

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **20-583**

MEDICAL REVIEW(S)

NOV 20 1995

Medical Officer's Review of NDA 20-583
Original

NDA #20-583
M.O. Review #1

Submission: 3/29/95
Review completed: 10/21/95
Revised date: 11/16/95

Generic name: Loteprednol Etabonate Ophthalmic Suspension, 0.5%
Proposed trade name: Lotemax
Chemical name: Chloromethyl-17 α -[(ethoxycarbonyl-oxy)-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 carboxylate

Sponsor: Pharmos Corporation
2 Innovation Drive
Suite A
Alachua, FL 32615

Pharmacologic Category: Steroid

Proposed Indication(s): Treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye.

Dosage Form and
Route of Administration: Ophthalmic suspension for topical ocular administration

NDA Drug Classification: 1S

Related INDs:

Related Reviews: Statistical Review dated: 6/29/95

NDA 20-583 Lotemax (loteprednol etabonate ophthalmic suspension)

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3 Material Reviewed Volumes 1.1, 1.20-40.

4 Chemistry/Manufacturing Controls

Raw Material	Quantity mg/mL	% label excess	Range
Loteprednol etabonate	5		
Povidone			
Benzalkonium Chloride,			
Edetate disodium			
Glycerin			
Tyloxapol			
Purified water	QS to 1 mL		
Sodium Hydroxide	Adjust pH		
Hydrochloric acid	Adjust pH		

Additional Specifications:

pH

Osmolality

Particle size

Sterility USP

Preservative efficacy USP

Reviewer's Comments: *The pH range is wider than necessary. It should be modified.*

Soft Contact Lens:

Reviewer's Comments: *Soft contact lenses usually absorb benzalkonium chloride. The extent of absorption of the drug product and benzalkonium chloride into contact lenses should be evaluated.*

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5 Animal Pharmacology/Toxicology

Wound Healing Effects:

In the rabbit eye model for wound healing, loteprednol etabonate (0.1%) did retard scar formation following a linear perforating corneal incision. The retardation was less marked than with dexamethasone sodium phosphate (0.1%).

Reviewer's Comments: *Delayed wound healing is common for all ocular steroids.*

6 Clinical Background

- | | | |
|-----|----------------------------------|---|
| 6.1 | Relevant <u>human</u> experience | No previous human experience. |
| 6.3 | Foreign experience | No foreign marketing experience. No pending foreign applications. |

6.4 Human Pharmacology, pharmacokinetics, pharmacodynamics

Loteprednol etabonate (LE) is a corticosteroid designed according to the "site active" concept (Bodor, 1984a, 1984b). Loteprednol etabonate was synthesized through structural modifications of prednisolone-related compounds such that it will undergo a transformation to an inactive metabolite. Although structurally similar to other corticosteroids, loteprednol etabonate does not have a ketone group at position 20 in the molecule. It has an ester function at this position which is hydrolyzed by tissue esterases to an inactive metabolite in a single step. This deactivation may occur when entering the systemic circulation or while penetrating ocular structures. Lower levels of loteprednol etabonate in the trabeculum are proposed to account for a potential lower propensity to elevate intraocular pressure (IOP).

In animals LE is predictably converted to Δ_1 cortienic acid etabonate (PJ-91).

Systemic Absorption from Ocular Dosing:

LE administered as eye drops 8 times daily for the first 2 days and then 4 times daily for the rest of the study. Blood samples were collected over the two hour periods following the 1st and 5th doses on Day 0 and then once on Days 7, 14, 21, 28, 28 and 35. On Day 42 blood samples were collected over the two hour period following dose 4. In all samples, both LE and PJ-91 were below the limits of quantitation.

Systemic Absorption from Single Oral Dose:

Six (6) normal, healthy adult male volunteers were enrolled and evaluated. Each subject was assigned to receive 40 mg (~0.5 mg/kg) of LE. The contents of eight bottles (5 mL per bottle) of unpreserved 0.1% sterile LE ophthalmic suspension were emptied into a cup containing approximately 10 mL of water. After stirring each mixture, they were presented to each study subject who drank the mixture. After the pre-treatment baseline sample, blood samples were obtained at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours after dosing. All subjects completed the study as planned. Both LE and PJ-91 (expected metabolite) were detected in the plasma at very low levels (0.5 ng/mL to 14 ng/mL). Analysis of the urine samples is currently in progress. Final results of this study are pending completion of the assays and analysis.

6.6 Proposed Directions for Use

One to two drops instilled into the conjunctival sac(s) four times daily. During the initial 24 to 48 hours the dosage may be safely increased to two drops every two hours. If no improvement after two weeks, consult physician. Care should be taken not to discontinue therapy prematurely.

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7 Description of Clinical Data Sources

Review Number	Protocol	Indication	Location	Design	Treatment Arms	Number in each arm	Age Range	% (d/9) B/W/O	Duration of treatment
1	107	Giant Papillary Conjunctivitis	US	Parallel Double masked	Loteprednol Vehicle	109 110	17-79	(25/75) 5/89/6	42 days
2	108	Giant Papillary Conjunctivitis	US	Parallel Double masked	Loteprednol Vehicle	111 109	18-70	(24/76) 5/85/10	42 days
3	121	Allergic Conjunctivitis	US	Parallel Double masked	Loteprednol Vehicle	145 143	18-87	(37/73) /245/44	42 days
4	122	Uveitis	US & UK	Parallel Double masked	Loteprednol Prednisolone	83 79	19-77	(52/48) 28/72/0	up to 42 days
5	106	Giant Papillary Conjunctivitis	US	Parallel Double masked	Loteprednol Vehicle	56 57	18-49	(39/61) 5/92/3	28 days
6	114	Seasonal Allergic Conjunctivitis	US	Parallel Double masked	Loteprednol Vehicle	4 5	19-50	(44/56) 0/100/0	42 days
7	103	Steroid Responders	US	Cross-over Double masked	Loteprednol Prednisolone	10 9			42 days

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NDA 20-583 Lotemax (loteprednol etabonate ophthalmic suspension)

8 Clinical Studies -

8.1 Indication # 1 Giant Papillary Conjunctivitis

8.1.1 Reviewer's Trial # 1 Sponsor's protocol # 107

Title: EFFICACY AND SAFETY EVALUATION OF LOTEPREDNOL ETABONATE IN GIANT PAPILLARY CONJUNCTIVITIS

Objective/Rationale

To evaluate the safety and effectiveness of loteprednol etabonate 0.5% ophthalmic suspension (LE) in reducing the ocular signs and symptoms accompanying contact lens-associated giant papillary conjunctivitis (GPC).

Design

A randomized, double-masked, placebo controlled, parallel group, multi-center comparison study.

Protocol

Test Drug Schedule:

Patients were randomly assigned to treatment with either loteprednol etabonate 0.5% ophthalmic suspension or the loteprednol etabonate vehicle (placebo) and instructed to instill one drop into each eye four times daily for six weeks. Follow-up examinations occurred on Days 2 or 3, 7, 14, 21, 28, 35 and 42 of masked therapy.

An off-therapy safety follow-up examination was conducted on Day 49.

Contact Lenses:

Concurrent lens wear was permitted for all patients. Instances where contact lenses which had been previously removed (i.e., overnight), patients were instructed to wait 10-15 minutes after instilling drops before re-inserting their lenses.

In addition, patients were asked to remove their lenses for the first 48 hours (or 72 hours) of the study while taking eye drops.

Valid Visits

Using the definition of a valid visit described below, the following were determined as invalid visits because they were outside the expected range:

Invalid Final Visits: # 247 and #272.

Invalid On-Study Visits: #450 (V7), and #641 (V5).

In the analysis by individual visit, some visits were included despite their occurring outside the visit schedule window in the protocol.

Visit Number	Scheduled Visit Window	Actual Visit Window	Ratio of patients outside window to total
2	Day 2 - 3	Day 1 - 5	16/217
3	Day 6 - 8	Day 4 - 12	27/197
4	Day 13 - 15	Day 12 - 19	26/198
5	Day 19 - 23	Day 18 - 25	9/187
6	Day 26 - 30	Day 25 - 32	12/198
7	Day 32 - 38	Day 32 - 39	4/198
8	Day 39 - 45	Day 39 - 50	8/199

Reviewer's Comments: *The "Actual Visit Windows" overlap and permit a single visit to be used for more than one visit. This is not acceptable.*

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Inclusion Criteria:

To be eligible for participation in the study, patients had to meet all of the following criteria before dosing:

- Age 18-55 years.
- Currently wearing contact lenses or discontinued wear within the past 48 hours.
- Clinical diagnosis of contact lens associated GPC, in one or both eyes.
- Active ocular signs and symptoms of GPC. Papillae at least 0.4 mm in diameter (i.e., grade 2 on the scale elaborated in section 4.6) in at least one eye. The superior palpebral conjunctiva - red and inflamed (i.e., have a "juicy-beefy" and opaque appearance). At least mild itching (grade 2) and partially controlled or worse (grade 2 or 3) lens intolerance in at least one eye.
- Willing to comply with the protocol instructions.
- The written informed consent obtained.
- Negative test to a blood or urine pregnancy test for women of childbearing potential only.

Exclusion Criteria:

Patients with any of the following conditions at the Enrollment Examination were to be excluded from the study

- Pregnant or lactating females.
- Females of childbearing potential using inadequate birth control methods (adequate birth control included the use of birth control pills, IUD, or diaphragm and foam).
- Previous allergy to prednisolone, LE or to any component of the study medications.
- Presence of any other ocular disease (corneal abrasion or erosion, infection, inflammation, glaucoma, dry eye, etc.) other than GPC.
- Concurrent use of any medication (steroids, non-steroidal anti-inflammatory agents, analgesics, mast cell stabilizers, immunosuppressive, anticholinergics, etc.) which may interfere with the evaluation of the patient's response to masked therapy in this study.
- Intraocular pressure > 21 mm Hg.
- Use of any ocular medication within the past 48 hours.
- Ocular surgery within the last six months.
- Best corrected distance visual acuity in either eye worse than or equal to 20/100.
- Participation by the patient in an investigational study under any other IND within the past 30 days.
- Unlikely to comply with the protocol instructions for whatever reason (confusion, infirmity, alcoholism, etc.).
- Previous treatment with loteprednol etabonate in this study.
- ~~Contact lenses that are poorly fitted or in poor condition such that the Investigator would consider it necessary to replace lenses.~~

The Sponsor reserved the right to declare a patient ineligible or unevaluable based on medical evidence that indicated the patient was unsuitable for the study.

Reviewer's Comments: *Acceptable.*

Study Schedule

	<u>Day</u>									
Procedure	0	2-3	7	14	21	28	35	42	49	
Informed Consent	x									
Inclusion/Exclusion	x									
Demographics, History	x									
Medication History	x									
Pregnancy Test ^a	x ^a							x ^a		
Dilated Funduscopy	x							x		
Intraocular Pressure	x	x	x	x	x	x	x	x	x	
Visual Acuity	x	x	x	x	x	x	x	x	x	
Ocular Symptoms	x	x	x	x	x	x	x	x	x	
Slit-Lamp Biomicroscopy	x	x	x	x	x	x	x	x	x	
Issue Medication	x	x ^b	x	x	x	x	x			
Discontinue Lens Wear	x									
Clinical Judgment		x	x	x	x	x	x	x		
Patient Opinion		x	x	x	x	x	x	x		
Resume Lens Wear		x	x	x	x	x	x	x	x	
Issue Patient Diary	x									
Review Patient Diary			x	x	x	x	x	x		
Exit Form									x	
Recover Medications								x		
Dismiss Patient									x	

^a Women of childbearing potential only.^b As needed

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Efficacy Criteria

Reductions in papillae (size and severity), lens intolerance and itching were the primary efficacy variables. Secondary efficacy variables were conjunctival injection (palpebral and bulbar) and global assessments (investigator and patient). Other signs and symptoms were erythema, discharge, foreign body sensation, photophobia, tearing and corneal disease. Most signs and symptoms were rated using a four point scale (0 - 3) where 0 = absent, 1 = mild, 2 = moderate and 3 = severe.

The global assessments (Physicians' clinical judgement and Patient's opinion of treatment) also used a 5 point scale (0-4) where 0=fully controlled, 1=reasonably controlled, 2=slight improvement, 3=unchanged and 4=worse.

Papillae (Primary Efficacy Variable)

Enlarged papillae are pathognomonic in contact-lens associated GPC. Papillae were graded on the following scale.

- 0 Smooth normal translucent appearance of superior conjunctiva of upper lid - papillae < 0.3 mm in diameter
- 1 Uniform "velvety" papillary appearance with 4-8 papillae per mm². Area surrounding papillae are opaque but not red or inflamed. Papillae should be >0.3 mm in diameter.
- 2 Non-uniform appearance with papillae covering the superior conjunctival surface. Papillae will range in size from 0.4 mm - 1.0 mm in diameter. Areas surrounding the papillae are red and opaque.
- 3 Non-uniform appearance with giant papillae scattered over the conjunctival surface. Papillae diameters are 1.0 mm or greater. Areas surrounding papillae are red and opaque.

For entry into the study, patients were required to have a minimum severity of 2 in the evaluated eye.

Lens Intolerance

- 0=Fully controlled Able to comfortably wear lenses longer than 6 hours.
- 1=Reasonably controlled Able to comfortably wear lenses longer than 3 hours but less than 6 hours.
- 2=Partially controlled Able to comfortably wear lenses longer than 45 minutes but less than 3 hours.
- 3=Uncontrolled Able to comfortably wear lenses for less than 45 minutes only.

Itching

- 0=absent No desire to scratch or rub eyelids
- 1=trace Rare need to scratch or rub eyelids but not completely absent
- 2=mild Occasional desire to rub or scratch eyelids
- 3=moderate Frequent desire to scratch or rub eyelids
- 4=severe Constant desire to scratch or rub eyelids

Discharge

- 0=Absent No discharge whatsoever
- 1=Mild Mucus or crustiness present, but in small amounts
- 2=Moderate Mucus present
- 3=Severe Large quantities of thick mucous strands

Photophobia

- 0=Absent Able to tolerate normal office light
- 1=Mild Mild discomfort in normal office light
- 2=Moderate Able to tolerate normal office light only with sunglasses
- 3=Severe Unable to tolerate normal office light even with sunglasses

Investigators:

John Alpar, M.D.	Amarillo, TX	(Investigator #141)
Gregg Berdy, M.D.	St. Louis, MO	(Investigator #130)
John Cooksey, M.D.	Monroe, LA	(Investigator #142)
Larry Davis, M.D.	St. Louis, MO	(Investigator #135)
Warren Fagadau, M.D.	Dallas, TX	(Investigator #143)
Lance Forstot, M.D.	Littleton, CO	(Investigator #140)
*Kenneth Fox, M.D.	McLean, VA	(Investigator #151)
*Mitchell Friedlaender, M.D.	La Jolla, CA	(Investigator #124)
Miles Friedlander, M.D.	New Orleans, LA	(Investigator #147)
N. Rex Ghormley, O.D.	St. Louis, MO	(Investigator #127)
Kristine Kunesh-Part, M.D.	Dayton, OH	(Investigator #161)
Robert Laibovitz, M.D.	Austin, TX	(Investigator #112)
Jerrold Levin, M.D.	Cincinnati, OH	(Investigator #158)
Monica L. Monica, M.D., Ph.D.	Metairie, LA	(Investigator #148)
James Pickett, M.D.	San Marcos, TX	(Investigator #145)
Jack Pierce, M.D.	Austin, TX	(Investigator #146)
John Sheets, M.D.	Odessa, TX	(Investigator #144)

Reviewer's Comments: *Kenneth Fox and Mitchell Friedlander where also investigators in Study #2 (Sponsor protocol 108).*

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			***** REASON STUDY INCOMPLETE *****						
INVESTIGATOR	TREATMENT	RANDOMIZED	COMPLETED TREATMENT	COMPLETED STUDY	LACK OF EFFICACY	ADVERSE EVENTS	OTHER UNRELATED	NO SAFETY FOLLOW-UP	EVALUABLE *****
112	LOTEPREDNOL	10	9 (90%)	8 (80%)	1 (10%)	0 (0%)	0 (0%)	1 (10%)	10
	PLACEBO	10	10 (100%)	10 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10
124	LOTEPREDNOL	12	11 (92%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	11 (92%)	12
	PLACEBO	12	8 (67%)	0 (0%)	1 (8%)	0 (0%)	3 (25%)	8 (67%)	11
127	LOTEPREDNOL	22	19 (86%)	18 (82%)	0 (0%)	3 (14%)	0 (0%)	1 (5%)	22
	PLACEBO	23	21 (91%)	20 (87%)	0 (0%)	1 (4%)	1 (4%)	1 (4%)	23
130	LOTEPREDNOL	8	7 (88%)	7 (88%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	8
	PLACEBO	8	8 (100%)	8 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8
140	LOTEPREDNOL	2	2 (100%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2
	PLACEBO	3	3 (100%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3
141	LOTEPREDNOL	7	7 (100%)	7 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7
	PLACEBO	7	6 (86%)	6 (86%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	7
142	LOTEPREDNOL	8	7 (88%)	7 (88%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)	7
	PLACEBO	7	7 (100%)	7 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7
143	LOTEPREDNOL	2	2 (100%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2
	PLACEBO	1	1 (100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
145	LOTEPREDNOL	4	3 (75%)	3 (75%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	4
	PLACEBO	4	4 (100%)	2 (50%)	0 (0%)	0 (0%)	0 (0%)	2 (50%)	4
146	LOTEPREDNOL	7	7 (100%)	6 (86%)	0 (0%)	0 (0%)	0 (0%)	1 (14%)	7
	PLACEBO	7	7 (100%)	7 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7
147	LOTEPREDNOL	10	9 (90%)	9 (90%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	10
	PLACEBO	11	10 (91%)	9 (82%)	0 (0%)	0 (0%)	1 (9%)	1 (9%)	10
148	LOTEPREDNOL	12	11 (92%)	10 (83%)	0 (0%)	0 (0%)	1 (8%)	1 (8%)	12
	PLACEBO	12	12 (100%)	11 (92%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	12
151	LOTEPREDNOL	6	6 (100%)	6 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6
	PLACEBO	7	5 (71%)	5 (71%)	0 (0%)	0 (0%)	2 (29%)	0 (0%)	6
161	LOTEPREDNOL	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
	PLACEBO	1	1 (100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
OVERALL	LOTEPREDNOL	110	100 (91%)	85 (77%)	1 (1%)	4 (4%)	5 (5%)	15 (14%)	109
	PLACEBO	113	103 (91%)	90 (80%)	2 (2%)	1 (1%)	7 (6%)	13 (12%)	110

Reviewer's Comments: *Investigator number 127 had twice as many subjects enrolled as any other investigator.*

Results

		LOTEPREDNOL	PLACEBO	p VALUE
AGE (yrs)				
=====				
	N	109	110	
	MEAN	33.4	31.8	p = 0.312
	SE	1.1	0.8	
	MIN	17.0	17.0	
	MAX	79.0	56.0	
	< 30 yrs	44%	43%	p = 0.838
	> = 30 yrs	56%	57%	

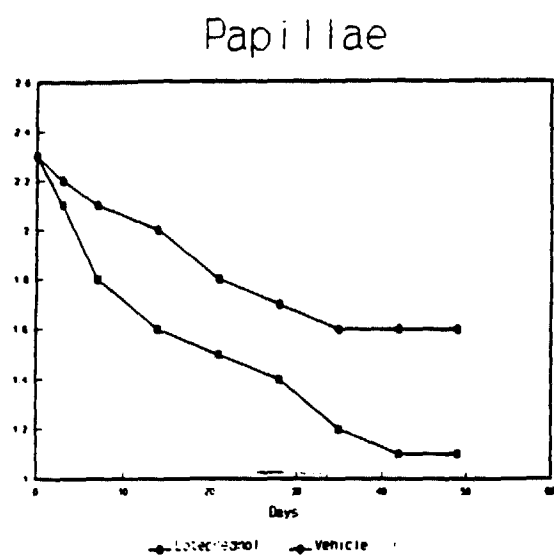
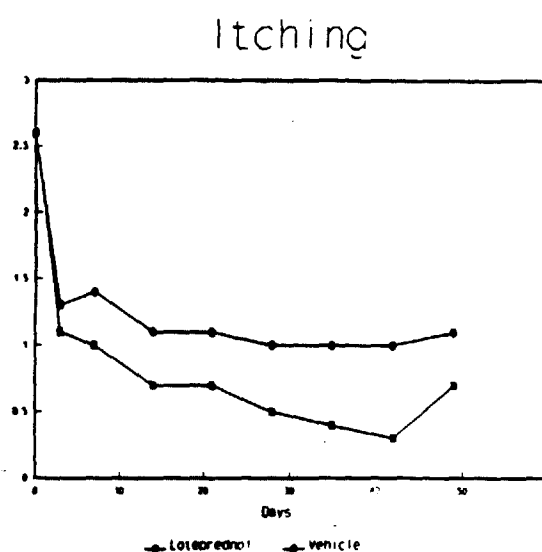
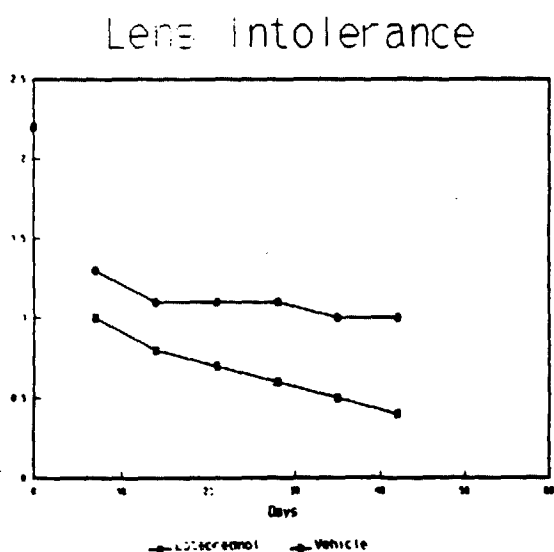
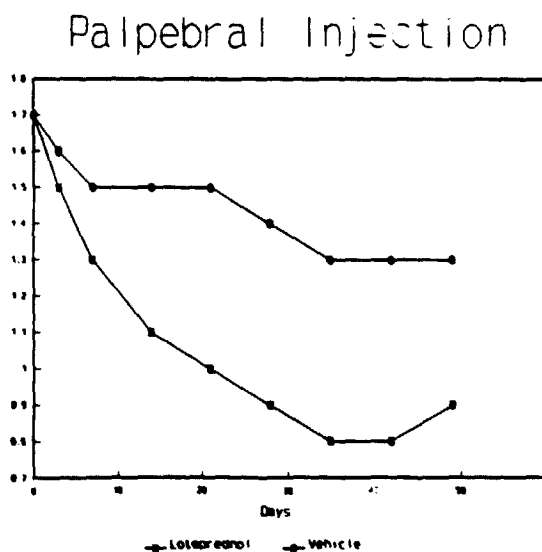
GENDER				
=====				
MALE	N	23	31	p = 0.228
FEMALE	N	86	79	

RACE				
=====				
CAUCASIAN	N	98	97	p = 0.655
BLACK	N	4	7	
ASIAN	N	1	1	
HISPANIC	N	5	3	
INDIAN	N	1	1	
PHILIPINO	N	0	1	

IRIS PIGMENTATION				
=====				
LIGHT	N	64	62	p = 0.711
DARK	N	45	48	

Reviewer's Comments: *There were no significant differences between groups.*

Mean Scores



Reviewer's Comments:

All evaluations favor loteprednol over vehicle. The differences from baseline are statistically different between groups although the mean scores are not statistically significantly different between groups (see following tables).

