology

Cc: NDA 21-066
HFD-550
HFD-340
HFD-550/PM/Rodriguez
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Hughes
HFD-550/PHARM TL/Weir
HFD-550/PHARM/ZChen
HFD-550/MO/Dunbar
HFD-550/SMO/Chambers 7/2/99

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-066

NDA 21-066
Safety

Submission Date: 4/20/99
Receive Date: 5/05/99
Review Date: 05/30/99

Drug name:	Ketotifen fumarate ophthalmic solution, 0.025% topical
Generic name:	Ketotifen fumarate ophthalmic solution
Sponsor:	CIBA Vision – A Novartis Company 11450 Johns Creek Parkway Duluth, Georgia 30097
Pharmacologic Category:	anti-histamine
Proposed Indication(s):	For the prevention of itching of the eye due to allergic conjunctivitis
Submitted:	Four month safety update for report period 12/31/98 through 4/30/99.
Reviewer Comments:	No new issues identified not otherwise identified in label.

/S/

Jennifer A. Dunbar MD
Medical Officer, Ophthalmology

Cc: NDA 21-066
HFD-550
HFD-340
HFD-550/PM/Rodriguez
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Hughes
HFD-550/PHARM TL/Weir
HFD-550/PHARM/ZChen
HFD-550/MO/Dunbar
HFD-550/SMO/Chambers WAC 6/2/99

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 21-066

NDA 21-066	Submission Date:	5/14/99 5/17/99
Safety	Receive Date:	5/1799 5/18/99
	Review Date:	06/1/99

Drug name:	Ketotifen fumarate ophthalmic solution, 0.025% topical
Generic name:	Ketotifen fumarate ophthalmic solution
Sponsor:	CIBA Vision – A Novartis Company 11450 Johns Creek Parkway Duluth, Georgia 30097
Pharmacologic Category:	anti-histamine
Proposed Indication(s):	For the prevention of itching of the eye due to allergic conjunctivitis
Submitted:	Two Safety update supplements 5/14/99 (final clinical trial report for SH/DR 42000-97-2 Double-masked, Randomized, Parallel Group, Multi-center comparison of Ophthalmic ketotifen with its Vehicle and with Levocabastine in Patients Suffering from Seasonal Allergic Conjunctivitis) 5/17/99 (final clinical trial report for UK/DR 42000-98-4 Double Masked, Randomized, Four-Treatment, four-Period Cross-Over study to evaluate the Effect of ketotifen 0.1% and 0.25% Ophthalmic Solutions on Cognitive Performance in Healthy Subjects, Using a Positive and a Placebo Control.)

APPEARS THIS WAY
ON ORIGINAL

Reviewer Comments:

In the supplement dated 5/14/99, ocular adverse events >1% not previously identified in the label include abnormal vision (1.2-1.7%), conjunctivitis (0.6-1.2%), and eye pain (1.2-1.7%). Non-ocular adverse events >1% not previously identified in the label include allergic reactions (1.7-3.5%) and Rash (1.2-2.9%).

In the supplement dated 5/17/99, no additional safety concerns not otherwise specified in the label were identified.

/S/

Jennifer A. Dunbar MD
Medical Officer, Ophthalmology

Cc: NDA 21-066
HFD-550
HFD-340
HFD-550/PM/Rodriguez
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Hughes
HFD-550/PHARM TL/Weir
HFD-550/PHARM/ZChen
HFD-550/MO/Dunbar
HFD-550/SMO/Chambers WRC 6/2/99

APPEARS THIS WAY
ON ORIGINAL