Efficacy endpoint outcomes **Papillae**

FREQUENCY DISTRIBUTION OF OBSERVED RATINGS

	VISIT 1 DAY 0	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL (ON MED)	SAFETY FU (OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 = <.3 mm	0 0%	0 0%	1 1%	7 7%	7 8%	11 11%	19 20%	21 21%	21 19%	19 22%
1 = .3-.4mm	0 0%	13 12%	28 28%	32 33%	38 42%	48 48%	46 48%	51 52%	54 50%	44 51%
2 = .4-1.1mm	73 67%	72 67%	59 58%	51 53%	36 40%	36 36%	25 26%	22 22%	28 26%	18 21%
3 = >1mm	36 33%	23 21%	13 13%	7 7%	10 11%	5 5%	6 6%	5 5%	6 6%	6 7%
NO	109	108	101	97	91	100	96	99	109	87
MEAN	2.3	2.1	1.8	1.6	1.5	1.4	1.2	1.1	1.2	1.1
SE	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 = <.3 mm	0 0%	0 0%	0 0%	1 1%	2 2%	2 2%	5 5%	8 8%	9 8%	6 6%
1 = .3-.4mm	0 0%	7 6%	11 11%	20 20%	28 29%	36 37%	37 36%	36 36%	36 33%	32 34%
2 = .4-1.1mm	79 72%	77 71%	68 71%	61 60%	51 53%	47 48%	49 48%	48 48%	54 49%	46 49%
3 = >1mm	31 28%	25 23%	17 18%	19 19%	15 16%	13 13%	11 11%	8 8%	11 10%	9 10%
NO	110	109	96	101	96	98	102	100	110	93
MEAN	2.3	2.2	2.1	2.0	1.8	1.7	1.6	1.6	1.6	1.6
SE	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
HO:LE=PLC	p=0.389									

FREQUENCY DISTRIBUTION OF CHANGE FROM BASELINE RATINGS

	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL (ON MED)	SAFETY FU (OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1	2 2%	1 1%	0 0%	1 1%	0 0%	1 1%	1 1%	1 1%	1 1%
0 NO CHANGE	83 77%	58 57%	45 46%	34 37%	27 27%	22 23%	16 16%	23 21%	15 17%
-1	18 17%	31 31%	36 37%	37 41%	50 50%	42 44%	48 48%	51 47%	42 48%
-2	5 5%	11 11%	14 14%	19 21%	21 21%	24 25%	26 26%	25 24%	21 24%
<-2 BETTER	0 0%	0 0%	2 2%	0 0%	2 2%	7 7%	8 8%	9 7%	8 9%
NO	108	101	97	91	100	96	99	109	87
MEAN	-0.2	-0.5	-0.7	-0.8	-1.0	-1.1	-1.2	-1.2	-1.2
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1	0 0%	3 3%	4 4%	2 2%	3 3%	2 2%	1 1%	2 2%	0 0%
0 NO CHANGE	96 88%	71 74%	68 67%	57 59%	49 50%	48 47%	44 44%	52 47%	45 48%
-1	13 12%	20 21%	22 22%	27 28%	34 35%	40 39%	39 39%	39 35%	35 38%
-2	0 0%	2 2%	6 6%	9 9%	11 11%	9 9%	14 14%	14 13%	10 11%
<-2 BETTER	0 0%	0 0%	1 1%	1 1%	1 1%	3 3%	2 2%	3 3%	3 3%
NO	109	96	101	96	98	102	100	110	93
MEAN	-0.1	-0.2	-0.3	-0.5	-0.6	-0.6	-0.7	-0.7	-0.7
SE	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
HO:LE=PLC	p=0.313	p=0.005	p<0.001	p=0.005	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

VISIT BEGINNING SUSTAINED RESPONSE

	N	N	N	N	N	N	N
LOTEPREDNOL	19	16	15	5	14	5	11
PLACEBO	8	9	9	8	10	4	8
HO:LE=PLC	p<0.001						

Itching

FREQUENCY DISTRIBUTION OF OBSERVED RATINGS

	VISIT 1 DAY 0	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	VISIT (ON MED)	SAFETY FU (OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 - ABSENT	0 0%	35 32%	37 37%	49 51%	49 54%	68 68%	68 71%	71 72%	76 70%	54 62%
1 - TRACE	0 0%	33 31%	29 29%	31 32%	30 33%	21 21%	19 20%	22 22%	25 23%	15 17%
2 - MILD	55 50%	31 29%	28 28%	12 12%	7 8%	8 8%	5 5%	6 6%	8 7%	9 10%
3 - MODERATE	45 41%	8 7%	7 7%	5 5%	4 4%	3 3%	3 3%	0 0%	0 0%	6 7%
4 - SEVERE	9 8%	1 1%	0 0%	0 0%	1 1%	0 0%	1 1%	0 0%	0 0%	3 3%
NO	109	108	101	97	91	100	96	99	109	87
MEAN	2.6	1.1	1.0	0.7	0.7	0.5	0.4	0.3	0.4	0.7
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 - ABSENT	0 0%	34 31%	29 30%	39 39%	37 39%	39 40%	44 43%	44 44%	48 44%	39 42%
1 - TRACE	0 0%	27 25%	23 24%	26 26%	24 25%	31 32%	29 28%	26 26%	28 25%	23 25%
2 - MILD	58 53%	35 32%	26 27%	24 24%	21 22%	17 17%	18 18%	19 19%	20 18%	19 20%
3 - MODERATE	41 37%	11 10%	15 16%	10 10%	12 13%	8 8%	9 9%	9 9%	10 9%	7 8%
4 - SEVERE	11 10%	2 2%	3 3%	2 2%	2 2%	3 3%	2 2%	2 2%	4 4%	5 5%
NO	110	109	96	101	96	98	102	100	110	93
MEAN	2.6	1.3	1.4	1.1	1.1	1.0	1.0	1.0	1.0	1.1
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

HO:LE=PLC p=0.482

FREQUENCY DISTRIBUTION OF CHANGE FROM BASELINE RATINGS

	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	VISIT (ON MED)	SAFETY FU (OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1	1 1%	2 2%	3 3%	4 4%	1 1%	3 3%	0 0%	0 0%	2 2%
0 NO CHANGE	28 26%	20 20%	8 8%	6 7%	5 5%	4 4%	5 5%	5 5%	11 13%
-1	25 23%	22 22%	22 23%	14 15%	16 16%	11 11%	13 13%	16 15%	13 15%
-2	35 32%	39 39%	38 39%	39 43%	45 45%	43 45%	42 42%	47 43%	37 43%
<-2 BETTER	19 18%	18 18%	26 27%	28 31%	33 33%	35 36%	39 39%	41 38%	24 28%
NO	108	101	97	91	100	96	99	109	87
MEAN	-1.4	-1.5	-1.8	-1.9	-2.1	-2.1	-2.2	-2.2	-1.8
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	1 1%
1	2 2%	4 4%	4 4%	3 3%	4 4%	4 4%	4 4%	7 6%	6 6%
0 NO CHANGE	34 31%	27 28%	19 19%	18 19%	13 13%	16 16%	13 13%	14 13%	11 12%
-1	29 27%	25 26%	28 28%	26 27%	27 28%	25 25%	23 23%	24 22%	27 29%
-2	23 21%	27 28%	32 32%	36 38%	34 35%	37 36%	44 44%	47 43%	32 34%
<-2 BETTER	21 19%	13 14%	18 18%	13 14%	20 20%	20 20%	16 16%	18 16%	16 17%
NO	109	96	101	96	98	102	100	110	93
MEAN	-1.3	-1.2	-1.5	-1.4	-1.6	-1.6	-1.6	-1.5	-1.4
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

HO:LE=PLC p=0.001 p=0.550 p=0.105 p=0.126 p=0.001 p=0.001 p=0.001 p<0.001 p<0.001 p=0.044

VISIT BEGINNING
SUSTAINED RESPONSE

	N	N	N	N	N	N	N
LOTEPREDNOL	61	12	14	5	6	2	4
PLACEBO	52	10	6	7	4	4	6

HO:LE=PLC p=0.007

Lens Intolerance

FREQUENCY DISTRIBUTION OF OBSERVED RATINGS

	DAY 0	WEEK 1 DAY 7	WEEK 2 DAY 14	WEEK 3 DAY 21	WEEK 4 DAY 28	WEEK 5 DAY 35	WEEK 6 DAY 42	FINAL (ON MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %
0 - FULL CONTROL	0 0%	35 35%	47 45%	48 48%	57 58%	58 60%	63 65%	65 60%
1 - REASONABLE	0 0%	32 32%	31 30%	39 39%	31 31%	31 32%	27 28%	28 26%
2 - PARTIAL CONTROL	83 76%	27 27%	22 21%	11 11%	9 9%	7 7%	5 5%	11 10%
3 - UNCONTROLLED	26 24%	6 6%	4 4%	2 2%	2 2%	1 1%	2 2%	5 5%
NO	109	100	104	100	99	97	97	109
MEAN	2.2	1.0	0.8	0.7	0.6	0.5	0.4	0.6
SE	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %
0 - FULL CONTROL	0 0%	27 26%	34 31%	34 32%	36 34%	39 39%	38 38%	40 36%
1 - REASONABLE	0 0%	30 29%	34 31%	35 33%	34 32%	32 32%	35 35%	39 35%
2 - PARTIAL CONTROL	88 80%	36 35%	31 29%	29 28%	26 25%	21 21%	19 19%	22 20%
3 - UNCONTROLLED	22 20%	11 11%	9 8%	7 7%	9 9%	8 8%	8 8%	9 8%
NO	110	104	108	105	105	100	100	110
MEAN	2.2	1.3	1.1	1.1	1.1	1.0	1.0	1.0
SE	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1

H0:LE=PLC p=0.446

FREQUENCY DISTRIBUTION OF CHANGE FROM BASELINE RATINGS

	WEEK 1 DAY 7	WEEK 2 DAY 14	WEEK 3 DAY 21	WEEK 4 DAY 28	WEEK 5 DAY 35	WEEK 6 DAY 42	FINAL WEEK (ON MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %
2 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1	3 3%	1 1%	1 1%	1 1%	0 0%	1 1%	2 2%
0 NO CHANGE	24 24%	22 21%	9 9%	8 8%	6 6%	5 5%	12 11%
-1	31 31%	28 27%	36 36%	27 27%	28 29%	24 25%	26 24%
-2	35 35%	41 39%	41 41%	49 49%	49 51%	50 52%	52 48%
-3 BETTER	7 7%	12 12%	13 13%	14 14%	14 14%	17 18%	17 16%
NO	100	104	100	99	97	97	109
MEAN	-1.2	-1.4	-1.6	-1.7	-1.7	-1.8	-1.6
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %
2 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1	6 6%	4 4%	3 3%	4 4%	5 5%	4 4%	4 4%
0 NO CHANGE	34 33%	29 27%	24 23%	25 24%	18 18%	17 17%	21 19%
-1	31 30%	36 33%	40 38%	35 33%	32 32%	36 36%	40 36%
-2	30 29%	34 31%	33 31%	35 33%	40 40%	37 37%	39 35%
-3 BETTER	3 3%	5 5%	5 5%	6 6%	5 5%	6 6%	6 5%
NO	104	108	105	105	100	100	110
MEAN	-0.9	-1.1	-1.1	-1.1	-1.2	-1.2	-1.2
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1
H0:LE=PLC	p=0.546	p=0.385	p=0.091	p=0.001	p=0.001	p=0.001	p=0.006

WEEK BEGINNING SUSTAINED RESPONSE	N	N	N	N	N	N
LOTEPREDNOL	61	15	12	1	3	3
PLACEBO	53	13	3	4	6	6

H0:LE=PLC p=0.004

Palpebral injection

- FREQUENCY DISTRIBUTION OF OBSERVED RATINGS

	VISIT 1 DAY 0	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL (ON MED)	SAFETY FU (OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 - ABSENT	0 0%	4 4%	7 8%	13 15%	16 20%	20 22%	29 35%	30 34%	31 32%	25 33%
1 - MILD	38 40%	48 51%	50 56%	54 63%	49 60%	60 67%	44 52%	47 53%	54 56%	39 51%
2 - MODERATE	47 49%	36 38%	30 34%	17 20%	14 17%	8 9%	9 11%	9 10%	9 9%	8 11%
3 - SEVERE	11 11%	7 7%	2 2%	2 2%	2 2%	1 1%	2 2%	2 2%	2 2%	4 5%
NO MEAN SE	96 1.7 0.1	95 1.5 0.1	89 1.3 0.1	86 1.1 0.1	81 1.0 0.1	89 0.9 0.1	84 0.8 0.1	88 0.8 0.1	96 0.8 0.1	76 0.9 0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 - ABSENT	0 0%	5 5%	7 8%	7 8%	6 7%	6 7%	9 10%	10 11%	10 10%	8 10%
1 - MILD	42 43%	38 40%	37 43%	40 45%	42 50%	47 53%	50 56%	50 57%	52 54%	46 58%
2 - MODERATE	45 46%	45 47%	38 44%	34 39%	28 33%	31 35%	24 27%	24 27%	29 30%	22 28%
3 - SEVERE	10 10%	8 8%	4 5%	7 8%	8 10%	5 6%	6 7%	4 5%	6 6%	4 5%
NO MEAN SE	97 1.7 0.1	96 1.6 0.1	86 1.5 0.1	88 1.5 0.1	84 1.5 0.1	89 1.4 0.1	89 1.3 0.1	88 1.3 0.1	97 1.3 0.1	80 1.3 0.1

HO:LE=PLC p=0.974

FREQUENCY DISTRIBUTION OF CHANGE FROM BASELINE RATINGS

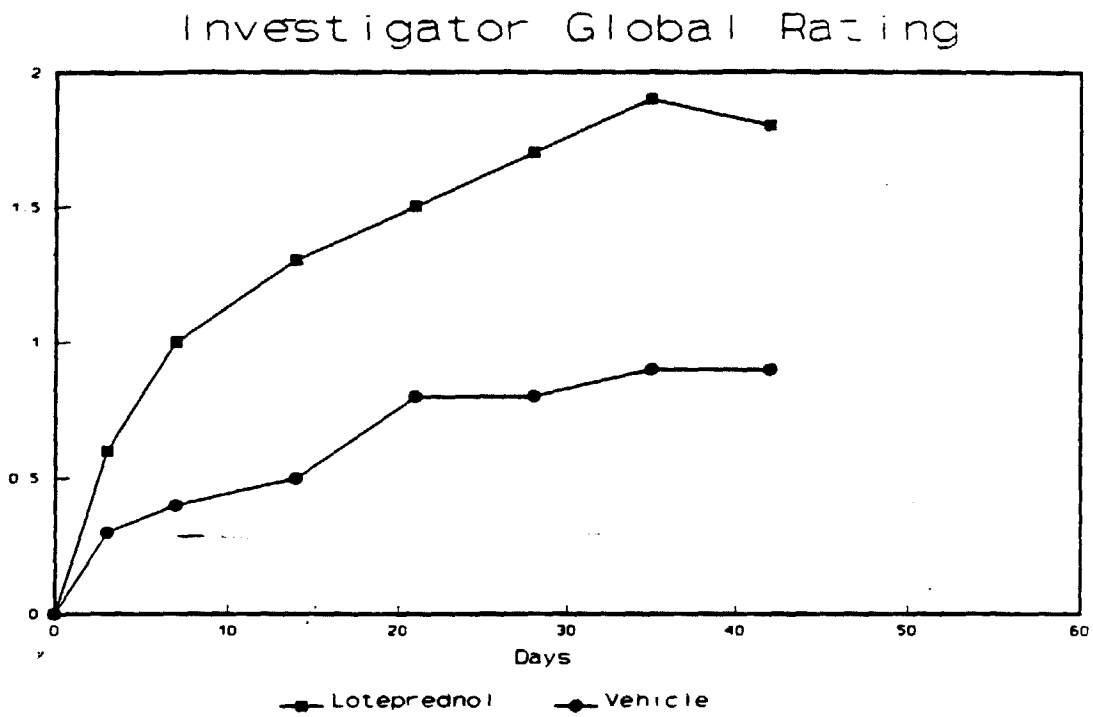
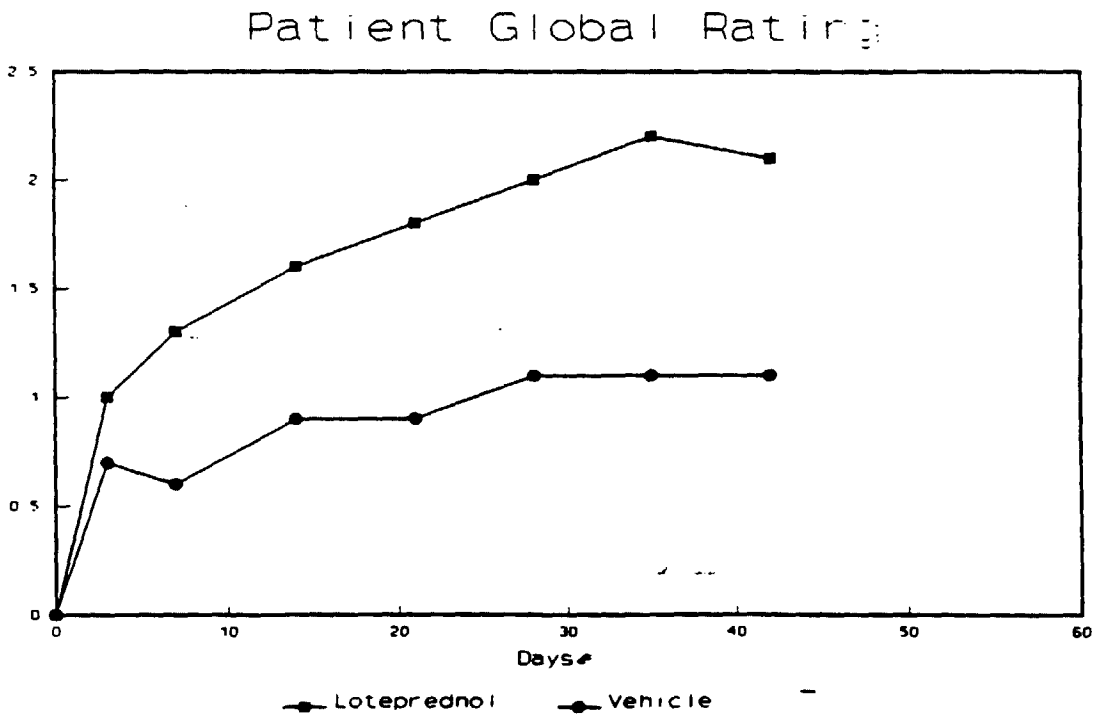
	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL VISIT (ON MED)	VISIT 9 SAFETY FU (OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1	5 5%	3 3%	1 1%	4 5%	1 1%	3 4%	4 5%	4 4%	3 4%
0 NO CHANGE	70 74%	55 62%	43 50%	28 35%	31 35%	25 30%	27 31%	30 31%	26 34%
-1	13 14%	22 25%	31 36%	36 44%	39 44%	33 39%	32 36%	37 39%	29 38%
-2	6 6%	8 9%	10 12%	12 15%	17 19%	21 25%	21 24%	21 22%	14 18%
<-2 BETTER	1 1%	1 1%	1 1%	1 1%	1 1%	2 2%	4 5%	4 4%	4 5%
NO MEAN SE	95 -0.2 0.1	89 -0.4 0.1	86 -0.6 0.1	81 -0.7 0.1	89 -0.8 0.1	84 -0.9 0.1	88 -0.9 0.1	96 -0.9 0.1	76 -0.9 0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	1 1%	2 2%	2 2%	0 0%	1 1%	1 1%	1 1%	2 3%
1	7 7%	6 7%	7 8%	8 10%	9 10%	11 12%	9 10%	11 11%	5 6%
0 NO CHANGE	74 77%	56 65%	53 60%	45 54%	49 55%	38 43%	40 45%	46 47%	37 46%
-1	14 15%	19 22%	23 26%	25 30%	27 30%	35 39%	30 34%	31 32%	32 40%
-2	1 1%	4 5%	3 3%	4 5%	4 4%	4 4%	8 9%	8 8%	3 4%
<-2 BETTER	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	1 1%
NO MEAN SE	96 -0.1 0.1	86 -0.2 0.1	88 -0.2 0.1	84 -0.3 0.1	89 -0.3 0.1	89 -0.3 0.1	88 -0.4 0.1	97 -0.4 0.1	80 -0.4 0.1

HO:LE=PLC p=0.637 p=0.578 p=0.015 p=0.004 p=0.001 p=0.001 p=0.001 p<0.001 p<0.001

VISIT BEGINNING
SUSTAINED RESPONSE

LOTEPREDNOL	N	N	N	N	N	N	N
PLACEBO	16	9	19	8	4	3	3
	8	7	3	6	3	8	4

HO:LE=PLC p<0.001



NDA 20-583 Lotemax (loteprednol etabonate ophthalmic suspension)

Investigator global rating:

FREQUENCY DISTRIBUTION OF GLOBAL ASSESSMENTS

	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL VISIT (ON MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %
1:WORSE	0 0%	1 1%	0 0%	1 1%	1 1%	1 1%	0 0%	0 0%
0:UNCHANGED	66 61%	33 33%	24 25%	13 14%	13 13%	8 8%	14 14%	19 17%
-1:SLIGHT IMPROVEMENT	24 22%	42 42%	34 35%	36 40%	27 27%	20 21%	16 16%	19 17%
-2:REASONABLE CONTROL	13 12%	15 15%	23 24%	24 26%	38 38%	41 43%	45 45%	45 41%
-3:CONTROLLED	5 5%	10 10%	16 16%	17 19%	21 21%	26 27%	24 24%	26 24%
NO	108	101	97	91	100	96	99	109
MEAN	-0.6	-1.0	-1.3	-1.5	-1.7	-1.9	-1.8	-1.7
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %
1:WORSE	1 1%	6 6%	7 7%	4 4%	6 6%	4 4%	3 3%	6 5%
0:UNCHANGED	79 72%	57 59%	54 53%	45 47%	41 42%	40 39%	39 39%	41 37%
-1:SLIGHT IMPROVEMENT	22 20%	24 25%	25 25%	24 25%	29 30%	29 28%	29 29%	33 30%
-2:REASONABLE CONTROL	7 6%	8 8%	10 10%	15 16%	13 13%	18 18%	19 19%	19 17%
-3:CONTROLLED	0 0%	1 1%	5 5%	8 8%	9 9%	11 11%	10 10%	11 10%
NO	109	96	101	96	98	102	100	110
MEAN	-0.3	-0.4	-0.5	-0.8	-0.8	-0.9	-0.9	-0.9
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
H0:LE=PLC	p=0.032	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

VISIT BEGINNING
SUSTAINED RESPONSE

	N	N	N	N	N	N	N
LOTEPREDNOL	30	25	12	11	6	3	3
PLACEBO	11	9	6	7	13	6	11

H0:LE=PLC p<0.001

THE SCALE AS RECORDED IN THE CASE REPORT FORM RANGED FROM 0=FULLY CONTROLLED TO 4=WORSE. THE SCALE WAS TRANSFORMED BY SUBTRACTING 3 FROM EACH RATING SO THAT CHANGE FROM BASELINE WAS MORE CONSISTENT WITH THE OTHER SCALES--I.E., -3 TO -1 = DECREASING LEVELS OF IMPROVEMENT. 0=UNCHANGED AND 1=WORSE.

APPEARS THIS WAY
ON ORIGINAL

Patient global rating

FREQUENCY DISTRIBUTION OF GLOBAL ASSESSMENTS

	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	VISIT (ON MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %
1: WORSE	0 0%	5 5%	2 2%	2 2%	0 0%	1 1%	1 1%	2 2%
0: UNCHANGED	42 39%	20 20%	17 18%	13 14%	13 13%	8 8%	12 12%	16 15%
-1: SLIGHT IMPROVEMENT	36 33%	31 31%	24 25%	16 18%	15 15%	11 11%	7 7%	9 8%
-2: REASONABLE CONTROL	22 20%	26 26%	32 33%	30 33%	28 28%	30 31%	34 34%	35 32%
-3: CONTROLLED	8 7%	19 19%	22 23%	30 33%	44 44%	46 48%	45 45%	47 43%
NO	108	101	97	91	100	96	99	109
MEAN	-1.0	-1.3	-1.6	-1.8	-2.0	-2.2	-2.1	-2.0
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %
1: WORSE	2 2%	13 14%	7 7%	7 7%	7 7%	4 4%	5 5%	8 7%
0: UNCHANGED	58 53%	35 36%	31 31%	30 31%	27 28%	35 34%	33 33%	35 32%
-1: SLIGHT IMPROVEMENT	30 28%	30 31%	38 38%	29 30%	29 30%	23 23%	22 22%	25 23%
-2: REASONABLE CONTROL	14 13%	14 15%	17 17%	21 22%	21 21%	27 26%	27 27%	27 25%
-3: CONTROLLED	5 5%	4 4%	8 8%	9 9%	14 14%	13 13%	13 13%	15 14%
NO	109	96	101	96	98	102	100	110
MEAN	-0.7	-0.6	-0.9	-0.9	-1.1	-1.1	-1.1	-1.1
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
H0: LE=PLC	p=0.018	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

VISIT BEGINNING
SUSTAINED RESPONSE

	N	N	N	N	N	N	N
LOTEPREDNOL	43	18	11	7	6	2	4
PLACEBO	15	10	13	4	7	10	8

H0: LE=PLC p<0.001

THE SCALE AS RECORDED IN THE CASE REPORT FORM RANGED FROM 0=FULLY CONTROLLED TO 4=WORSE. THE SCALE WAS TRANSFORMED BY SUBTRACTING 3 FROM EACH RATING SO THAT CHANGE FROM BASELINE WAS MORE CONSISTENT WITH THE OTHER SCALES--I.E., -3 TO -1 = DECREASING LEVELS OF IMPROVEMENT, 0=UNCHANGED AND 1=WORSE.

APPEARS THIS WAY
ON ORIGINAL

Other variables

FINAL VISIT RESPONSE RATE (improvement of at least 1 unit)

VARIABLE	LE GROUP		PLACEBO GROUP		p-VALUE
	N	%	N	%	
ERYTHEMA	29	83	24	73	0.318
DISCHARGE	32	91	28	72	0.032
FOREIGN BODY SENSATION	80	87	59	63	< 0.001
TEARING	55	92	36	65	0.001
PHOTOPHOBIA	36	82	33	60	0.020

AREA UNDER THE CURVE

VARIABLE	LE GROUP		PLACEBO GROUP		p VALUE
	N	%	N	%	
ERYTHEMA	35	-28.6	33	-22.8	0.042
DISCHARGE	35	-45.4	39	-26.7	0.002
FOREIGN BODY SENSATION	92	-56.0	94	-35.1	0.005
TEARING	60	-42.9	55	-31.1	0.004
PHOTOPHOBIA	44	-46.8	55	-33.3	0.342

APPEARS THIS WAY
ON ORIGINAL

IOP Responses:

<u>Baseline</u>	<u>N (Patients)</u>	<u>Mean</u>	<u>S.E.</u>
LE	110	14.6	0.3
PLACEBO	113	15.1	0.3
P = 0.125			

<u>Armaly (≥ 6 mm Hg)</u>	<u>N (Eyes)</u>	<u>Each Visit</u>	<u>Any Visit</u>
LE	109	3% - 14%	25%
PLACEBO	110	1% - 5%	10%
p = 0.004			

<u>Becker (≥ 20 mm Hg)</u>	<u>N (Eyes)</u>	<u>Each Visit</u>
LE	211	4% - 12%
PLACEBO	213	1% - 7%

<u>Stewart (≥ 10 mm Hg)</u>	<u>N (Eyes)</u>	<u>Each Visit</u>	<u>Any Visit</u>
LE	109	1 - 4%	7%
PLACEBO	110	0%	0%
p = 0.004			

<u>Mean Changes</u>	<u>N (Eyes)</u>	<u>Each Visit</u>	
LE	111	+0.3 to +1.1	p < 0.001 to 0.024
PLACEBO	109	-0.4 to -0.8	

Reviewer's Comments: *Regardless of the method used to evaluate an IOP response, loteprednol had more responders. This is a significant safety issue for this indication.*

IOP

FREQUENCY DISTRIBUTION OF OBSERVED RATINGS (INDIVIDUAL EYES)

	VISIT 1 DAY 0	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL VISIT	VISIT 9 SAFETY FU
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
<20 mmHg	211 96%	208 96%	189 94%	186 96%	174 94%	176 88%	177 92%	175 88%	187 85%	164 95%
20-25 mmHg	9 4%	8 4%	12 6%	6 3%	12 6%	22 11%	15 8%	22 11%	28 13%	8 5%
26-31 mmHg	0 0%	0 0%	1 0%	0 0%	0 0%	2 1%	0 0%	1 1%	3 1%	0 0%
>31 mmHg	0 0%	0 0%	0 0%	2 1%	0 0%	0 0%	0 0%	0 0%	2 1%	0 0%
NO	110	108	101	97	93	100	96	99	110	86
MEAN	14.6	14.9	15.1	15.3	15.2	15.6	15.4	15.7	16.0	14.4
SE	0.3	0.3	0.3	0.4	0.3	0.3	0.3	0.3	0.4	0.3
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
<20 mmHg	213 94%	210 96%	188 99%	193 96%	179 93%	191 97%	200 97%	187 94%	214 95%	183 98%
20-25 mmHg	13 6%	8 4%	2 1%	9 4%	13 7%	5 3%	6 3%	11 6%	12 5%	3 2%
26-31 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
>31 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
NO	113	109	95	101	96	98	103	99	113	93
MEAN	15.1	14.4	14.5	14.4	14.5	14.3	14.5	14.4	14.5	14.0
SE	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
HO: LE=PLC	p=0.125									

FREQUENCY DISTRIBUTION OF CHANGE FROM BASELINE RATINGS (INDIVIDUAL EYES)

	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL VISIT	VISIT 9 SAFETY FU
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %
<6 mmHg	212 98%	191 95%	184 95%	172 92%	183 92%	181 94%	177 89%	192 87%	165 96%
6-9 mmHg	3 1%	9 4%	8 4%	11 6%	11 6%	10 5%	18 9%	21 10%	7 4%
10-15 mmHg	1 0%	2 1%	0 0%	3 2%	6 3%	1 1%	3 2%	5 2%	0 0%
>15 mmHg	0 0%	0 0%	2 1%	0 0%	0 0%	0 0%	0 0%	2 1%	0 0%
NO	108	101	97	93	100	96	99	110	86
MEAN	0.3	0.8	0.7	0.7	1.0	0.8	1.1	1.4	0.0
SE	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.4	0.3
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %
<6 mmHg	217 100%	185 97%	199 99%	186 97%	194 99%	201 98%	194 98%	222 98%	182 98%
6-9 mmHg	1 0%	5 3%	3 1%	6 3%	2 1%	5 2%	4 2%	4 2%	4 2%
10-15 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
>15 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
NO	109	95	101	96	98	103	99	113	93
MEAN	-0.7	-0.6	-0.5	-0.4	-0.8	-0.6	-0.7	-0.7	-1.0
SE	0.2	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.3
HO: LE=PLC	p=0.003	p<0.001	p=0.002	p=0.024	p<0.001	p<0.001	p<0.001	p<0.001	p=0.010

IOP (continued):

FREQUENCY DISTRIBUTION (PATIENTS - EITHER EYE)

RESPONSE: CHG>=6 mmHg		VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	FINAL	VISIT 9
=====		N %	N %	N %	N %	N %	N %	N %	N %	N %
LOTEPREDNOL		3 3%	9 9%	6 6%	10 11%	10 10%	8 8%	14 14%	17 15%	6 7%
PLACEBO		1 1%	3 3%	2 2%	5 5%	2 2%	4 4%	3 3%	3 3%	3 3%
H0:LE=PLC		p=0.304	p=0.090	p=0.105	p=0.143	p=0.019	p=0.150	p=0.003	p=0.001	p=0.253
RESPONSE: CHG>=10 mmHg		N %	N %	N %	N %	N %	N %	N %	N %	N %
=====		N %	N %	N %	N %	N %	N %	N %	N %	N %
LOTEPREDNOL		1 1%	1 1%	1 1%	3 3%	4 4%	1 1%	3 3%	5 5%	0 0%
PLACEBO		0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
H0:LE=PLC		p=0.317	p=0.317	p=0.340	p=0.069	p=0.044	p=0.280	p=0.070	p=0.025	
TIME TO CHG>=6 mmHg NEVER		N %	N %	N %	N %	N %	N %	N %	N %	N %
=====		N %	N %	N %	N %	N %	N %	N %	N %	N %
LOTEPREDNOL	83 75%	3 3%	6 5%	4 4%	5 5%	3 3%	2 2%	4 4%		
PLACEBO	102 90%	1 1%	2 2%	2 2%	4 4%	0 0%	1 1%	1 1%		
H0:LE=PLC		p=0.004								
TIME TO CHG>=10 mmHg		N %	N %	N %	N %	N %	N %	N %	N %	N %
=====		N %	N %	N %	N %	N %	N %	N %	N %	N %
LOTEPREDNOL	102 93%	1 1%	0 0%	1 1%	3 3%	2 2%	0 0%	1 1%		
PLACEBO	113 100%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%		
H0:LE=PLC		p=0.004								

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IOP CHANGE FROM BASELINE (*: CHG>=7)

INV	TRT	PAT	TRT	TRT	FINAL	BASELINE	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	SAFETY FU
TRT	TRT	TRT	TRT	TRT	DAY CHG	DAY OBS	DAY CHG	DAY CHG	DAY CHG	DAY CHG	DAY CHG	DAY CHG	DAY CHG	DAY CHG
112	LE	403	OD	OD	35 6*	0 18	2 2	7 2	14 4	19 4	28 5	35 6*	47 4	54 4
			OS	OS	7*	18	2 2	2 2	4 4	4 4	6*	7*	6*	4
124	LE	751	OS	OS	14 21*	0 17	2 0	7 -1	14 21*					
			OS	OS	21*	17	0 0	-1 -1	21*					
127	LE	254	OD	OD	42 4	0 12	2 2	7 2	14 2		28 1	35 5	42 4	49 0
			OS	OS	7*	10	2 2	4 4	5 5		4 4	6*	7*	2
127	LE	721	OD	OD	31 14*	0 16	3 -3	10 -1	16 1	24 6*	31 14*			
			OS	OS	12*	16	-2 -2	0 0	0 0	4 4	12*			
127	LE	729	OD	OD	42 6*	0 8	1 2	7 5	14 7*	21 5	28 4	35 5	42 6*	49 3
			OS	OS	3	8	2 2	4 4	7* 7*	6* 6*	4 4	3 3	3 3	4 4
127	LE	737	OD	OD	17 9*	0 13	3 3	10 3	17 9*					
			OS	OS	8*	14	2 2	2 2	8* 8*					
130	LE	446	OD	OD	42 7*	0 13	1 2	6 2	12 5	19 5	28 9*	33 2	42 7*	52 -2
			OS	OS	8*	13	2 2	3 3	2 2	7* 7*	10* 10*	5 5	8* 8*	0
130	LE	452	OD	OD	42 4	0 12	2 4	6 4	14 4	21 6*	28 4	35 4	42 4	49 6*
			OS	OS	4	12	4 4	4 4	5 5	6* 6*	4 4	4 4	4 4	8*
140	LE	482	OD	OD	42 12*	0 10	2 2	9 7*	14 9*	21 10*	30 9*	37 9*	42 12*	49 6*
			OS	OS	7*	12	0 0	5 5	0 0	7* 7*	6* 6*	7* 7*	7* 7*	4
140	LE	484	OS	OS	42 6*	0 19	2 0	7 0	14 0	21 2	28 5	37 5	42 6*	49 0
			OS	OS	7*	19	-1 -1	-4 -4	0 0	2 2	2 2	5 5	7* 7*	0
141	LE	281	OD	OD	43 3	0 13	2 3	8 3	14 5	22 2	29 7*	36 3	43 3	50 -1
			OS	OS	5	13	3 3	5 5	4 4	3 3	7* 7*	4 4	5 5	0
141	LE	291	OD	OD	43 5	0 9	2 3	7 7*	14 5	22 5	27 9*	35 7*	43 5	48 1
			OS	OS	3	10	2 2	5 5	4 4	5 5	8* 8*	7* 7*	3 3	2
142	LE	321	OD	OD	42 9*	0 12	2 3	7 6*	14 3	21 10*	28 9*	35 4	42 9*	49 -2
			OS	OS	11*	9	5 5	7* 7*	5 5	9* 9*	12* 12*	10* 10*	11* 11*	2
142	LE	324	OD	OD	46 4	0 15	3 -4	7 0		18 1	29 3	35 -1	46 4	49 2
			OS	OS	8*	13	-4 -4	0 0	6* 6*	1 1	5 5	-1 -1	8* 8*	3
42	LE	326	OD	OD	43 6*	0 12	3 4	8 2	15 6*	22 4	29 3	36 3	43 6*	50 5
			OS	OS	7*	14	4 4	6* 6*	8* 8*	10* 10*	1 1	2 2	7* 7*	7*
142	LE	327	OD	OD	42 -1	0 15	3 3	7 -1	14 -2	21 -3	28 4	35 -2	42 -1	49 1
			OS	OS	-1	14	-3 -3	-2 -2	-2 -2	5 5	7* 7*	4 4	-1 -1	1
142	LE	329	OD	OD	40 4	0 13	2 11*	7 13*	12 3	21 6*	28 10*		40 4	54 2
			OS	OS	9*	11	8* 8*	13* 13*	1 1	7* 7*	12* 12*		9* 9*	1
147	LE	540	OD	OD	42 -4	0 18	3 -5	6 0	14 0	21 -2	28 -1	35 1	42 -4	49 -5
			OS	OS	-2	18	-5 -5	2 2	-2 -2	0 0	1 1	7* 7*	-2 -2	-5
148	LE	362	OS	OD	43 9*	0 11	2 0	8 1		22 5	29 5	36 5	43 9*	47 1
			OS	OS	10*	10	1 1	2 2		6* 6*	6* 6*	6* 6*	10* 10*	0
148	LE	382	OS	OD	43 5	0 11	2 0	9 1	16 1	24 3	32 3	36 5	43 5	51 5
			OS	OS	7*	11	0 0	1 1	1 1	3 3	5 5	5 5	7* 7*	7*
112	PLC	413	OD	OD	42 1	0 12	2 -2	8 -4	14 9*	21 -3	28 -2	35 -2	42 1	49 -3
			OS	OS	1	12	0 0	-2 -2	5 5	-2 -2	-1 -1	-1 -1	1 1	-1
140	PLC	481	OD	OD	42 -2	0 9	2 0	7 -1	14 -1	21 -1	28 -1	35 9*	42 -2	49 -1
			OS	OS	-3	11	-1 -1	-1 -1	-3 -3	-1 -1	-1 -1	7* 7*	-3 -3	-2
142	PLC	525	OD	OD	45 6*	0 10	3 5	7 8*	14 4	19 6*	28 6*	35 8*	45 6*	66 6*
			OS	OS	4	12	2 2	6* 6*	2 2	4 4	-2 -2	4 4	4 4	4
147	PLC	331	OD	OD	42 2	0 15	2 -8	11 -3	14 7*	21 -3	28 3	35 -4	42 2	49 3
			OS	OS	3	15	0 0	0 0	6* 6*	-3 -3	3 3	6* 6*	3 3	4
148	PLC	364	OS	OD	42 2	0 12	2 0	7 6*	14 2	21 2	28 8*	35 2	42 2	49 1
			OS	OS	2	12	0 0	6* 6*	2 2	2 2	5 5	2 2	2 2	4
149	PLC	366	OD	OD	43 -1	0 12	1 5	8 4	15 2	22 0	29 0	36 4	43 -1	53 -2
			OS	OS	1	10	8* 8*	7* 7*	4 4	2 2	2 2	8* 8*	1 1	1
151	PLC	779	OS	OD	42 7*	0 13	2 2	7 2	14 3	21 7*	29 5	35 5	42 7*	48 4
			OS	OS	6*	14	2 2	1 1	2 2	6* 6*	4 4	4 4	6* 6*	3

Reviewer's Comments: IOP elevations occur more frequently in the loteprednol group.

ELICITED/OBSERVED EVENTS - Loteprednol (n=110)

Placebo (n=113)

	Patients Reporting			Patients Reporting		
	At least once		Total	At least once		Total
FOREIGN BODY SENSATION (EYE/GEN)	19	17%	20	16	14%	16
ITCHING, EYE (EYE/GEN)	13	12%	16	14	12%	14
EPIPHORA (EYE/APP)	11	10%	15	15	13%	16
INJECTION (EYE/CON)	9	8%	9	27	24%	32
DISCHARGE, EYE (EYE/GEN)	8	7%	9	11	10%	13
PHOTOPHOBIA (EYE/VIS)	7	6%	9	15	13%	15
PAPILLA (EYE/APP)	3	3%	3	9	8%	10
CORNEAL ABNORMALITY (EYE/COR)	1	1%	1	2	2%	2
ERYTHEMA, EYELIDS (EYE/APP)	1	1%	1	4	4%	5
IOP, INCREASED (EYE/IOP)	28	25%	37	12	11%	17
ABNORMAL VISION (EYE/VIS)	16	15%	22	20	18%	21
HEADACHE (HEAD)	15	14%	19	13	12%	26
FLU SYNDROME (GEN)	6	5%	6	4	4%	4
RHINITIS (NOSE)	5	5%	6	4	4%	5
PHARYNGITIS (NASP)	4	4%	5	3	3%	4
CONJUNCTIVITIS (EYE/CON)	4	4%	6	3	3%	3
DRY EYES (EYE/GEN)	3	3%	3	1	1%	1
INFECTION (GEN)	2	2%	2	7	6%	8
COUGH INCREASED (GEN)	2	2%	2	3	3%	3
BURNING, EYE (EYE/GEN)	2	2%	4	3	3%	3
SINUSITIS (SINS)	2	2%	2	0	0%	0
CONTACT LENS INTOL (EYE/GEN)	2	2%	2	1	1%	1
ABDOMINAL PAIN (ABDO)	1	1%	1	0	0%	0
ACCIDENTAL INJURY (GEN)	1	1%	1	0	0%	0
ASTHENIA (GEN)	1	1%	1	0	0%	0
BACK PAIN (BACK)	1	1%	1	2	2%	2
CHILLS (GEN)	1	1%	1	0	0%	0
FACE EDEMA (HEAD)	1	1%	1	1	1%	1
FEVER (GEN)	1	1%	1	0	0%	0
PAIN (GEN)	1	1%	1	0	0%	0
DYSPEPSIA (GEN)	1	1%	1	0	0%	0
TOOTH DISORDER (BUC)	1	1%	1	0	0%	0
EDEMA (WB)	1	1%	1	0	0%	0
PARESTHESIA (PNS)	1	1%	1	1	1%	1
BRONCHITIS (LUNG)	1	1%	1	0	0%	0
ACNE (DERM/ACN)	1	1%	1	0	0%	0
NAIL DISORDER (NAIL)	1	1%	1	0	0%	0
BURN, EYE, ON INSTIL	1	1%	1	0	0%	0
EYE PAIN (EYE/GEN)	1	1%	2	0	0%	0
EYE/VISION, BLURRED (EYE/VIS)	1	1%	1	2	2%	2
EYELID ABNORMALITY (EYE/APP)	1	1%	1	0	0%	0
INFECTION, EAR, NOS (EAR/GEN)	1	1%	1	0	0%	0
KERATITIS (EYE/COR)	1	1%	1	2	2%	3
CYSTITIS (UT/B/H)	1	1%	3	0	0%	0
ENDOMETRIAL DISORDER (FG/UTRS)	1	1%	1	0	0%	0
MENSTRUAL DISORDER (FG/MENS)	1	1%	1	1	1%	1
UTERINE DISORDER (FG/UTRS)	1	1%	1	0	0%	0
ALLERGIC REACTION (GEN)	0	0%	0	6	5%	6
CHEST PAIN (THOR)	0	0%	0	1	1%	1
GASTROENTERITIS (GEN)	0	0%	0	1	1%	1
NAUSEA (GEN)	0	0%	0	2	2%	2
HYPOTHYROIDISM (THYR)	0	0%	0	1	1%	1
WEIGHT GAIN (WT)	0	0%	0	1	1%	1
LUNG DISORDER (LUNG)	0	0%	0	1	1%	1
DRY SKIN (GEN)	0	0%	0	1	1%	1
RASH (DERM/ERY)	0	0%	0	2	2%	2
BLEPHARITIS (EYE/APP)	0	0%	0	1	1%	1
CORNEAL LESION (EYE/COR)	0	0%	0	3	3%	3
MEIBOMIAN GLAND ABN (EYE/APP)	0	0%	0	1	1%	1
STINGING, EYE, ON INSTIL	0	0%	0	1	1%	3
TINNITUS (EAR/HER)	0	0%	0	1	1%	1
BREAST NEOPLASM (FG/BRST)	0	0%	0	1	1%	1
DYSMENORRHEA (FG/MENS)	0	0%	0	1	1%	1

Reviewer's Comments:

1. *There were a large number of misclassifications in the table presented above.*
 - a. *Similar events were not always coded in the same manner. For example:*

"Blurry" vision was sometimes coded "Abnormal vision" and sometimes coded as "Blurred vision."

Cold was sometimes coded as "Flu Syndrome" and sometimes classified as "Infection."

Puffy lids and swollen lids should have been coded together.
 - b. *Unlike events were sometimes coded in the same category. For example:*

Itching was coded as a "Rash" and increased erythema was classified as a "Rash."
2. *Investigator 124 did not perform the final safety follow-up visits on his patients (19 patients).*

ALL INFORMATION CONTAINED
HEREIN IS UNCLASSIFIED
DATE 01-10-2010 BY 60322
ON ORIGINAL

Study #1 Conclusions: -

1. Loteprednol etabonate has demonstrated superiority over its vehicle in the treatment of GPC while contact lenses are left in place (after the first 48 hours) based on evaluations of signs and symptoms of GPC and the global investigator and patient scores.
2. There is an acceptable safety profile, however, individual adverse experiences may need to be re-coded/classified.
3. Loteprednol etabonate has demonstrated the ability to cause elevated intraocular pressure in some patients (10-20%).
4. There were no significant differences with respect to age, race or eye color. Females had a slightly better response with respect to papillae than males (data not shown) although the difference is unlikely to be clinically significant.

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8.1.2 Reviewer's Trial # 2 Sponsor's protocol # 108

Title: EFFICACY AND SAFETY EVALUATION OF LOTEPREDNOL ETABONATE IN GIANT PAPILLARY CONJUNCTIVITIS

Objective/Rationale Same as Study #1.

Design Same as Study #1.

Protocol

Test Drug Schedule: Same as Study #1 except that photographs were taken at baseline and day 42.

Valid Visits

Using the definition of a valid visit described, the following were determined as invalid visits because they were outside the expected range:

Invalid Final Visits: # 2051, 2056, 2284, 2294, 2330, 2343 and 2402.

Invalid On-Study Visits: #2128 (V3), and #2133 (V5, V6 and V7).

In the analysis by individual visit, some visits were included despite their occurring outside the visit schedule window in the protocol.

Visit Number	Scheduled Visit Window	Actual Visit Window	Ratio of patients outside window to total
2	Day 2 - 3	Day 1 - 6	19/203
3	Day 6 - 8	Day 5 - 11	13/211
4	Day 13 - 15	Day 11 - 18	19/197
5	Day 19 - 23	Day 18 - 25	9/193
6	Day 26 - 30	Day 25 - 31	10/170
7	Day 32 - 38	Day 32 - 39	1/180
8	Day 39 - 45	Day 37 - 50	2/192

Reviewer's Comments: *The "Actual Visit Windows" overlap and permit a single visit to be used for more than one visit. This is not acceptable.*

Inclusion Criteria: Same as Study #1.

Exclusion Criteria: Same as Study #1.

Efficacy Criteria: Same as Study #1.

Investigators:

Penny Asbell, M.D.	New York, NY	(Investigator #155)
Joe Barr, O.D./Yvonne Johnson, O.D.	Columbus, OH	(Investigator #156)
Jimmy Bartlett, O.D.	Birmingham, AL	(Investigator #136)
Arthur Charap, M.D.	Anaheim Hills, CA	(Investigator #139)
Andrew Dahl, M.D.	Fishkill, NY	(Investigator #149)
*Kenneth Fox, M.D.	McLean, VA	(Investigator #151)
*Mitchell Friedlaender, M.D.	La Jolla, CA	(Investigator #124)
Miles Galin, M.D.	New York, NY	(Investigator #152)
Barry Horwitz, M.D.	Houston, TX	(Investigator #122)
Brian Levy, O.D.	San Francisco, CA	(Investigator #138)
Jacqueline Lustgarten, M.D.	Paramus, NJ	(Investigator #153)
Norbert Toussaint, Jr., M.D.	Madison, WI	(Investigator #154)

Reviewer's Comments: *Kenneth Fox and Mitchell Friedlander where also investigators in Study #1 (Sponsor protocol 107).*

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ON ORIGINAL

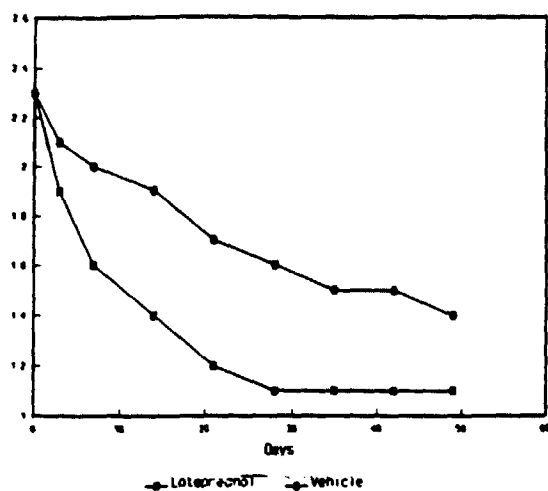
INVESTIGATOR	TREATMENT	RANDOMIZED	COMPLETED TREATMENT	COMPLETED STUDY	***** REASON STUDY INCOMPLETE *****			
					LACK OF EFFICACY	ADVERSE EVENTS	OTHER UNRELATED	NO SAFETY FOLLOW-UP
122	LOTEPREDNOL	10	10 (100%)	10 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	PLACEBO	10	9 (90%)	9 (90%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)
124	LOTEPREDNOL	13	11 (85%)	0 (0%)	0 (0%)	1 (8%)	1 (8%)	11 (85%)
	PLACEBO	13	10 (77%)	0 (0%)	0 (0%)	1 (8%)	2 (15%)	10 (77%)
136	LOTEPREDNOL	3	3 (100%)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	PLACEBO	4	4 (100%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
138	LOTEPREDNOL	8	5 (63%)	5 (63%)	1 (13%)	1 (13%)	1 (13%)	0 (0%)
	PLACEBO	8	7 (88%)	7 (88%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)
139	LOTEPREDNOL	7	6 (86%)	6 (86%)	0 (0%)	0 (0%)	1 (14%)	0 (0%)
	PLACEBO	5	4 (80%)	4 (80%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)
151	LOTEPREDNOL	14	13 (93%)	13 (93%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)
	PLACEBO	17	16 (94%)	15 (88%)	0 (0%)	1 (6%)	0 (0%)	1 (6%)
152	LOTEPREDNOL	17	17 (100%)	16 (94%)	0 (0%)	0 (0%)	0 (0%)	1 (6%)
	PLACEBO	17	8 (47%)	8 (47%)	9 (53%)	0 (0%)	0 (0%)	0 (0%)
153	LOTEPREDNOL	10	10 (100%)	10 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	PLACEBO	10	9 (90%)	9 (90%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
154	LOTEPREDNOL	5	5 (100%)	5 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	PLACEBO	4	4 (100%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
155	LOTEPREDNOL	10	9 (90%)	9 (90%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)
	PLACEBO	8	8 (100%)	8 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
156	LOTEPREDNOL	14	12 (86%)	12 (86%)	0 (0%)	1 (7%)	1 (7%)	0 (0%)
	PLACEBO	13	12 (92%)	12 (92%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
OVERALL	LOTEPREDNOL	111	101 (91%)	89 (80%)	1 (1%)	4 (4%)	5 (5%)	12 (11%)
	PLACEBO	109	91 (83%)	80 (73%)	11 (10%)	3 (3%)	4 (4%)	11 (10%)

Results

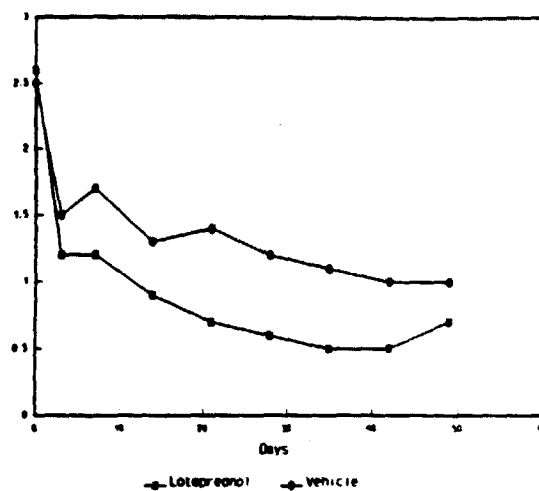
		LOTEPREDNOL	PLACEBO	
AGE (yrs)	N	111	109	p = 0.401
=====	MEAN	34.1	33.1	
	SE	1.0	1.0	
	MIN	18.0	18.0	
	MAX	70.0	70.0	
	<30 yrs	42	48	p = 0.335
	≥30 yrs	69	61	
GENDER				
=====				
MALE	N	28	25	p = 0.697
FEMALE	N	83	84	
RACE				
=====				
CAUCASIAN	N	92	95	p = 0.370
BLACK	N	5	6	
ASIAN	N	5	4	
HISPANIC	N	7	2	
INDIAN	N	1	0	
CHINESE AMERICAN	N	1	0	
ASIAN AMERICAN	N	0	2	
IRIS PIGMENTATION				
=====				
LIGHT	N	47	56	p = 0.159
DARK	N	64	53	

Reviewer's Comments: *No significant differences between groups.*

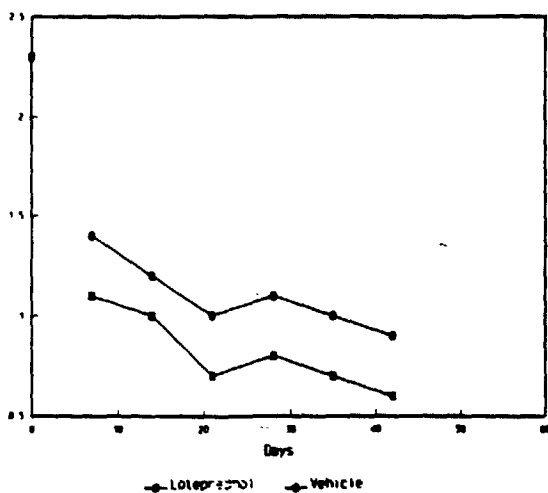
Papillae



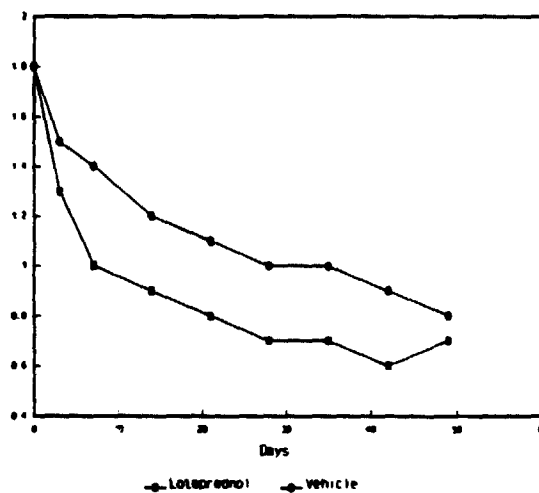
Itching



Lens intolerance



Palpebral Injection

**Reviewer's Comments:**

All evaluations favor loteprednol over vehicle. The differences from baseline are statistically different between groups although the mean scores are not statistically significantly different between groups.

Papillae

FREQUENCY DISTRIBUTION OF OBSERVED RATINGS

	BASELINE	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	FINAL	SAFETY FU
	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	VISIT 8	VISIT 9	VISIT 9
	DAY 0	DAY 2-3	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	(ON MED)	(OFF MED)	(OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 = <.3 mm	0 0%	3 3%	13 12%	14 14%	23 23%	22 24%	19 20%	31 31%	32 29%	24 27%	
1 = .3-.4mm	0 0%	16 16%	29 27%	39 39%	40 40%	41 44%	47 50%	37 37%	41 37%	38 43%	
2 = .4-1.0mm	82 74%	73 72%	57 53%	43 43%	35 35%	27 29%	27 29%	29 29%	34 31%	24 27%	
3 = >1mm	29 26%	10 10%	9 8%	5 5%	3 3%	3 3%	1 1%	4 4%	4 4%	3 3%	
NO	111	102	108	101	101	93	94	101	111	89	
MEAN	2.3	1.9	1.6	1.4	1.2	1.1	1.1	1.1	1.1	1.1	
SE	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 = <.3 mm	0 0%	1 1%	1 1%	2 2%	4 4%	4 5%	6 7%	9 10%	9 8%	8 10%	
1 = .3-.4mm	1 1%	10 10%	17 17%	20 21%	28 30%	32 41%	33 38%	35 38%	35 32%	33 41%	
2 = .4-1.0mm	78 72%	72 71%	64 62%	61 64%	49 53%	36 46%	41 48%	40 44%	48 44%	36 45%	
3 = >1mm	30 28%	18 18%	21 20%	13 14%	11 12%	7 9%	6 7%	7 8%	17 16%	3 4%	
NO	109	101	103	96	92	79	86	91	109	80	
MEAN	2.3	2.1	2.0	1.9	1.7	1.6	1.5	1.5	1.7	1.4	
SE	0.0	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	

H0:LE=PLC p=0.779

FREQUENCY DISTRIBUTION OF CHANGE FROM BASELINE RATINGS

	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	FINAL	VISIT 9
	DAY 2-3	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	VISIT 9	SAFETY FU
	N %	N %	N %	N %	N %	N %	N %	(ON MED)	(OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1	0 0%	1 1%	1 1%	1 1%	1 1%	1 1%	2 2%	2 2%	2 2%
0 NO CHANGE	72 71%	55 51%	37 37%	27 27%	22 24%	17 18%	21 21%	26 23%	15 17%
-1	23 23%	36 33%	44 44%	43 43%	42 45%	50 53%	41 41%	45 41%	42 47%
-2	5 5%	9 8%	10 10%	20 20%	18 19%	16 17%	26 26%	27 24%	23 26%
<-2 BETTER	2 2%	7 6%	9 9%	10 10%	10 11%	10 11%	11 11%	11 10%	7 8%
NO	102	108	101	101	93	94	101	111	89
MEAN	-0.4	-0.7	-0.9	-1.1	-1.2	-1.2	-1.2	-1.2	-1.2
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1	1 1%	4 4%	4 4%	3 3%	1 1%	1 1%	2 2%	7 6%	0 0%
0 NO CHANGE	79 78%	74 72%	59 61%	46 50%	37 47%	35 41%	35 38%	47 43%	33 41%
-1	19 19%	21 20%	28 29%	36 39%	33 42%	41 48%	42 46%	43 39%	33 41%
-2	1 1%	3 3%	4 4%	5 5%	5 6%	6 7%	7 8%	7 6%	10 13%
<-2 BETTER	1 1%	1 1%	1 1%	2 2%	3 4%	3 3%	5 5%	5 5%	4 5%
NO	109	101	103	96	92	79	86	91	109
MEAN	-16.6	-0.2	-0.3	-0.4	-0.5	-0.6	-0.7	-0.8	-0.6
SE	2.5	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

H0:LE=PLC p<0.001 p=0.037 p<0.001 p<0.001 p<0.001 p<0.001 p<0.001 p<0.001 p<0.001 p=0.013

VISIT BEGINNING
SUSTAINED RESPONSE

	N	N	N	N	N	N	N
LOTEPREDNOL	25	21	15	8	5	7	2
PLACEBO	11	10	11	7	4	7	5

H0:LE=PLC p<0.001

Itching

FREQUENCY DISTRIBUTION OF OBSERVED RATINGS

	BASELINE	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	FINAL	SAFETY FU
	VISIT 1	DAY 2-3	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	VISIT 9	VISIT 9
	DAY 0								(ON MED)	(OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 = ABSENT	0 0%	33 32%	33 31%	37 37%	54 53%	58 62%	59 62%	69 68%	73 66%	48 54%
1 = TRACE	0 0%	30 29%	34 31%	37 37%	29 29%	23 25%	25 26%	22 22%	24 22%	24 27%
2 = MILD	55 50%	29 28%	31 29%	24 24%	14 14%	7 8%	8 8%	7 7%	10 9%	10 11%
3 = MODERATE	45 41%	10 10%	10 9%	3 3%	3 3%	4 4%	2 2%	2 2%	3 3%	7 8%
4 = SEVERE	11 10%	0 0%	0 0%	0 0%	1 1%	1 1%	1 1%	1 1%	1 1%	0 0%
NO	111	102	108	101	101	93	95	101	111	89
MEAN	2.6	1.2	1.2	0.9	0.7	0.6	0.5	0.5	0.5	0.7
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 = ABSENT	0 0%	19 19%	16 16%	27 28%	19 21%	23 29%	25 29%	33 36%	34 31%	29 36%
1 = TRACE	1 1%	28 28%	33 32%	30 31%	30 33%	28 35%	36 42%	32 35%	34 31%	29 36%
2 = MILD	56 51%	37 37%	29 28%	23 24%	30 33%	19 24%	15 17%	19 21%	25 23%	13 16%
3 = MODERATE	44 40%	14 14%	20 19%	15 16%	12 13%	9 11%	9 10%	7 8%	13 12%	9 11%
4 = SEVERE	8 7%	3 3%	5 5%	1 1%	1 1%	0 0%	1 1%	0 0%	3 3%	0 0%
NO	109	101	103	96	92	79	86	91	109	80
MEAN	2.5	1.5	1.7	1.3	1.4	1.2	1.1	1.0	1.2	1.0
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

HO:LE=PLC p=0.685

FREQUENCY DISTRIBUTION OF CHANGE FROM BASELINE RATINGS

	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8	FINAL	VISIT 9
	DAY 2-3	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	VISIT 9	SAFETY FU
								(ON MED)	(OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1	1 1%	4 4%	1 1%	1 1%	1 1%	1 1%	1 1%	1 1%	0 0%
0 NO CHANGE	25 25%	22 20%	12 12%	8 8%	6 6%	6 6%	4 4%	8 7%	7 8%
-1	25 25%	30 28%	32 32%	22 22%	15 16%	14 15%	16 16%	17 15%	22 25%
-2	30 29%	31 29%	33 33%	44 44%	44 47%	46 48%	45 45%	48 43%	37 42%
< -2 BETTER	21 21%	21 19%	23 23%	26 26%	27 29%	28 29%	35 35%	37 33%	23 26%
NO	102	108	101	101	93	95	101	111	89
MEAN	-1.5	-1.4	-1.7	-1.9	-2.1	-2.1	-2.2	-2.1	-1.9
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	1 1%	1 1%	1 1%	1 1%	0 0%	0 0%	0 0%	1 1%	0 0%
1	5 5%	8 8%	4 4%	1 1%	4 5%	3 3%	2 2%	6 6%	3 4%
0 NO CHANGE	31 31%	31 30%	19 20%	25 27%	13 16%	13 15%	11 12%	19 17%	10 13%
-1	35 35%	32 31%	30 31%	31 34%	24 30%	25 29%	27 30%	31 28%	20 25%
-2	17 17%	24 23%	32 33%	23 25%	28 35%	35 41%	37 41%	38 35%	36 45%
< -2 BETTER	12 12%	7 7%	10 10%	11 12%	10 13%	10 12%	14 15%	14 13%	11 14%
NO	101	103	96	92	79	86	91	109	80
MEAN	-1.0	-0.9	-1.2	-1.2	-1.4	-1.4	-1.6	-1.3	-1.6
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

HO:LE=PLC

p=0.013

p<0.001

p=0.006

p<0.001

p<0.001

p<0.001

p<0.001

p<0.001

p<0.001

p<0.001

p<0.001

p=0.101

VISIT BEGINNING
SUSTAINED RESPONSE

LOTEPREDNOL	N	N	N	N	N	N	N
LOTEPREDNOL	57	16	15	3	3	4	4
PLACEBO	40	9	9	5	7	5	8

HO:LE=PLC p<0.001

Lens Intolerance

- FREQUENCY DISTRIBUTION OF OBSERVED RATINGS

BASELINE		WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	FINAL
DAY 0		DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	WEEK (ON MED)
N %		N %	N %	N %	N %	N %	N %	N %
LOTEPREDNOL (LE)								
0 - FULL CONTROL		26 24%	34 32%	48 48%	45 46%	49 51%	51 53%	55 50%
1 - REASONABLE		47 44%	40 38%	34 34%	32 33%	30 31%	31 32%	34 31%
2 - PARTIAL CONTROL		29 27%	29 27%	18 18%	19 19%	17 18%	14 14%	19 17%
3 - UNCONTROLLED		6 6%	3 3%	1 1%	2 2%	1 1%	1 1%	3 3%
NO		111	108	106	98	97	97	111
MEAN		2.3	1.1	1.0	0.8	0.7	0.6	0.7
SE		0.0	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)								
N %		N %	N %	N %	N %	N %	N %	N %
0 - FULL CONTROL		25 24%	26 27%	30 32%	26 28%	36 40%	36 40%	37 34%
1 - REASONABLE		28 27%	34 35%	34 37%	33 36%	20 22%	26 29%	28 26%
2 - PARTIAL CONTROL		35 33%	31 32%	24 26%	28 30%	30 34%	26 29%	32 29%
3 - UNCONTROLLED		17 16%	6 6%	5 5%	5 5%	3 3%	2 2%	12 11%
NO		109	105	97	92	89	90	109
MEAN		2.3	1.4	1.2	1.1	1.0	0.9	1.2
SE		0.0	0.1	0.1	0.1	0.1	0.1	0.1

H0:LE=PLC p=0.728

FREQUENCY DISTRIBUTION OF CHANGE FROM BASELINE RATINGS

WEEK 1		WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	FINAL
DAY 7		DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	WEEK (ON MED)
N %		N %	N %	N %	N %	N %	N %
LOTEPREDNOL (LE)							
2 WORSE		0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1		3 3%	2 2%	1 1%	1 1%	0 0%	0 0%
0 NO CHANGE		23 21%	23 22%	13 13%	12 12%	12 12%	18 16%
-1		46 43%	32 30%	27 27%	27 28%	24 25%	23 24%
-2		28 26%	43 41%	49 49%	45 46%	48 49%	54 49%
-3 BETTER		8 7%	6 6%	11 11%	11 11%	12 12%	13 12%
NO		108	106	101	98	97	97
MEAN		-1.1	-1.3	-1.6	-1.5	-1.6	-1.6
SE		0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)							
N %		N %	N %	N %	N %	N %	N %
2 WORSE		0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1		7 7%	3 3%	3 3%	1 1%	2 2%	1 1%
0 NO CHANGE		34 32%	26 27%	19 20%	24 26%	21 24%	20 22%
-1		33 31%	31 32%	30 32%	31 34%	23 26%	23 26%
-2		25 24%	33 34%	37 40%	34 37%	38 43%	41 46%
-3 BETTER		6 6%	4 4%	4 4%	2 2%	5 6%	5 5%
NO		105	97	93	92	89	90
MEAN		-0.9	-1.1	-1.2	-1.1	-1.3	-1.3
SE		0.1	0.1	0.1	0.1	0.1	0.1
p=0.046		p=0.156	p=0.012	p=0.006	p=0.038	p=0.041	p=0.002

WEEK BEGINNING SUSTAINED RESPONSE

	N	N	N	N	N	N
LOTEPREDNOL	72	5	6	1	4	5
PLACEBO	50	8	4	1	5	4

H0:LE=PLC p=0.007

Palpebral injection

FREQUENCY DISTRIBUTION OF OBSERVED RATINGS

	BASELINE VISIT 1 DAY 0	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL VISIT (ON MED)	SAFETY FU VISIT 9 (OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 - ABSENT	0 0%	9 9%	22 21%	26 27%	35 36%	37 42%	37 41%	44 46%	46 43%	37 44%
1 - MILD	46 43%	57 58%	63 61%	55 57%	46 48%	44 50%	40 44%	44 46%	51 48%	34 40%
2 - MODERATE	40 38%	26 27%	18 17%	15 16%	15 16%	7 8%	12 13%	8 8%	9 8%	12 14%
3 - SEVERE	20 19%	6 6%	0 0%	0 0%	0 0%	0 0%	1 1%	0 0%	0 0%	1 1%
NO	106	98	103	96	96	88	90	96	106	84
MEAN	1.8	1.3	1.0	0.9	0.8	0.7	0.7	0.6	0.7	0.7
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
0 - ABSENT	0 0%	5 5%	5 5%	8 9%	14 16%	15 20%	18 22%	24 28%	24 23%	26 34%
1 - MILD	37 36%	45 47%	59 60%	62 67%	56 64%	45 60%	49 59%	46 53%	51 49%	38 50%
2 - MODERATE	53 51%	38 40%	27 27%	20 22%	15 17%	14 19%	16 19%	17 20%	21 20%	12 16%
3 - SEVERE	14 13%	8 8%	8 8%	2 2%	3 3%	1 1%	0 0%	0 0%	8 8%	0 0%
NO	104	96	99	92	88	75	83	87	104	76
MEAN	1.8	1.5	1.4	1.2	1.1	1.0	1.0	0.9	1.1	0.8
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

H0:LE=PLC p<0.849

FREQUENCY DISTRIBUTION OF CHANGE FROM BASELINE RATINGS

	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL VISIT (ON MED)	VISIT 9 SAFETY FU (OFF MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
1	2 2%	2 2%	0 0%	4 4%	2 2%	2 2%	1 1%	1 1%	3 4%
0 NO CHANGE	58 59%	41 40%	41 43%	25 26%	24 27%	27 30%	24 25%	29 27%	22 26%
-1	29 30%	42 41%	33 34%	40 42%	35 40%	36 40%	42 44%	45 42%	37 44%
-2	7 7%	11 11%	13 14%	18 19%	16 18%	15 17%	18 19%	20 19%	14 17%
<-2 BETTER	2 2%	7 7%	9 9%	9 9%	11 13%	10 11%	11 11%	11 10%	8 10%
NO	98	103	96	96	88	90	96	106	84
MEAN	-0.5	-0.8	-0.9	-1.0	-1.1	-1.0	-1.1	-1.1	-1.0
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %
> 1 WORSE	0 0%	0 0%	0 0%	1 1%	0 0%	0 0%	0 0%	0 0%	0 0%
1	5 5%	7 7%	9 10%	3 3%	4 5%	4 5%	4 5%	10 10%	2 3%
0 NO CHANGE	63 66%	53 54%	31 34%	31 35%	28 37%	31 37%	28 32%	37 36%	24 32%
-1	24 25%	32 32%	44 48%	43 49%	33 44%	31 37%	39 45%	41 39%	32 42%
-2	3 3%	6 6%	7 8%	8 9%	7 9%	14 17%	11 13%	11 11%	14 18%
<-2 BETTER	1 1%	1 1%	1 1%	2 2%	3 4%	3 4%	5 6%	5 5%	4 5%
NO	96	99	92	88	75	83	87	104	76
MEAN	-0.3	-0.4	-0.6	-0.7	-0.7	-0.8	-0.8	-0.7	-0.9
SE	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

H0:LE=PLC

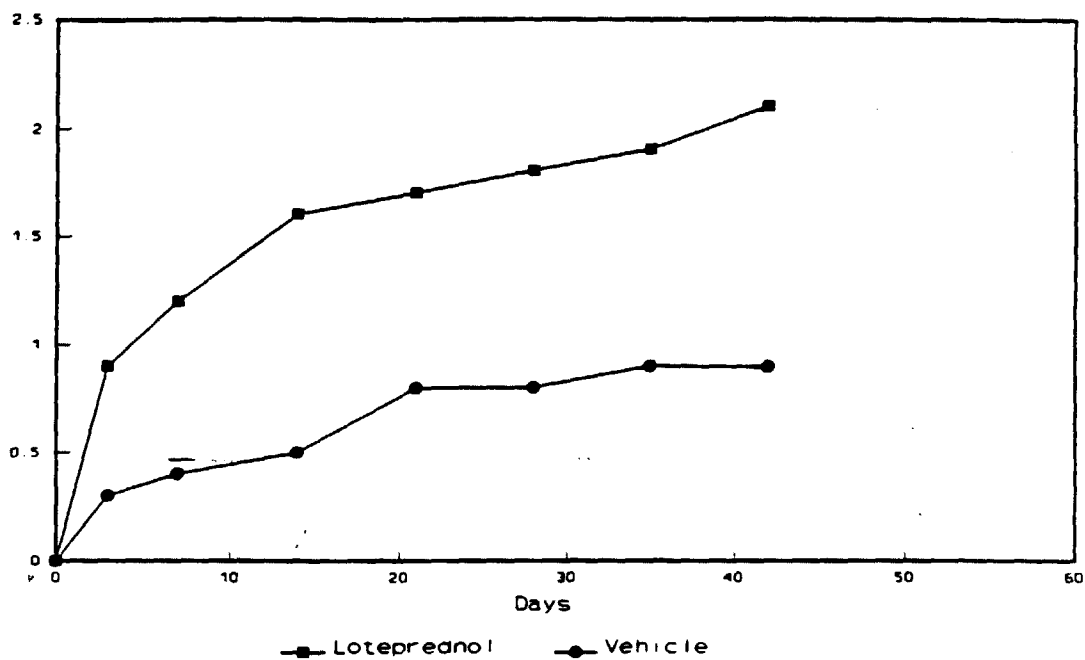
p=0.023 p=0.001 p=0.131 p=0.055 p=0.024 p=0.193 p=0.061 p<0.001 p=0.947

VISIT BEGINNING
SUSTAINED RESPONSE

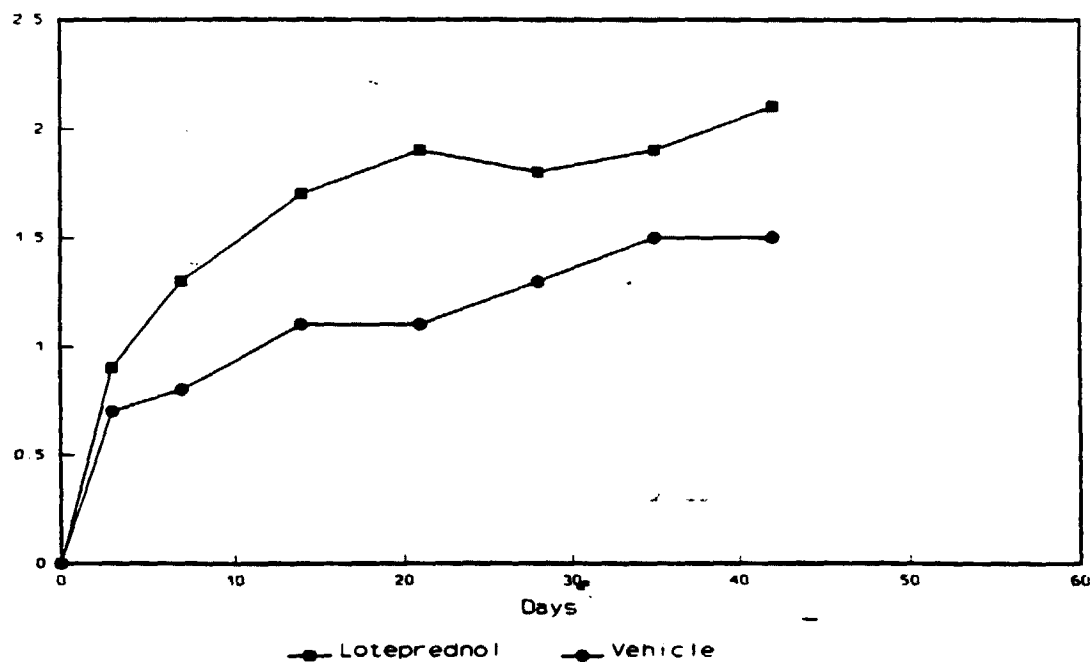
	N	N	N	N	N	N	N
LOTEPREDNOL	28	15	6	7	4	5	11
PLACEBO	13	13	14	1	4	4	8

H0:LE=PLC p=0.023

Investigator Global Rating



Patient Global Rating



Investigator global rating:

FREQUENCY DISTRIBUTION OF GLOBAL ASSESSMENTS

	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL VISIT (ON MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %
1:WORSE	0 0%	1 1%	0 0%	2 2%	1 1%	2 2%	0 0%	0 0%
0:UNCHANGED	45 45%	29 27%	13 13%	12 12%	10 11%	10 11%	9 9%	13 12%
-1:SLIGHT IMPROVEMENT	33 33%	38 35%	37 37%	27 27%	26 28%	16 17%	16 16%	17 15%
-2:REASONABLE CONTROL	16 16%	28 26%	31 31%	37 37%	30 32%	34 36%	35 35%	37 33%
-3:CONTROLLED	7 7%	12 11%	19 19%	23 23%	26 28%	33 35%	41 41%	44 40%
NO MEAN	101	108	100	101	93	95	101	111
SE	-0.9	-1.2	-1.6	-1.7	-1.8	-1.9	-2.1	-2.0
	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %
1:WORSE	6 6%	11 11%	4 4%	5 5%	3 4%	2 2%	3 3%	14 13%
0:UNCHANGED	56 55%	40 39%	33 34%	32 35%	25 32%	26 30%	27 30%	31 28%
-1:SLIGHT IMPROVEMENT	25 25%	33 32%	33 34%	28 30%	21 27%	24 28%	19 21%	21 19%
-2:REASONABLE CONTROL	11 11%	14 14%	20 21%	19 21%	20 25%	22 26%	24 27%	26 24%
-3:CONTROLLED	3 3%	5 5%	6 6%	8 9%	10 13%	12 14%	17 19%	17 16%
NO MEAN	101	103	96	92	79	86	90	109
SE	-0.5	-0.6	-0.9	-0.9	-1.1	-1.2	-1.3	-1.0
	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
H0:LE=PLC	p=0.001	p<0.001	p<0.001	p<0.001	p=0.001	p<0.001	p<0.001	p<0.001
POSITIVE RESPONSE								
LOTEPREDNOL	N %	N %	N %	N %	N %	N %	N %	N %
PLACEBO	56 55%	78 72%	87 87%	87 86%	82 88%	83 87%	92 91%	98 88%
	39 39%	52 50%	59 61%	55 60%	51 65%	58 67%	60 67%	64 59%
H0:LE=PLC	p=0.006	p=0.001	p<0.001	p<0.001	p=0.001	p=0.003	p<0.001	p<0.001
VISIT BEGINNING								
SUSTAINED RESPONSE								
LOTEPREDNOL	N	N	N	N	N	N	N	
PLACEBO	44	22	14	3	4	5	6	
	20	10	8	5	8	7	6	
H0:LE=PLC	p<0.001							

THE SCALE AS RECORDED IN THE CASE REPORT FORM RANGED FROM 0-FULLY CONTROLLED TO 4-WORSE. THE SCALE WAS TRANSFORMED BY SUBTRACTING 3 FROM EACH RATING SO THAT CHANGE FROM BASELINE WAS MORE CONSISTENT WITH THE OTHER SCALES--i.e., -3 TO -1 = DECREASING LEVELS OF IMPROVEMENT, 0=UNCHANGED AND 1=WORSE.

APPEARS THIS WAY
ON ORIGINAL

Patient global rating

FREQUENCY DISTRIBUTION OF GLOBAL ASSESSMENTS

	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL VISIT (ON MED)
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %
1:WORSE	0 0%	1 1%	1 1%	4 4%	1 1%	4 4%	0 0%	1 1%
0:UNCHANGED	46 46%	31 29%	15 15%	10 10%	12 13%	12 13%	12 12%	14 13%
-1:SLIGHT IMPROVEMENT	27 27%	28 26%	27 27%	20 20%	20 22%	14 15%	13 13%	15 14%
-2:REASONABLE CONTROL	17 17%	33 31%	31 31%	29 29%	29 31%	21 22%	28 28%	31 28%
-3:CONTROLLED	11 11%	15 14%	26 26%	38 38%	31 33%	44 46%	48 48%	50 45%
NO MEAN SE	101 -0.9 0.1	108 -1.3 0.1	100 -1.7 0.1	101 -1.9 0.1	93 -1.8 0.1	95 -1.9 0.1	101 -2.1 0.1	111 -2.0 0.1
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %
1:WORSE	6 6%	14 14%	7 7%	7 8%	6 8%	2 2%	3 3%	15 14%
0:UNCHANGED	48 48%	32 31%	26 27%	32 35%	20 25%	23 27%	23 26%	26 24%
-1:SLIGHT IMPROVEMENT	28 28%	27 26%	23 24%	15 16%	17 22%	17 20%	15 17%	17 16%
-2:REASONABLE CONTROL	11 11%	20 19%	29 30%	21 23%	15 19%	21 24%	20 22%	21 19%
-3:CONTROLLED	8 8%	10 10%	11 11%	17 18%	21 27%	23 27%	29 32%	30 28%
NO MEAN SE	101 -0.7 0.1	103 -0.8 0.1	96 -1.1 0.1	92 -1.1 0.1	79 -1.3 0.1	86 -1.5 0.1	90 -1.5 0.1	109 -1.2 0.1
H0:LE=PLC	p=0.053	p=0.001	p=0.001	p<0.001	p=0.026	p=0.005	p=0.002	p=0.001
POSITIVE RESPONSE	N %	N %	N %	N %	N %	N %	N %	N %
LOTEPREDNOL	55 54%	76 70%	84 84%	87 86%	80 86%	79 83%	89 88%	96 86%
PLACEBO	47 47%	57 55%	63 66%	53 58%	53 67%	61 71%	64 71%	68 62%
H0:LE=PLC	p=0.226	p=0.016	p=0.004	p<0.001	p=0.012	p=0.093	p=0.008	p<0.001
VISIT BEGINNING SUSTAINED RESPONSE	N	N	N	N	N	N	N	
LOTEPREDNOL	44	20	13	8	3	2	6	
PLACEBO	24	10	7	5	8	8	6	
H0:LE=PLC	p<0.001							

THE SCALE AS RECORDED IN THE CASE REPORT FORM RANGED FROM 0=FULLY CONTROLLED TO 4=WORSE. THE SCALE WAS TRANSFORMED BY SUBTRACTING 3 FROM EACH RATING SO THAT CHANGE FROM BASELINE WAS MORE CONSISTENT WITH THE OTHER SCALES--i.e., -3 TO -1 = DECREASING LEVELS OF IMPROVEMENT, 0=UNCHANGED AND 1=WORSE.

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Other variables**FINAL VISIT RESPONSE RATE (improvement of at least 1 unit)**

VARIABLE	LE GROUP		PLACEBO GROUP		p-VALUE
	N	%	N	%	
ERYTHEMA	44	83	31	65	0.035
DISCHARGE	44	77	38	69	0.335
FOREIGN BODY SENSATION	76	83	65	68	0.019
TEARING	62	87	53	67	0.004
PHOTOPHOBIA	52	88	34	64	0.003

AREA UNDER THE CURVE

VARIABLE	LE GROUP		PLACEBO GROUP		p VALUE
	N	%	N	%	
ERYTHEMA	53	-50.7	48	-31.4	< 0.001
DISCHARGE	57	-40.6	55	-24.3	0.002
FOREIGN BODY SENSATION	92	-46.7	96	-36.8	0.006
TEARING	71	-49.8	79	-34.4	< 0.001
PHOTOPHOBIA	59	-49.0	53	-29.3	< 0.001

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IOP Evaluations

<u>Baseline</u>	<u>N (Patients)</u>	<u>Mean</u>	<u>S.E.</u>	
LE	111	14.7	0.2	
PLACEBO	109	14.9	0.2	p = 0.626

<u>Armaly (≥ 6 mm Hg)</u>	<u>N (Patients)</u>	<u>Each Visit</u>	<u>Any Visit</u>	
LE	111	2% - 10%	15%	
PLACEBO	109	0% - 1%	4%	p = 0.004

<u>Becker (≥ 20 mm Hg)</u>	<u>N (Eyes)</u>	<u>Each Visit</u>	
LE	215	3% - 10%	
PLACEBO	213	1% - 4%	

<u>Stewart (≥ 10 mm Hg)</u>	<u>N (Patients)</u>	<u>Each Visit</u>	<u>Any Visit</u>	
LE	111	0% - 2%	3%	
PLACEBO	109	0%	0%	p = 0.099

<u>Mean Changes</u>	<u>N (Patients)</u>	<u>Each Visit</u>	
LE	111	-0.1 to +1.0	
PLACEBO	109	0.0 to -1.3	

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IOP Summary

INTRAOCULAR PRESSURE (mmHg)
FREQUENCY DISTRIBUTION OF OBSERVED RATINGS (INDIVIDUAL EYES)

	VISIT 1 DAY 0	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL VISIT	VISIT 9 SAFETY FU
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
<20 mmHg	215 97%	196 96%	213 97%	192 94%	193 94%	172 90%	171 90%	192 95%	209 94%	175 98%
20-25 mmHg	7 3%	8 4%	7 3%	12 6%	13 6%	20 10%	17 9%	10 5%	11 5%	3 2%
26-31 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	2 1%	0 0%	2 1%	0 0%
>31 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
NO	111	102	110	102	103	96	95	101	111	89
MEAN	14.7	15.0	14.9	15.0	15.2	15.6	15.7	15.5	15.6	14.5
SE	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.2	0.3	0.2
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %	N %
<20 mmHg	213 98%	198 98%	204 98%	190 98%	176 96%	152 96%	170 99%	181 99%	217 100%	158 100%
20-25 mmHg	5 2%	4 2%	4 2%	4 2%	8 4%	6 4%	2 1%	1 1%	1 0%	0 0%
26-31 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
>31 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
NO	109	101	104	97	92	79	86	91	109	79
MEAN	14.9	14.9	14.6	14.5	14.2	14.3	14.4	14.4	14.2	13.7
SE	0.2	0.2	0.2	0.2	0.3	0.3	0.2	0.2	0.2	0.3

H0: LE=PLC p=0.626

FREQUENCY DISTRIBUTION OF CHANGE FROM BASELINE RATINGS (INDIVIDUAL EYES)

	VISIT 2 DAY 2-3	VISIT 3 DAY 7	VISIT 4 DAY 14	VISIT 5 DAY 21	VISIT 6 DAY 28	VISIT 7 DAY 35	VISIT 8 DAY 42	FINAL VISIT	VISIT 9 SAFETY FU
LOTEPREDNOL (LE)	N %	N %	N %	N %	N %	N %	N %	N %	N %
<6 mmHg	198 97%	216 98%	195 96%	193 94%	175 91%	177 93%	190 94%	208 94%	175 98%
6-9 mmHg	4 2%	3 1%	9 4%	12 6%	13 7%	10 5%	12 6%	12 5%	3 2%
10-15 mmHg	2 1%	1 0%	0 0%	1 0%	4 2%	3 2%	0 0%	2 1%	0 0%
>15 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
NO	102	110	102	103	96	95	101	111	89
MEAN	0.3	0.2	0.4	0.5	1.0	0.8	0.7	0.8	-0.1
SE	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3	0.3
PLACEBO (PLC)	N %	N %	N %	N %	N %	N %	N %	N %	N %
<6 mmHg	200 99%	208 100%	192 99%	183 99%	157 99%	171 99%	182 100%	218 100%	158 100%
6-9 mmHg	2 1%	0 0%	2 1%	1 1%	1 1%	1 1%	0 0%	0 0%	0 0%
10-15 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
>15 mmHg	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%	0 0%
NO	101	104	97	92	79	86	91	109	79
MEAN	0.0	-0.3	-0.6	-0.7	-0.7	-0.6	-0.7	-0.7	-1.3
SE	0.2	0.2	0.2	0.3	0.3	0.2	0.2	0.2	0.3

H0: LE=PLC p=0.234 p=0.117 p=0.008 p=0.003 p=0.001 p=0.002 p<0.001 p<0.001 p=0.003

IOP Summary

FREQUENCY DISTRIBUTION (PATIENTS - EITHER EYE)

RESPONSE: CHG>=6 mmHg	VISIT 2		VISIT 3		VISIT 4		VISIT 5		VISIT 6		VISIT 7		VISIT 8		FINAL		VISIT 9	
*****	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
LOTEPREDNOL	3	3%	2	2%	7	7%	8	8%	10	10%	8	8%	7	7%	8	7%	2	2%
PLACEBO	1	1%	0	0%	1	1%	1	1%	1	1%	1	1%	0	0%	0	0%	0	0%
H0:LE=PLC	p=0.352		p=0.189		p=0.029		p=0.023		p=0.006		p=0.023		p=0.010		p=0.005		p=0.160	

RESPONSE: CHG>=10 mmHg	VISIT 2		VISIT 3		VISIT 4		VISIT 5		VISIT 6		VISIT 7		VISIT 8		FINAL		VISIT 9	
*****	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
LOTEPREDNOL	1	1%	1	1%	0	0%	1	1%	2	2%	2	2%	0	0%	1	1%	0	0%
PLACEBO	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
H0:LE=PLC - NOT TESTED																		

TIME TO CHG>=6 mmHg	NEVER															
*****	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
LOTEPREDNOL	94	85%	3	3%	0	0%	5	5%	3	3%	3	3%	2	2%	1	1%
PLACEBO	105	96%	1	1%	0	0%	1	1%	1	1%	1	1%	0	0%	0	0%
H0:LE=PLC	p=0.004															

TIME TO CHG>=10 mmHg	VISIT 2		VISIT 3		VISIT 4		VISIT 5		VISIT 6		VISIT 7		VISIT 8	
*****	N	%	N	%	N	%	N	%	N	%	N	%	N	%
LOTEPREDNOL	108	97%	1	1%	1	1%	0	0%	0	0%	0	0%	1	1%
PLACEBO	109	100%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
H0:LE=PLC	p=0.099													

p < 0.001 to 0.234

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IOP Individual Listing

INV	TRT	PAT	TRT EYE	EYE	FINAL DAY CHG		BASELINE DAY OBS	CHANGE FROM BASELINE (*: CHG-6)																SAFETY FU
								VISIT 2 DAY CHG	VISIT 3 DAY CHG	VISIT 4 DAY CHG	VISIT 5 DAY CHG	VISIT 6 DAY CHG	VISIT 7 DAY CHG	VISIT 8 DAY CHG										
122	LE	2247	00	00	42	4	0 11	4	1	7	5	14	5	21	6*	28	7*	35	3	42	4	49	5	
				OS		4	11		2		5		5		7*			5			4		5	
139	LE	2087	00	00	40	4	0 11			5	0	14	0	21	3	29	6*			40	4	56	4	
				OS		4	12				0		1		2		5				4		4	
151	LE	2498	05	00	43	3	0 12	4	1	8	0	15	6*	22	4	29	7*	36	5	43	3	50	3	
				OS		2	13		-1		-1		5		3		6*		4	2		2		
151	LE	2184	05	00	43	6*	0 14	3	0	8	0	17	0	22	1	29	5	36	3	43	6*	50	3	
				OS		6*	14		0		0		0		0		5		4	6*		2		
152	LE	2413	05	00	44	4	0 13	2	0	7	0	14	1	21	-2	28	5	35	5	44	4	49	4	
				OS		6*	13		1		-3		1		-2		5		6*		4	4		
153	LE	2205	00	00	42	2	0 10	2	7*	7	2	14	5	21	6*	29	4	35	3	42	2	49	5	
				OS		1	11		6*		1		5		4		1		1	1		4		
154	LE	2441	00	00	42	8*	0 17	3	-2	7	0	14	2	21	3	28	3	35	6*	42	8*	49	1	
				OS		7*	17		-2		-1		2		3		1		3	7*		0		
155	LE	2123	00	00	40	0	0 14	4	0	6	0	15	4	21	6*	27	2	35	6*	40	0	49	-2	
				OS		0	14		2		0		6*		6*		2		6*	0		-2		
155	LE	2126	00	00	45	9*	0 8	3	9*	10	10*	18	6*	24	10*	31	11*	38	10*	45	9*	52	8*	
				OS		5	12		6*		6*		2		6*		10*		6*	5		4		
155	LE	2132	00	00	42	5	0 12	2	2	7	4	14	3	21	4	28	3	35	2	42	5	49	2	
				OS		5	12		2		4		7*		4		3		3	5		2		
155	LE	2128	00	00	44	4	0 12	2	4	8	4	15	6*	23	3	28	0	32	5	44	4	46	2	
				OS		4	12		4		5		5		3		0		5	4		2		
156	LE	2321	00	00	44	8*	0 14	2	1	7	1	15	6*	22	6*	28	7*	36	8*	44	8*	50	-1	
				OS		7*	12		3		5		6*		7*		7*		9*	7*		0		
156	LE	2323	00	00	35	11*	0 17	2	2	8	3	14	4	21	5	28	6*	35	11*					
				OS		14*	16		3		3		5		6*		7*		14*					
156	LE	2331	05	00	42	4	0 12	2	-1	7	0	14	3	21	5	28	5	35	5	42	4	49	4	
				OS		5	11		-1		1		3		6*		6*		6*	5		5		
156	LE	2528	05	00	42	9*	0 8	2	11*	7	7*	14	8*	21	9*	28	10*	35	8*	42	9*	49	6*	
				OS		9*	8		11*		7*		8*		9*		10*		8*	9*		6*		
156	LE	2333	00	00	43	-3	0 17	2	-2	8	-5	15	-3	22	-3	29	5	36	-3	43	-3	50	2	
				OS		-3	17		0		-3		-3		-3		7*		-3	-3		-2		
156	LE	2336	00	00	41	6*	0 12	3	3	7	4	13	0	20	3	27	7*			41	6*	49	-2	
				OS		6*	12		3		4		3		3		7*			6*		2		
N = 17																								
153	PLC	2209	00	00	21	3	0 11			8	1	14	6*	21	3									
				OS		3	11				2		6*		3									
155	PLC	2125	00	00	44	4	0 8			8	3	15	4	22	6*	29	3	37	6*	44	4	50	3	
				OS		0	12				-1		0		2		-4	2	2	0		-1		
155	PLC	2135	00	00	43	2	0 12	2	6*	8	5	15	4	22	4	30	4	36	3	43	2	50	2	
				OS		2	12		6*		5		4		4		4		3	2		2		
156	PLC	2329	05	00	44	0	0 12	2	0	7	5	14	5	22	3	29	2	35	4	44	0	52	3	
				OS		1	12		2		5		5		2		6*		4	1		3		
N = 4																								

ELICITED/OBSERVED EVENTS

	Loteprednol (n=111)			Placebo (n=109)		
	Patients Reporting			Patients Reporting		
	At least once	Total		At least once	Total	
DISCHARGE, EYE (EYE/GEN)	14	13%	17	14	13%	14
FOREIGN BODY SENSATION (EYE/GEN)	13	12%	14	21	19%	22
INJECTION (EYE/CON)	12	11%	14	21	19%	24
EPIPHORA (EYE/APP)	10	9%	12	13	12%	15
PHOTOPHOBIA (EYE/VIS)	7	6%	7	14	13%	16
PAPILLA (EYE/APP)	5	5%	5	9	8%	9
ITCHING, EYE (EYE/GEN)	4	4%	4	18	17%	20
CORNEAL ABNORMALITY (EYE/COR)	3	3%	3	2	2%	2
ERYTHEMA, EYELIDS (EYE/APP)	3	3%	3	9	8%	9
INTRAOCULAR PRESSURE, INC (EYE/IOP)	17	15%	20	4	4%	5
HEADACHE (HEAD)	13	12%	16	15	14%	25
ABNORMAL VISION (EYE/VIS)	6	5%	8	4	4%	6
INFECTION (GEN)	5	5%	6	5	5%	6
PHARYNGITIS (NASP)	4	4%	4	2	2%	2
CORNEAL LESION (EYE/COR)	3	3%	3	1	1%	1
ALLERGIC REACTION (GEN)	2	2%	3	4	4%	5
FLU SYNDROME (GEN)	2	2%	2	2	2%	3
DYSPEPSIA (GEN)	2	2%	2	1	1%	1
PERIODONTAL ABSCESS (BUC)	2	2%	2	0	0%	0
COUGH INCREASED (GEN)	2	2%	2	0	0%	0
BURNING, EYE (EYE/GEN)	2	2%	3	2	2%	2
EAR PAIN (EAR/GEN)	2	2%	2	0	0%	0
ABDOMINAL PAIN (ABDO)	1	1%	1	0	0%	0
ASTHENIA (GEN)	1	1%	1	0	0%	0
CHEST PAIN (THOR)	1	1%	1	0	0%	0
FEVER (GEN)	1	1%	1	2	2%	2
NECK PAIN (NECK)	1	1%	1	1	1%	1
PAIN (GEN)	1	1%	1	1	1%	1
HYPERTENSION (VASC/BP)	1	1%	1	0	0%	0
MIGRAINE (VASC/ART)	1	1%	1	0	0%	0
DIARRHEA (EC)	1	1%	1	1	1%	1
NAUSEA AND VOMITING (GEN)	1	1%	1	0	0%	0
EDEMA (WB)	1	1%	1	0	0%	0
GENERALIZED SPASM (MUS)	1	1%	1	0	0%	0
DIZZINESS (CNS/B)	1	1%	1	1	1%	1
NERVOUSNESS (CNS/B)	1	1%	1	0	0%	0
RHINITIS (NOSE)	1	1%	1	2	2%	2
SINUSITIS (SINS)	1	1%	1	1	1%	1
AMBLYOPIA (EYE/VIS)	1	1%	1	0	0%	0
BURNING, EYE, ON INSTILLATION (EYE/GEN)	1	1%	1	1	1%	1
DISCOMFORT, EYE (EYE/GEN)	1	1%	1	0	0%	0
DRY EYES (EYE/GEN)	1	1%	1	0	0%	0
EYE DISORDER (EYE/GEN)	1	1%	1	0	0%	0
IRRITATION, EYE (EYE/GEN)	1	1%	1	1	1%	1
KERATITIS (EYE/COR)	1	1%	1	0	0%	0
TASTE PERVERSION (TST)	1	1%	1	0	0%	0
DYSMENORRHEA (FG/MENS)	1	1%	1	1	1%	1
URINARY TRACT INFECTION (UT/GEN)	1	1%	1	2	2%	2
CYST (GEN)	0	0%	0	1	1%	1
MOUTH ULCERATION (BUC)	0	0%	0	1	1%	1
NAUSEA (GEN)	0	0%	0	1	1%	1
ECCHYMOSIS (COAG/GEN)	0	0%	0	1	1%	1
VERTIGO (CNS/B)	0	0%	0	1	1%	1
EPISTAXIS (NOSE)	0	0%	0	1	1%	2
MACULOPAPULAR RASH (DERM/ERY)	0	0%	0	1	1%	1
RASH (DERM/ERY)	0	0%	0	1	1%	2
URTICARIA (DERM/GEN)	0	0%	0	1	1%	1
TWITCHING (GEN)	0	0%	0	1	1%	1
CATARACT SPECIFIED (EYE/LEN)	0	0%	0	1	1%	1
CONJUNCTIVITIS (EYE/CON)	0	0%	0	2	2%	2
EYE PAIN (EYE/GEN)	0	0%	0	1	1%	1
KERATOCONJUNCTIVITIS (EYE/CON)	0	0%	0	2	2%	2
MEIBOMIAN GLAND ABNORMALITY (EYE/APP)	0	0%	0	1	1%	1

Study #2 Conclusions:

1. Loteprednol etabonate has demonstrated superiority over its vehicle in the treatment of GPC while contact lenses are left in place (after the first 48 hours) based on evaluations of signs and symptoms of GPC and the global investigator and patient scores.
2. There is an acceptable safety profile, however, individual adverse experiences may need to be re-coded/classified. The case of amblyopia should be explained.
3. Loteprednol etabonate has demonstrated the ability to cause elevated intraocular pressure in some patients (5-15%).
4. There were no significant differences with respect to age, gender, race or eye color (data not shown).

APPEARS THIS WAY
ON ORIGINAL

8.2 Indication # 2 Seasonal Allergic Conjunctivitis

8.2.1 Reviewer's Trial # 3 Sponsor's protocol # 121

Title: Safety and Efficacy of Loteprednol Etabonate in Seasonal Allergic Conjunctivitis

Objective:

A prophylactic study to evaluate the safety and effectiveness of loteprednol etabonate 0.5% ophthalmic suspension (LE) in preventing the ocular signs and symptoms accompanying seasonal allergic conjunctivitis (SAC), during peak pollen levels.

Study Design:

A randomized, double-masked, placebo controlled, parallel group, multi-center (13) comparison study.

	Day									
Procedure	0	2-3	7	14	21	28	35	42	49	
Informed Consent	x									
Inclusion/Exclusion	x									
Demographics. History	x									
Medication History	x									
Pregnancy Test*	x*							x*		
Dilated Funduscopy	x							x		
Skin Test Results	x									
Intraocular Pressure	x	x	x	x	x	x	x	x	x	
Visual Acuity	x	x	x	x	x	x	x	x	x	
Ocular Symptoms	x	x	x	x	x	x	x	x	x	
Slit-Lamp Biomicroscopy	x	x	x	x	x	x	x	x	x	
Issue Medication	x	x*	x	x	x	x	x			
Issue Diary	x	x	x	x	x	x	x	x	x	
Recover Diary Card		x	x	x	x	x	x	x	x	
Investigator's Clinical Judgment		x	x	x	x	x	x	x		
Investigator's Global Assessment		x	x	x	x	x	x	x		
Recover Medication		x	x	x	x	x	x	x	x	
Exit Form									x	
Dismiss Patient									x	
Environmental Allergens Report	x	x	x	x	x	x	x	x	x	

* Women of childbearing potential only.
^a As needed

Ragweed				
Investigator	Start Date (Day)	Stop Date (Day)	Average Count (parts/m ²)	Peak Period Range (parts/m ²)
112	23 September 93(67)	13 October 93(87)	186.5	80 - 290
122	23 September 93(25)	13 October 93(45)	46.8	0 - 130
130	25 August 93(38)	14 September 93(58)	222.0	110 - 570
151	29 August 93(33)	10 September 93(53)	32.3	0 - 55
157	25 August 93(30)	14 September 93(50)	348.5	0 - 570
158	30 August 93(43)	19 September 93(63)	66.1	30 - 140
159	21 August 93(20)	10 September 93(40)	62.0	10 - 140
160	05 September 93(42)	25 September 93(62)	80.2	40 - 180
161	25 August 93(38)	14 September 93(58)	133.8	30 - 250

Mountain Cedar				
Investigator	Start Date (Day)	Stop Date (Day)	Average Count (parts/m ²)	Peak Period Range (parts/m ²)
107	25 December 93(25)	14 January 94(43)	890.3	70 - 2350
112	26 December 93(52)	15 January 94(72)	885.0	60 - 2800
174	27 December 93(49)	16 January 94(69)	902.4	70 - 2350
175	27 December 93(49)	16 January 94(69)	6926.7	20 - 25000
176	27 December 93(49)	16 January 94(69)	6926.7	20 - 25000

Number in parenthesis is the pollen day number e.g. pollen day 69 is the 69th day since the Investigator started recording daily pollen counts.

Reviewer's Comments: *As prospectively defined in the protocol, evaluations were performed over a six week period but efficacy was based on the evaluations performed at the peak pollen periods.*

Inclusion Criteria:

To be eligible for participation in the study, patients had to meet all of the following criteria before dosing:

- Age 18-75 years.
- A history of seasonal allergic conjunctivitis for two previous years to the allergen prevalent at each investigative site at the time the study was to be conducted.
- Evidence of a positive history of a seasonal allergy (i.e. to mountain cedar, elm, oak, ragweed, etc.) with either a positive skin (prick or intradermal) or RAST test (within the past 36 months) to the seasonal allergen prevalent at the investigative site at the time of the study.
- Willing to comply with the protocol instructions.
- The written informed consent obtained.
- Negative test to a blood or urine pregnancy test (Women of childbearing potential only).

Exclusion Criteria:

Patients with any of the following conditions at the Enrollment Examination were to be excluded from the study.

- Absent or minimal symptoms of seasonal allergic conjunctivitis during the previous year to the allergen prevalent at each investigative site at the time the study was to be conducted.
- No requirement for medication to control seasonal allergic conjunctivitis during the previous year's season.
- Active signs and symptoms of seasonal allergic conjunctivitis greater than
 - i. 2+ itching
 - ii. 1+ bulbar conjunctival injection
 - iii. 1+ palpebral conjunctival injection
 - iv. 1+ tearing
- Pregnant or lactating female.
- Female of childbearing potential using inadequate birth control methods.
- Previous allergy to corticosteroids, LE or to any component of the study medications.
- Concurrent therapy with non-steroidal anti-inflammatory agents, mast cell stabilizers, antihistamines, decongestants or beta-blocker during the period of masked medication treatment and within two (2) days prior to Visit #2 (Day 0).
- Therapy with oral or topical corticosteroids within two weeks prior to the start of the study.
- Any abnormality preventing reliable applanation tonometry in either eye.
- Intraocular pressure > 21 mm Hg or any type of glaucoma.
- Ocular surgery within the past six months.
- Best corrected distance visual acuity in either eye worse than or equal to 20/100.
- Anticipated travel for more than a 24 hour period greater than 50 miles away from home.
- Presence of any ocular pathology other than acute, seasonal allergic conjunctivitis (i.e., excluded is vernal conjunctivitis, GPC, viral or bacterial conjunctivitis) or perennial allergic conjunctivitis.
- History of any severe/serious ocular pathology or medical condition that could result in the patient's inability to complete this study.
- Previous participation in this study
- Participation in an IND study within the past 30 days.
- Unlikely to comply with the protocol instructions for whatever reason (confusion, infirmity, alcohol abuse, or drug abuse, etc.).

Efficacy Criteria

The primary efficacy variable was a composite score equal to the sum of the individual scores for ocular itching and bulbar conjunctival injection.

The secondary efficacy variable was the Investigator Global Assessment at the end of the peak evaluation period. This was to be based on the evaluation of the control of the patient's ocular allergic signs and symptoms as demonstrated through the patient diary entries over a period encompassing the two previous visits and the current visit (e.g., Visits #2 through Visit #4) as well as the ophthalmic examinations findings and weekly Investigator's clinical judgement from the same two previous visits and current visit (e.g., Visits #2 through #4).

The supportive data came from a secondary composite which was equal to the sum of the individual scores for tearing, erythema, chemosis and discomfort.

Other signs and symptoms were foreign body sensation, photophobia, discharge, burning/stinging and corneal disease.

Most signs and symptoms were rated using a four point scale (0 - 3) where 0 = absent, 1 = mild, 2 = moderate and 3 = severe.

For itching a five point scale (0-4) was used where 0-absent, 1-trace, 2=mild, 3=moderate and 4=severe.

The Investigator global assessment used a 5 point scale (0-4) where 0=fully controlled, 1=reasonably controlled, 2=slight improvement, 3=unchanged and 4=worse.

For selected parameters definitions were provided with the scales, as shown below.

Itching

0	absent	No desire to scratch or rub eyelids
1	trace	Rare need to scratch or rub eyelids but sensation is not completely absent
2	mild	Occasional desire to rub or scratch eyelids
3	moderate	Frequent desire to scratch or rub eyelids
4	severe	Constant desire to scratch or rub eyelids

Discharge

0	Absent	No discharge whatsoever
1	Mild	Mucus or crustiness present, but in small amounts
2	Moderate	Mucus present
3	Severe	Large quantities of thick mucus strands

Photophobia

0	Absent	Able to tolerate normal office light
1	Mild	Mild discomfort in normal office light
2	Moderate	Able to tolerate normal office light only with sunglasses
3	Severe	Unable to tolerate normal office light even with sunglasses

Investigators:

Greg Berdy, M.D.	St. Louis, MO	(Investigator #130)
Steven Dell, M.D.	Austin, TX	(Investigator #174)
Stacy Embry, O.D.	Evansville, IN	(Investigator #157)
Kenneth Fox, M.D.	McLean, VA	(Investigator #151)
Barry Horwitz, M.D.	Houston, TX	(Investigator #122)
Kristine Kunesch-Part., M.D.	Dayton, OH	(Investigator #161)
Robert Laibovitz, M.D.	Austin, TX	(Investigator #112)
Jerrold Levin, M.D.	Cincinnati, OH	(Investigator #158)
George Lowry, M.D.	San Antonio, TX	(Investigator #175)
Richard Orlando, M.D.	Columbus, OH	(Investigator #159)
David Parks, M.D.	Bowling Green, KY	(Investigator #160)
David Shulman, M.D.	San Antonio, TX	(Investigator #176)
Tom Walters, M.D.	Austin, TX	(Investigator #107)

Reviewer's Comments: *A number of these investigators where also investigators in Studies #1 and #2 (Berdy, Fox, Laibovitz, Levin).*

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INVESTIGATOR	TREATMENT	RANDOMIZED	***** REASON STUDY INCOMPLETE *****					
			COMPLETED TREATMENT	COMPLETED STUDY	LACK OF EFFICACY	MEDICAL EVENTS	OTHER UNRELATED	NO SAFETY FOLLOW-UP
107	LOTEPREDNOL PLACEBO	9	8 (89%)	8 (89%)	0 (0%)	0 (0%)	1 (11%)	0 (0%)
		10	9 (90%)	9 (90%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)
112	LOTEPREDNOL PLACEBO	10	10 (100%)	10 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		10	7 (70%)	7 (70%)	1 (10%)	0 (0%)	2 (20%)	0 (0%)
122	LOTEPREDNOL PLACEBO	8	8 (100%)	8 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		8	7 (88%)	7 (88%)	0 (0%)	0 (0%)	1 (13%)	0 (0%)
130	LOTEPREDNOL PLACEBO	4	4 (100%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		4	4 (100%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
151	LOTEPREDNOL PLACEBO	11	10 (91%)	10 (91%)	0 (0%)	0 (0%)	1 (9%)	0 (0%)
		12	10 (83%)	10 (83%)	0 (0%)	0 (0%)	2 (17%)	0 (0%)
157	LOTEPREDNOL PLACEBO	12	11 (92%)	11 (92%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)
		12	9 (75%)	9 (75%)	0 (0%)	1 (8%)	2 (17%)	0 (0%)
158	LOTEPREDNOL PLACEBO	4	3 (75%)	3 (75%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)
		4	3 (75%)	3 (75%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)
159	LOTEPREDNOL PLACEBO	8	8 (100%)	8 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		7	7 (100%)	7 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
160	LOTEPREDNOL PLACEBO	14	8 (57%)	8 (57%)	1 (7%)	1 (7%)	4 (29%)	0 (0%)
		13	9 (69%)	9 (69%)	1 (8%)	1 (8%)	2 (15%)	0 (0%)
161	LOTEPREDNOL PLACEBO	4	4 (100%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		4	3 (75%)	3 (75%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)
174	LOTEPREDNOL PLACEBO	21	14 (67%)	14 (67%)	0 (0%)	3 (14%)	4 (19%)	0 (0%)
		20	16 (80%)	16 (80%)	0 (0%)	2 (10%)	2 (10%)	0 (0%)
175	LOTEPREDNOL PLACEBO	19	19 (100%)	19 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		22	20 (91%)	20 (91%)	2 (9%)	0 (0%)	0 (0%)	0 (0%)
176	LOTEPREDNOL PLACEBO	22	19 (86%)	19 (86%)	2 (9%)	0 (0%)	1 (5%)	0 (0%)
		21	18 (86%)	18 (86%)	0 (0%)	1 (5%)	2 (10%)	0 (0%)
OVERALL	LOTEPREDNOL PLACEBO	146	126 (86%)	126 (86%)	3 (2%)	6 (4%)	11 (8%)	0 (0%)
		147	122 (83%)	122 (83%)	5 (3%)	6 (4%)	14 (10%)	0 (0%)

DEFINITIONS

VALID VISIT: MEDICATION WAS TO BE TAKEN WITH 48 HOURS OF EVALUATION.

COMPLETED TREATMENT: PATIENTS WERE TO HAVE A VALID VISIT 8 EVALUATION (PROTOCOL: DAY 39-45; ACTUAL: DAY 39-47).

COMPLETED STUDY: PATIENTS WERE TO RETURN FOR A SAFETY FOLLOW-UP (VISIT 9) AFTER TREATMENT COMPLETION.

REASON STUDY INCOMPLETE: LACK OF EFFICACY, MEDICAL EVENTS AND OTHER UNRELATED REFER TO PATIENTS WHO DID NOT COMPLETE TREATMENT. MEDICAL EVENTS REFER TO ANY EVENT LEADING TO DISCONTINUATION WITHOUT REGARD TO RELATIONSHIP TO TREATMENT. OTHER UNRELATED REASONS INCLUDE MISSED VISITS, INCORRECT DOSING AND OTHER CAUSES UNRELATED TO TREATMENT.

NO SAFETY FOLLOW-UP RELATES ONLY TO PATIENTS WHO COMPLETE TREATMENT BUT DO NOT RETURN FOR THEIR SAFETY EVALUATION.

AGE (yrs)		LOTEPREDNOL	PLACEBO	
=====				
	N	145	143	p=0.442
	MEAN	42.1	41.8	
	SE	1.1	1.1	
	MIN	20.0	18.0	
	MAX	87.	75.0	
	<30 yrs	22	29	p=0.246
	≥30 yrs	123	114	

GENDER				
=====				
MALE	N	51	55	p=0.578
FEMALE	N	94	88	

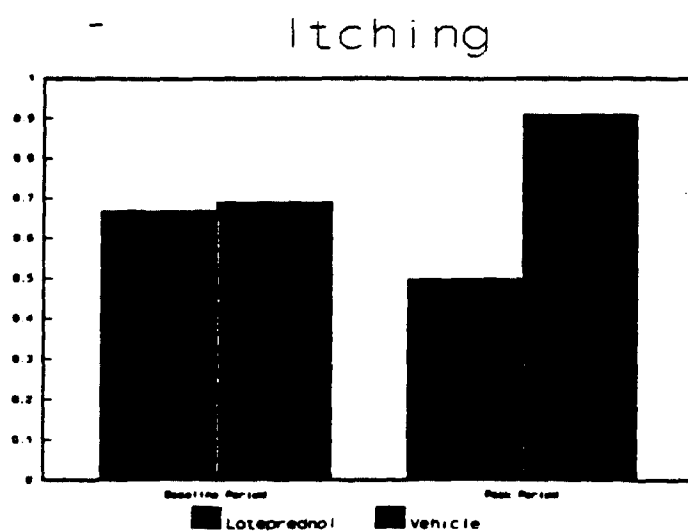
RACE				
=====				
CAUCASIAN	N	121	123	p=0.461
OTHER	N	24	20	

PIGMENTATION				
=====				
LIGHT	N	80	81	p=0.719
DARK	N	65	62	

ALLERGEN				
=====				
RAGWEED	N	69	67	p=0.680
MTN CEDAR	N	76	76	

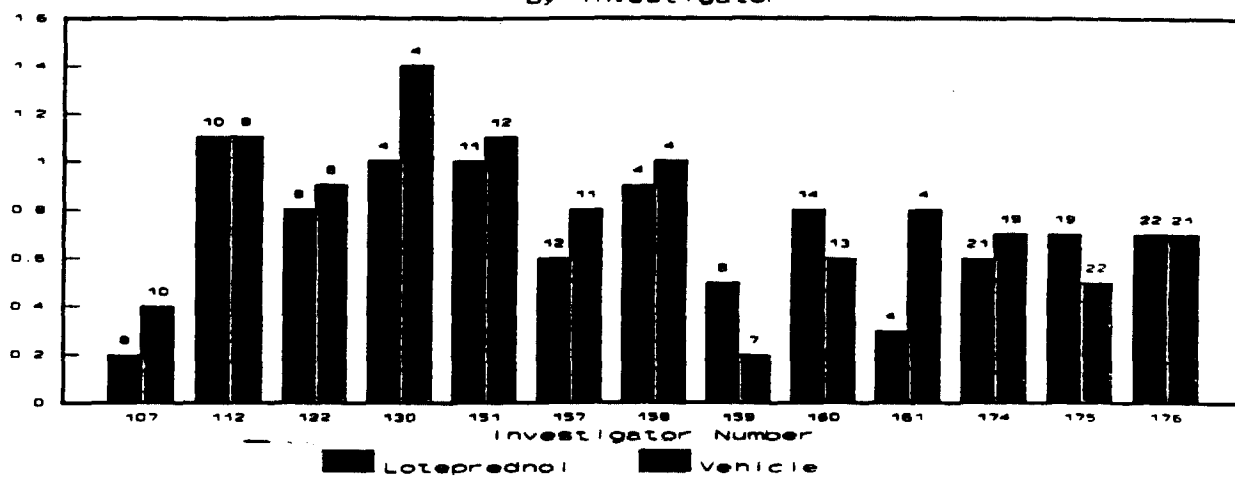
BASELINE CLIN JUDGEMENT				
=====				
ABSENT	N	35	36	p=0.823
PRESENT	N	110	107	

Reviewer's Comments: *There were no significant differences between groups. The category "other" should be more specifically identified.*

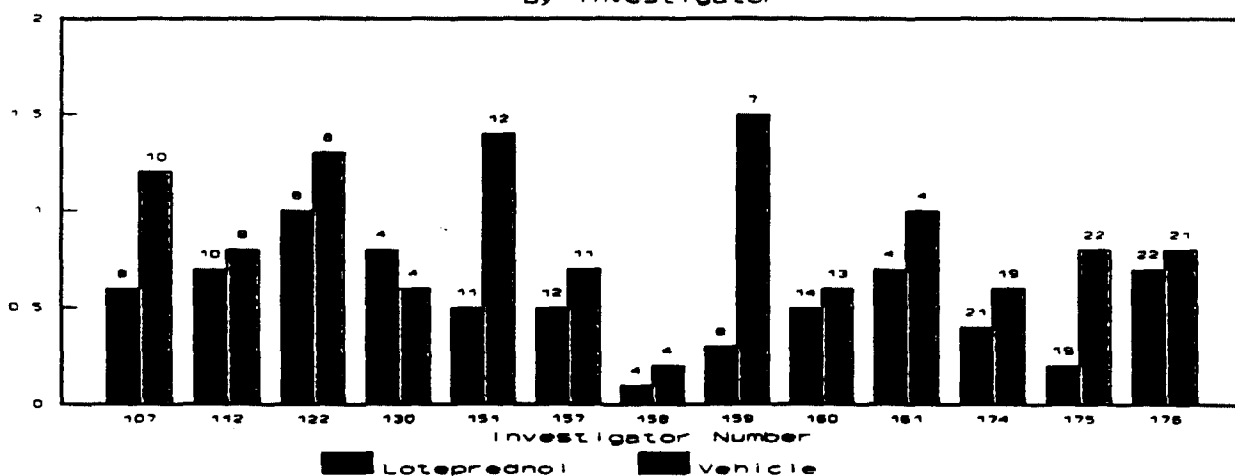


Reviewer's Comments: *The differences in itching and injection (redness) are statistically significant, but are of marginal clinical significance.*

Itching - Baseline Period
By Investigator



Itching - Peak Period
By Investigator



The number of subjects in each group is shown above the bar for each group.

Reviewer's Comments: *There was significant investigator interaction at the Peak Period. This is of concern because of the minimal differences between groups.*

Itching & Redness - Per Protocol

	ITCHING		BULBAR INJECTION	
	BASELINE	PEAK	BASELINE	PEAK
LOTEPREDNOL				
N	132	132	132	132
MEAN	0.67	0.50	0.47	0.37
SE	0.06	0.05	0.04	0.04
MIN				
MAX				
PLACEBO				
N	126	126	126	126
MEAN	0.69	0.91	0.41	0.62
SE	0.06	0.06	0.04	0.04
MIN				
MAX				

RESULTS OF ANALYSIS

SOURCE	df	p	df	p	df	p	df	p
TREATMENT	1	0.824	1	0.001	1	0.458	1	0.001
INVESTIGATOR	10	0.011	10	0.002	10	0.001	10	0.001
INTERACTION			10	0.109			10	0.150
ERROR			236				236	

ESTIMATE

LE - PLC

-0.44

-0.26

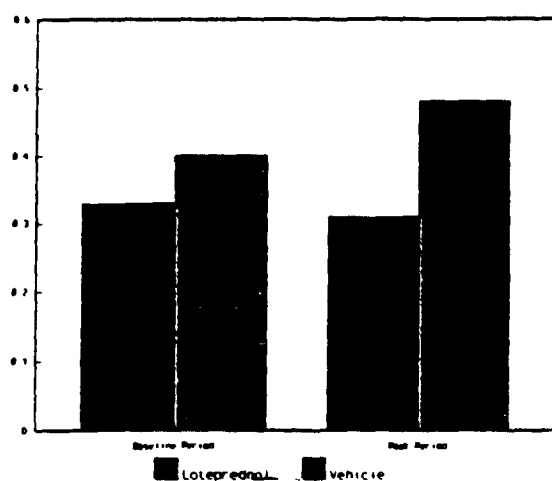
95% CONF LIMITS

LOWER

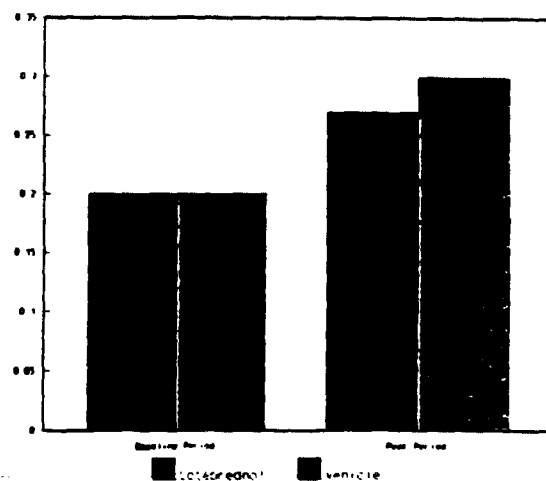
UPPER

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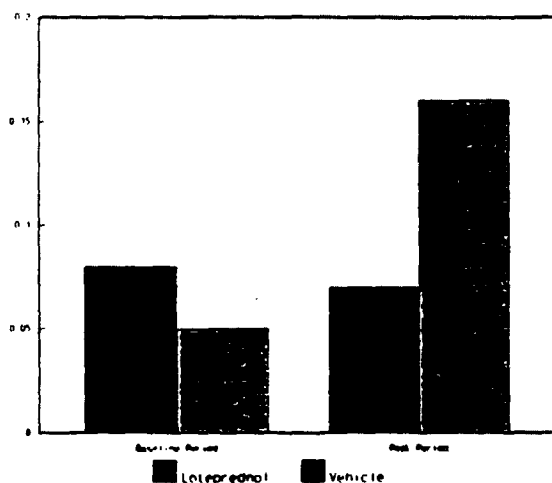
Discomfort



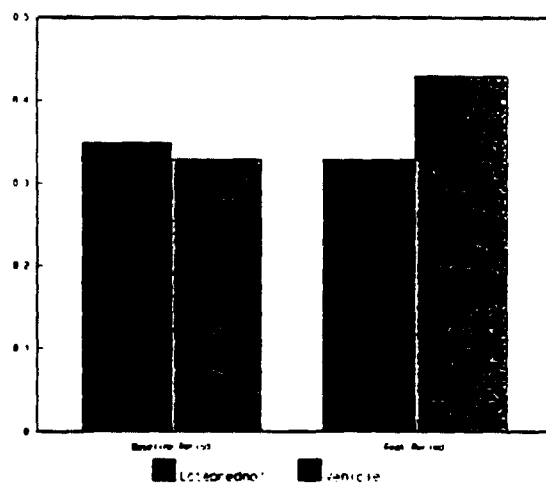
Chemosis



Erythema



Tearing

**Reviewer's Comments:**

The differences in chemosis and tearing are not statistically significant. The differences in discomfort and erythema are statistically significant but are of marginal clinical significance.

IOP

<u>Baseline</u>	<u>N (Patients)</u>	<u>Mean</u>	<u>S.E.</u>
LE	145	15.0	0.2
PLACEBO	143	14.6	0.2

p = 0.190

<u>Armaly ($\Delta = \geq 6$ mm Hg)</u>	<u>N (Patients)</u>	<u>Each Visit</u>	<u>Any Visit</u>
LE	145	4% - 10%	17%
PLACEBO	143	1% - 7%	12%

p = 0.153

<u>Becker (> 20 mm Hg)</u>	<u>N (Eyes)</u>	<u>Each Visit</u>
LE	269	8% - 12%
PLACEBO	278	2% - 5%

<u>Stewart ($\Delta = \geq 10$ mm Hg)</u>	<u>N (Patients)</u>	<u>Each Visit</u>	<u>Any Visit</u>
LE	145	0%	0%
PLACEBO	143	0% - 1%	1%

p = 0.296

<u>Mean Changes</u>	<u>N (Patients)</u>	<u>Each Visit</u>
LE	145	0.4 to +1.0
PLACEBO	143	-0.0 to 0.4

p < 0.013 to 0.376

Reviewer's Comments: *The IOP levels in the loteprednol is consistently higher than in the placebo group.*

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	Loteprednol (n=146)			Placebo (n=147)		
	Patients Reporting		Total	Patients Reporting		Total
	At least once			At least once		
RHINITIS (NOSE)	74	51%	120	69	47%	125
HEADACHE (HEAD)	50	34%	111	45	31%	118
ITCHING, EYE (EYE/GEN)	40	27%	47	56	38%	64
INJECTION (EYE/CON)	32	22%	40	60	41%	71
DISCOMFORT, EYE (EYE/GEN)	30	21%	32	43	29%	46
INTRAOCULAR PRESSURE, INCREASED (EYE/IOP)	28	19%	34	19	13%	25
EPIPHORA (EYE/APP)	27	18%	30	37	25%	41
BURNING, EYE (EYE/GEN)	24	16%	26	42	29%	49
CHEMOSIS (EYE/CONJ)	21	14%	24	23	16%	25
DISCHARGE, EYE (EYE/GEN)	20	14%	23	27	18%	27
COUGH INCREASED (GEN)	17	12%	21	17	12%	18
PHARYNGITIS (NASP)	17	12%	18	21	14%	22
FOREIGN BODY SENSATION (EYE/GEN)	16	11%	17	29	20%	30
PHOTOPHOBIA (EYE/VIS)	13	9%	14	23	16%	25
ERYTHEMA, EYELIDS (EYE/APP)	12	8%	12	19	13%	20
PAIN (GEN)	9	6%	12	11	7%	13
ALLERGIC REACTION (GEN)	7	5%	16	13	9%	25
ABNORMAL VISION (EYE/VIS)	7	5%	7	4	3%	4
DRY EYES (EYE/GEN)	5	3%	5	7	5%	8
FEVER (GEN)	5	3%	5	6	4%	7
EDEMA (WB)	4	3%	4	1	1%	2
SINUSITIS (SINS)	4	3%	4	7	5%	7
BACK PAIN (BACK)	3	2%	3	6	4%	7
CHILLS (GEN)	3	2%	3	0	0%	0
FLU SYNDROME (GEN)	3	2%	3	3	2%	4
MIGRAINE (VASC/ART)	3	2%	6	0	0%	0
EAR DISORDER (EAR/GEN)	3	2%	3	5	3%	5
EYE PAIN (EYE/GEN)	3	2%	4	3	2%	4
MYALGIA (MUS)	3	2%	3	1	1%	1
DYSMENORRHEA (FG/MENS)	3	2%	4	3	2%	4
AMBLYOPIA (EYE/VIS)	3	2%	3	3	2%	4
BURNING, EYE, ON INSTILLATION (EYE/GEN)	3	2%	3	2	1%	3
VOMITING (GEN)	2	1%	2	3	2%	3
ASTHENIA (GEN)	2	1%	2	4	3%	4
LUNG DISORDER (LUNG)	2	1%	2	3	2%	3
CONJUNCTIVITIS (EYE/CON)	2	1%	2	4	3%	4
VOICE ALTERATION (LRNX)	1	1%	1	3	2%	3

Reviewer's Comments: *There are several misclassifications, similar to those observed in earlier studies.*

APPEARS THIS WAY
ON ORIGINAL

Study #3 Conclusions: -

1. Loteprednol etabonate has demonstrated marginal superiority over its vehicle in some of the signs and symptoms of seasonal allergic conjunctivitis.
2. There is an acceptable safety profile, however, individual adverse experiences may need to be re-coded/classified.
3. Loteprednol etabonate has demonstrated the ability to cause elevated intraocular pressure in some patients.
4. There were no significant differences with respect to age, race or eye color (data not shown).

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ON ORIGINAL

8.3 Indication # 3 Acute Anterior Uveitis**8.3.1 Reviewer's Trial # 4 Sponsor's protocol # 122**

Title: Safety and Efficacy of Loteprednol Etabonate in Acute Anterior Uveitis

Objective:

To evaluate and compare the safety and effectiveness of loteprednol etabonate 0.5% ophthalmic suspension (LE) with prednisolone acetate 1.0% ophthalmic suspension (PA) in reducing the ocular signs and symptoms associated with acute anterior uveitis (AAU).

Study Design:

A randomized, double-masked, active controlled, parallel group, multi-center (11) comparison study. Eight sites were in the U.S. and 3 were in the U.K.

Dosing Schedule:

For the on-treatment-phase all patients were to follow the same treatment regimen through Visit 5 (Day 21). The initial dosing regimen was 8x/day until Day 7, then 6x/day until Day 14, and 4x/day until Day 21. From Visit 5 through Visit 7 the regimen continued with 4x/day. At Visits 5-7 patients became eligible for concluding treatment if the anterior chamber cell rating were 0. Treatment was to be concluded by tapering the number of doses per day from 4 down to 0 in steps of 1 dose per day over a 14 day period. The on-treatment phase was from Visit 1 through the visit at which the cell rating reached 0, or Visit 7 occurred, or the patient discontinued prematurely from treatment.

Concomitant Therapy

Except for the assigned masked test medications (LE or PA), cycloplegics to control posterior synechiae, and ocular hypertensives to lower IOP, no other concomitant ocular therapy was to be used during the study. Any patient requiring adjunctive ocular therapy to control their uveitis condition during the conduct of this trial was to be discontinued from the study as a treatment failure and placed on appropriate medication.

Study Schedule

	Visit #1 (Day 0)	Visit #2,3 & 4 (48-72 hrs (Day 7 & 14)	Visit # 5,6,& 7 (Days 21, 28 & 35)	Visit #8 (Day 42)	Visit #9 (Day 49)
Informed Consent	x				
Inclusion/Exclusion	x				
Demographics, History	x				
HLA-B27 Test	x				
Pregnancy Test	x	x ^a	x ^a	x ^a	x
Visual Acuity	x	x	x	x	x
Ocular Symptoms	x	x	x	x	x
Slit-Lamp Biomicroscopy	x	x	x	x	x
Intraocular Pressure	x	x	x	x	x
Fundusoscopic Examination	x	x ^a	x ^a	x ^a	x
Reduced Dosing			x ^b	x	
Issue Medication	x	x ^c	x	x	x
Recover Medication		x ^c	x	x	x
Exit Form		x ^a	x ^a	x ^a	x
Dismiss Patient		x ^a	x ^d	x ^a	x

^a If the patient has been discontinued from the study or Dosing Schedule has been completed.

^b Visit #5 (Day 21 $\pm$ 2 days) ONLY - REDUCED DOSING, see schedule #1 or schedule #2

^c As needed.

^d Day 35 ONLY - Discontinue patient from the study if "0" cell rating has not been achieved.

	On-Treatment Phase							Final Dose Reduction Phase		
SCHEDULED VISIT	1	2	3	4	5	6	7	1	2	3
								(Days Since Cell = 0)		
DAY:	0	2-3	7	14	21	28	35	(0)	(+7)	(+14)
BEGIN REGIMEN - DOSE/DAY:	8→		6→	4→				3→2→	1→0→	
VARIATIONS IN SCHEDULE										
DAY (REGIMEN) FOR CELL =0 @ V-5	0(8)	2-3(8)	7(8)	14(4)	*			21 (3,2)	28(1,0)	35
DAY (REGIMEN) FOR CELL =0 @ V-6	0(8)	2-3(8)	7(8)	14(4)	21(4)	*		28(3,2)	35(1,0)	42
DAY (REGIMEN) FOR CELL =0 @ V-7	0(8)	2-3(8)	7(8)	14(4)	21(4)	28(4)	*	35(3,2)	42(1,0)	49
DAY (REGIMEN) FOR CELL NEVER 0 @ V-5, 6 or 7	0(8)	2-3(8)	7(8)	14(4)	21(4)	28(4)	35	42	49+	
* FINAL ON-TREATMENT VISIT ** CHANGE TO CONVENTIONAL THERAPY										

Inclusion Criteria:

To be eligible for participation in the study, patients had to meet all of the following criteria before dosing:

- Age 18-75 years.
- Clinical diagnosis of acute anterior uveitis with the following signs and symptoms (see grading criteria in section 4.6).
 - i. an active anterior chamber cell reaction of at least 1.5+ and no presence of hypopyon.
 - ii. presence of at least 1+ ocular pain
 - iii. presence of at least 1+ photophobia
 - iv. presence of at least 1+ flare
 - v. presence of ciliary flush
- If the patient had previous episodes of acute anterior uveitis, the most recent attack should have been greater than three (3) months prior to enrollment (later amended to six weeks).
- Willing to comply with the protocol instructions.
- Has read (or has had read to), understood, and signed an Informed Consent.
- Females of childbearing potential who are using adequate birth control must test negative to a blood or urine pregnancy test.

Exclusion Criteria:

Patients with any of the following conditions at the Enrollment Examination were to be excluded from the study

- Pregnant or lactating female.
- Female of childbearing potential using inadequate birth control methods (adequate birth control includes the use of birth control pills, IUD, or diaphragm and foam).
- History of allergy or sensitivity to an ophthalmic medication, corticosteroid, LE, or to any components (including the preservative) of the current study medications.
- Any abnormality preventing reliable tonometry in either eye.
- Ocular hypertension with intraocular pressure greater than or equal to 25 mm Hg in either eye.
- Uncontrolled primary open angle glaucoma. (Amended later to exclude all types of glaucoma - see Section 4.12).
- Presence of hyphema.
- Presumptive diagnosis, known history, or clearly overt symptoms of acute anterior uveitis secondary to a local or systemic infectious disease (e.g., tuberculosis, syphilis, herpes, etc.).
- History of anterior uveitis secondary to systemic inflammatory disease that necessitates an unstable dosing regimen of a systemic therapy (e.g. systemic lupus erythematosus, Wegeners' granulomatosis, etc.). Dosing regimen was considered unstable if there had been changes in dose or frequency within the past month or if a change in dose or frequency was anticipated during the course of the study.
- Concomitant posterior uveitis, pars planitis, choroiditis or significant macular edema.
- Unstable dosing regimen of any systemic or topical medication that could effect the inflammatory response (e.g., corticosteroids, immunosuppressive medications, non-steroidal anti-inflammatory medications, etc.). Dosing regimen was considered unstable if a change in dose or frequency occurred in the past month or, was anticipated during the course of the study.
- History of severe/serious ocular pathology or other medical condition that could result in the patient's ability to safely complete the study.
- Participation by the patient in an Investigational study under any other IND within the past 30 days.
- Previous treatment with masked medication on this study.
- Unlikely to comply with the protocol instructions for any reason (confusion, infirmity, drug or alcohol abuse).

Efficacy Criteria

The primary variables in this study were:

- The median time to a rating of 0 for the cell reaction in the anterior chamber
- Area under curve as an estimate of severity over the first 21 days of treatment
- Proportion of patients with a score of 0 cell reaction at the Final Visit
- The proportion of patients with at least a one unit decrease in the anterior chamber cell rating.
- Time to resolution of flare was a secondary variable
- Time to resolution of other signs and symptoms required to be present at baseline were supportive

Many of the signs and symptoms were rated using a four point scale (0 - 3) where 0 = absent, 1 = mild, 2 = moderate and 3 = severe.

Cells: (Per evaluable field)

0	Less than or equal to 4 cells
0.5	5 to 7 cells
1.0	8 to 10 cells
1.5	11 to 15 cells
2.0	16 to 20 cells
2.5	21 to 30 cells
3.0	31 to 40 cells
3.5	41 to 50 cells
4.0	greater than 50 cells
5.0	Hypopyon

Flare:

0	None to trace	
1	Mild	Clearly noticeable, visible
2	Moderate	Without plastic aqueous
3	Marked	With plastic aqueous
4	Severe	With fibrin deposits and/or clots

Pain:

0	None	Absence of positive sensation
1	Mild	Awareness of one's eyes, difficulty in describing specific type of discomfort (e.g., fullness or heaviness, mild aching).
2	Moderate	Ability to describe the pain modality in specific terms (e.g., moderate aching, etc.).
3	Severe	Exquisite ocular, periocular, or radiating pain (e.g., throbbing, headache) requiring analgesia and/or sedation and which may be accompanied by nausea and vomiting.

Photophobia:

0	None	Absence of positive sensation
1	Mild	Very minimal light intolerance which may require some degree of sunglass protection to eliminate the symptom, noticed primarily in sunlight.
2	Moderate	Infrequent or intermittent discomfort in the globe associated with exposure to room light or sunlight which is only partially relieved by dark glasses or subdued light. The symptoms still persist to some degree even with sunglasses.
3	Severe	Constant or nearly constant exquisite pain in the eye that is not relieved by sunglasses and is only relieved by total occlusion of the eye. This total occlusion can be achieved with an eye patch or by closing the eyes. This sensation is so significant that frequently bed rest and occasionally systemic sedation is required to relieve this severe grade of symptom.

Ciliary Flush:

0	Absent
1	Present

Keratic Precipitates (KP):

0	None	Absence of inflammatory or pigmentary KP.
1	Mild	Fine granular KP usually noted overlying the inferior one half of the endothelium.
2	Moderate	Medium sized KP. An occasional mutton-fat KP may also be seen.
3	Severe	Diffuse proliferation of mutton-fat KP and/or deposition of fibrin strands on the posterior cornea.

Primary Analysis

The null hypothesis of equality in the distribution of time to resolution in the two treatment groups was tested by estimating the survival function by the life table method. Six intervals were defined with the scheduled visit as their midpoints. Patients whose rating failed to reach 0 were right censored at their Final Visit with two exceptions: 1) those who reached Visit 7 were censored at Day 35 and 2) those who were discontinued prematurely due to lack of efficacy were censored at Day 35 unless their rating for signs and symptoms other than cell reaction had reached 0 prior to their Final Visit. It was conservatively assumed that in the second case, in the absence of evidence to the contrary, the rating would not have reached 0 even if the patient had been observed for an adequate period (through Visit 7). The log-rank statistic was used to test the null hypothesis.

Investigators:

John Forrester, M.D., FRCSE	Aberdeen, UK	(Investigator #171)
Stephen Foster, M.D.	Boston, MA	(Investigator #150)
Ken Fox, M.D.	McLean, VA	(Investigator #151)
George John, M.D.	Louisville, KY	(Investigator #167)
Susan Lightman, Ph.D., FRCP	London, UK	(Investigator #172)
Robert Nozik, M.D.	San Bruno, CA	(Investigator #162)
Michael Raizman, M.D.	Boston, MA	(Investigator #163)
James Rosenbaum, M.D.	Portland, OR	(Investigator #164)
David Spalton, FRCP, FRCS	London, UK	(Investigator #173)
Joseph Tauber, M.D.	Kansas City, MO	(Investigator #168)
Stefan Trocme, M.D.	Galveston, TX	(Investigator #169)

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INVESTIGATOR	TREATMENT	RANDOMIZED	COMPLETING ON-TREATMENT PHASE	REASON FOR EARLY DISCONTINUATION						EVALUABLE FOR EFFICACY	REASON NOT EVALUABLE	
				LACK OF EFFICACY	MEDICAL EVENT	LOST TO FOLLOW UP	UNRELATED TO TRT	OTHER			2ND EYE ENROLLED	NO ON-TRT VISIT
150	LE	11	11(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	11(100%)	0(0%)	0(0%)	
	PA	11	10(91%)	1(9%)	0(0%)	0(0%)	0(0%)	0(0%)	11(100%)	0(0%)	0(0%)	
151	LE	0	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	
	PA	1	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(100%)	0(0%)	0(0%)	
162	LE	0	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	
	PA	1	1(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	1(100%)	0(0%)	0(0%)	
163	LE	4	2(50%)	1(25%)	0(0%)	0(0%)	0(0%)	1(25%)	4(100%)	0(0%)	0(0%)	
	PA	2	1(50%)	0(0%)	0(0%)	1(50%)	0(0%)	0(0%)	1(50%)	0(0%)	1(50%)	
164	LE	5	3(60%)	1(20%)	0(0%)	1(20%)	0(0%)	0(0%)	4(80%)	0(0%)	1(20%)	
	PA	4	3(75%)	1(25%)	0(0%)	0(0%)	0(0%)	0(0%)	4(100%)	0(0%)	0(0%)	
167	LE	2	2(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	2(100%)	0(0%)	0(0%)	
	PA	3	3(100%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	3(100%)	0(0%)	0(0%)	
168	LE	6	5(83%)	0(0%)	0(0%)	1(17%)	0(0%)	0(0%)	6(100%)	0(0%)	0(0%)	
	PA	4	3(75%)	0(0%)	0(0%)	1(25%)	0(0%)	0(0%)	4(100%)	0(0%)	0(0%)	
169	LE	8	6(75%)	0(0%)	0(0%)	1(13%)	1(13%)	0(0%)	7(88%)	1(13%)	0(0%)	
	PA	8	7(88%)	0(0%)	0(0%)	0(0%)	1(13%)	0(0%)	7(88%)	1(13%)	0(0%)	
171	LE	12	8(67%)	4(33%)	0(0%)	0(0%)	0(0%)	0(0%)	12(100%)	0(0%)	0(0%)	
	PA	11	9(82%)	0(0%)	0(0%)	2(18%)	0(0%)	0(0%)	10(91%)	0(0%)	1(9%)	
172	LE	18	10(56%)	7(39%)	0(0%)	0(0%)	0(0%)	1(6%)	18(100%)	0(0%)	0(0%)	
	PA	18	15(83%)	1(6%)	0(0%)	2(11%)	0(0%)	0(0%)	17(94%)	0(0%)	1(6%)	
173	LE	17	10(59%)	5(29%)	0(0%)	1(6%)	0(0%)	1(6%)	17(100%)	0(0%)	0(0%)	
	PA	16	15(94%)	1(6%)	0(0%)	0(0%)	0(0%)	0(0%)	16(100%)	0(0%)	0(0%)	
OVERALL	LE	83	57(69%)	18(22%)	0(0%)	4(5%)	1(1%)	3(4%)	81(98%)	1(1%)	1(1%)	
	PA	79	68(86%)	4(5%)	0(0%)	6(8%)	1(1%)	0(0%)	75(95%)	1(1%)	3(4%)	

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		LOTEPREDNOL	PREDNISOLONE	
AGE (yrs)				
=====	N	83	79	
	MEAN	43.5	43.2	p = 0.73
	SE	1.5	1.4	
	MIN	19.0	22.0	
	MAX	77.0	72.0	
	<30 yrs	11	11	p = .86
	≥30 yrs	72	68	
SEX				
=====				
MALE	N	42	42	p = .74
FEMALE	N	41	37	
RACE				
=====				
CAUCASIAN	N	59	58	p = .77
OTHER	N	24	21	
IRIS PIGMENTATION				
=====				
LIGHT	N	38	38	p = .77
DARK	N	45	41	
HLA RESPONSE				
=====				
POSITIVE	N	30	33	p = .28
NEGATIVE	N	30	21	
SITE OF UVEITIS				
=====				
IRITIS	N	74	64	p = .10
IRIDOCYCLITIS	N	9	15	
TYPE OF PATHOLOGY				
=====				
NONGRANULOMATOUS	N	79	76	p = .59
GRANULOMATOUS	N	4	2	

Reviewer's Comments: *The category "other" should be more specifically identified*

Anterior Chamber Cells

	TREATMENT GROUP	VISIT: DAY: REGIMEN: (DOSE/DAY)	V1	V2	V3	V4	V5	V6	V7	FINAL VISIT (LOCF)	21 DAY AUC (V1-V5)
			0	2-3	7	14	21	28	35		
OBSERVED *****	LE	N	81	74	69	60	57	19	7	81	81
		MEAN	2.6	2.3	1.3	0.6	0.4	0.6	1.1	1.0	33.1
		S.E.	0.1	0.1	0.1	0.1	0.1	0.2	0.5	0.2	2.6
		MIN									
		MAX									
	PA	N	75	72	71	67	67	17	8	75	75
		MEAN	2.5	2.0	1.0	0.5	0.3	0.5	0.2	0.3	24.5
		S.E.	0.1	0.1	0.1	0.1	0.1	0.2	0.2	0.1	2.3
		MIN									
		MAX									
PROPORTION WITH SCORE=0 *****	LE N(%)			0(0)	14(20)	29(48)	39(68)	10(53)	3(43)	52(64)	
	PA N(%)			2(3)	18(25)	38(57)	48(72)	11(65)	7(88)	67(89)	
	P (H0:LE=PA)			0.183	0.374	0.372	0.894	0.663	0.183	<.001	
	95% C.L. LOWER (%)										
	UPPER (%)										

SURVIVAL ANALYSIS:

TIME TO 1ST
SCORE=0

P=0.003 (MEDIAN DAY TO RESOLUTION: LE=23 DAYS, PA=20 DAYS)

CHANGE FROM
BASELINE

LE	N	74	69	60	57	19	7	81
	MEAN	-0.3	-1.2	-2.0	-2.2	-2.1	-1.2	-1.6
	S.E.	0.1	0.1	0.1	0.1	0.3	0.7	0.2
	MIN							
	MAX							
PA	N	72	71	67	67	17	8	75
	MEAN	-0.5	-1.4	-2.0	-2.1	-2.3	-2.5	-2.2
	S.E.	0.1	0.1	0.1	0.1	0.2	0.3	0.1
	MIN							
	MAX							

ANALYSIS OF MEAN
RANK (V1-FINAL)
OR MEAN (AUC)

BASELINE	D.F.									<.001
TREATMENT	1	0.419	0.268	0.606	0.963	0.268	0.918	0.552	0.075	0.211
INVESTIGATOR	7									0.359
TRT X INVEST	7									0.386
ERROR	139									
EST. MEAN (LE-PA)										4.6
95% C.L. LOWER										-2.7
UPPER										11.9

DISTRIBUTION OF
CHANGE FROM
BASELINE: N(%)

LE	>+2							
	WORSE-- +2							
	+1							
	UNCHANGED 0	26(35)	12(17)	3(5)	5(9)	2(11)	2(29)	9(11)
	-1							
BETTER--	-2							
	<-2							
	TOTAL							
PA	>+2							
	WORSE-- +2							
	+1							
	UNCHANGED 0	25(35)	9(13)	5(7)	3(4)	1(6)	0(0)	0(0)
	-1							
BETTER--	-2							
	<-2							
	TOTAL							

Anterior Chamber Cells - US Population Only

			VISIT:	V1	V2	V3	V4	V5	V6	V7	FINAL	21 DAY
			DAY:	0	2-3	7	14	21	28	35	VISIT	AUC(V1-V5)
			REGIMEN:	-----	8-----	-- 6 --	-----	4-----	-----			(UNIT*DAY)
			(DOSE/DAY)									
OBSERVED *****	LE	N		34	29	33	29	29	11	4	34	34
		MEAN		2.5	2.0	1.2	0.6	0.5	0.6	1.8	0.7	25.2
		S.E.		0.1	0.2	0.2	0.1	0.2	0.3	0.7	0.2	3.4
		MIN		1.5	0.5	0.0	0.0	0.0	0.0	0.0	0.0	2.8
		MAX		4.0	5.0	3.0	3.0	3.5	3.0	3.5	4.0	84.0
	PA	N		32	30	30	29	29	7	4	32	32
		MEAN		2.4	1.7	0.9	0.5	0.4	0.5	0.0	0.4	21.4
		S.E.		0.1	0.2	0.2	0.2	0.1	0.3	0.0	0.2	4.1
		MIN		1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0
		MAX		4.0	5.0	4.0	4.0	3.0	2.0	0.0	5.0	104.0
PROPORTION WITH SCORE=0 *****	LE	N(%)			0(0)	11(33)	14(48)	18(62)	6(55)	1(25)	25(74)	
	PA	N(%)			1(3)	11(37)	20(69)	20(69)	4(57)	4(100)	28(88)	
	P (H0:LE=PA)				0.378	0.837	0.146	0.700	0.746	0.090	0.194	
	95% C.L. LOWER (%)				-9.9	-26.9	-46.0	-31.4	-49.7	-142	-33.2	
	UPPER (%)				3.3	20.2	4.7	17.6	44.5	-7.9	5.2	

SURVIVAL ANALYSIS:
TIME TO 1ST
SCORE=0

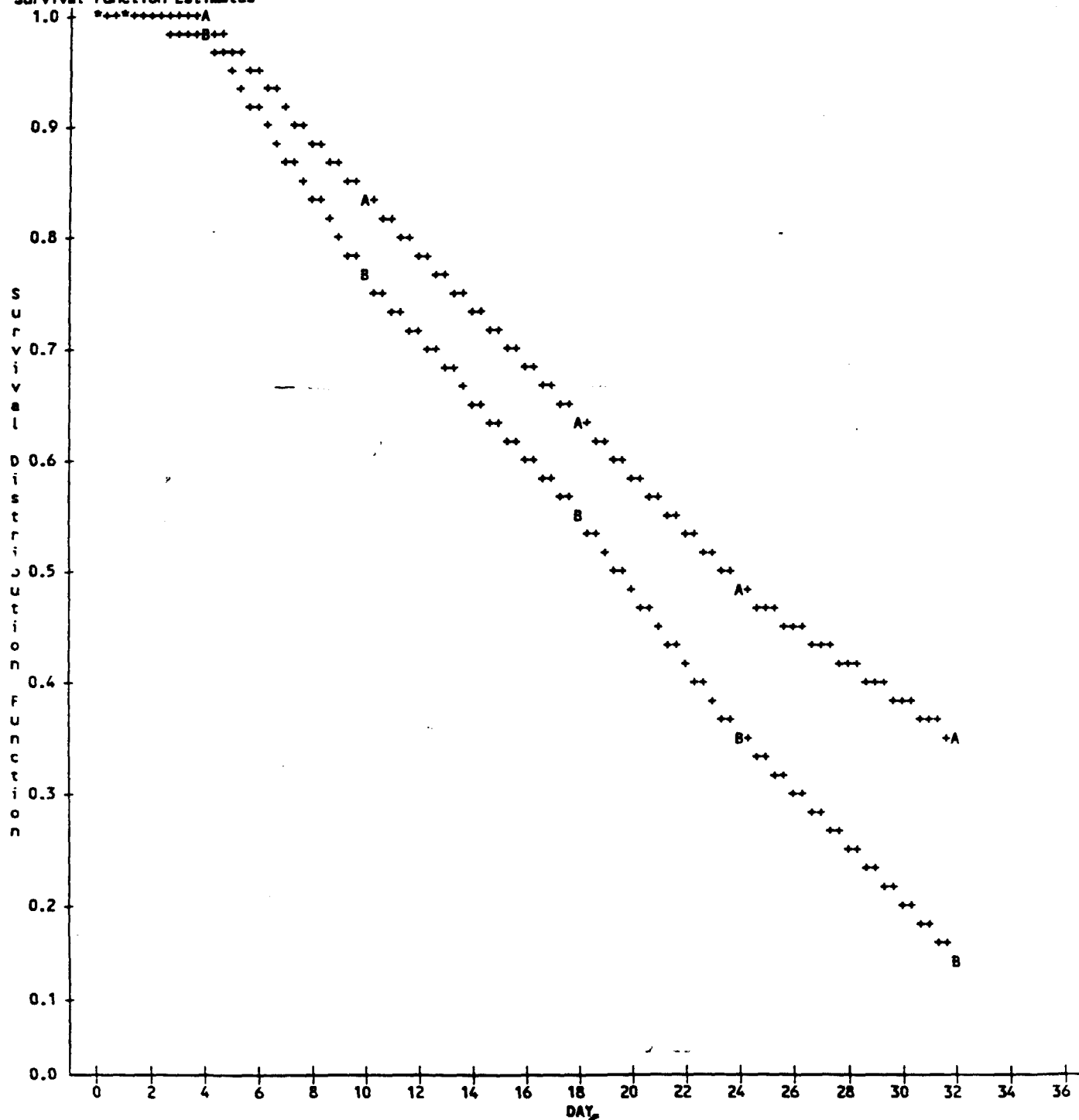
P=0.280 (MEDIAN DAY TO RESOLUTION: LE=19 DAYS, PA=15 DAYS)

Reviewer's Comments:

The US Population is consistent with the entire population, however, there are not enough patients to show a statistically significant change.

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Anterior Chamber Cell - Time to 0 Rating
Survival Function Estimates



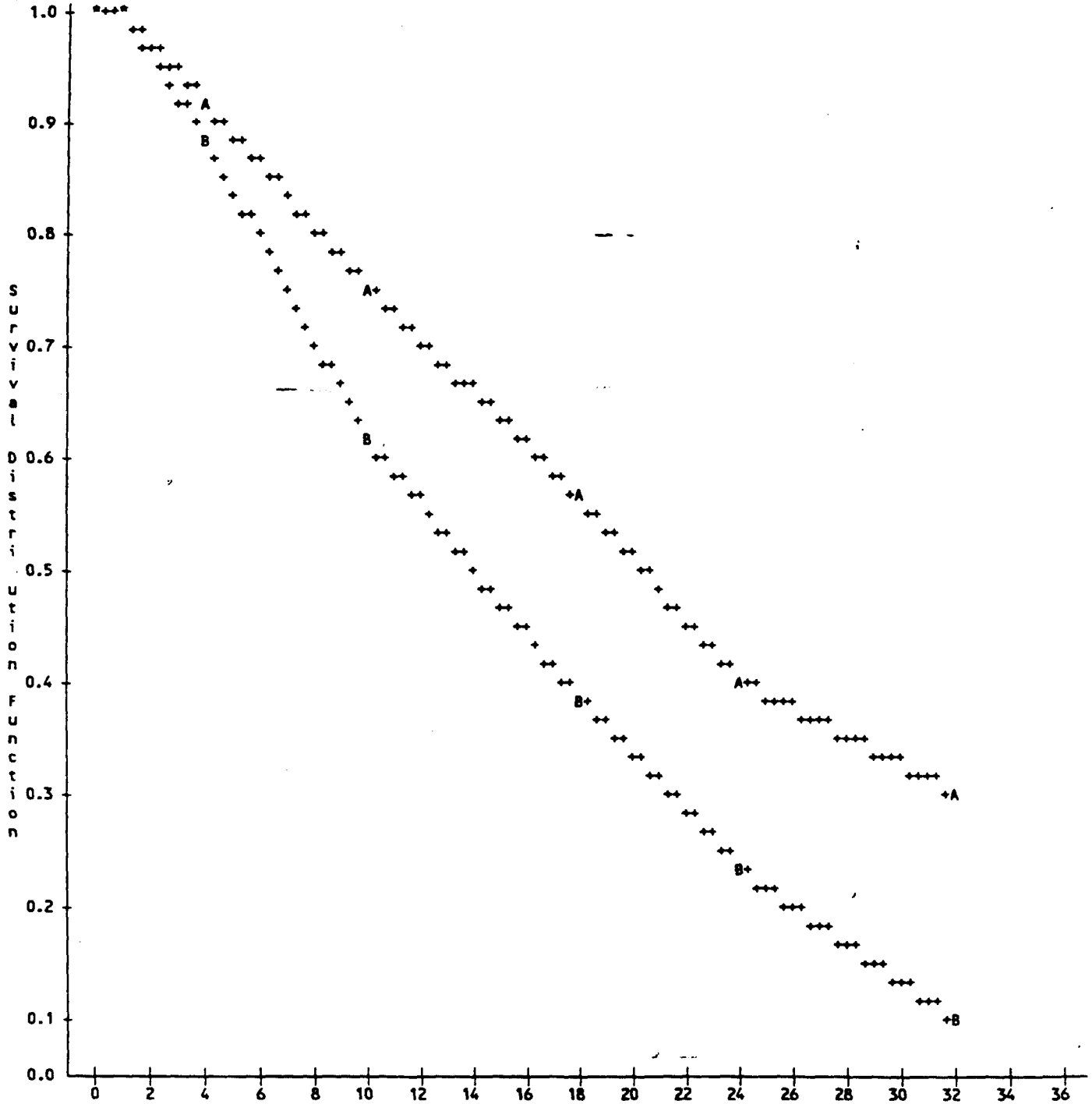
A = Loteprednol etabonate 0.5% B = Prednisolone acetate 1%

NDA 20-583 Lotemax (loteprednol etabonate ophthalmic suspension)

Anterior Chamber Flare

		VISIT: DAY:	V1	V2	V3	V4	V5	V6	V7	FINAL VISIT	21 DAY AUC
		REGIMEN: (DOSE/DAY)	0	2-3	7	14	21	28	35	(LOCF)	(V1-V5)
OBSERVED *****	LE	N	81	74	69	60	57	19	7	81	81
		MEAN	2.0	1.6	1.0	0.6	0.4	0.4	0.9	0.9	26.2
		S.E.	0.1	0.1	0.1	0.1	0.1	0.2	0.5	0.1	2.3
		MIN									
		MAX									
	PA	N	75	72	71	67	67	17	8	75	75
		MEAN	1.8	1.3	0.7	0.4	0.2	0.2	0.1	0.3	17.2
		S.E.	0.1	0.1	0.1	0.1	0.0	0.1	0.1	0.1	1.8
		MIN									
		MAX									
PROPORTION WITH SCORE=0 *****	LE N(%)		7(9)	19(28)	29(48)	42(74)	13(68)	4(57)	51(63)		
	PA N(%)		10(14)	32(45)	44(66)	55(82)	14(82)	7(88)	65(87)		
	P (HO:LE=PA)		0.317	0.013	0.051	0.338	0.491	0.345	<.001		
	95% C.L. LOWER (%)										
	UPPER (%)										
SURVIVAL ANALYSIS:											
TIME TO 1ST SCORE=0											
P=0.002 (MEDIAN DAY TO RESOLUTION: LE=20 DAYS, PA=14 DAYS)											
CHANGE FROM BASELINE *****	LE	N	74	69	60	57	19	7	81		
		MEAN	-0.5	-1.0	-1.4	-1.6	-1.8	-1.4	-1.2		
		S.E.	0.1	0.1	0.1	0.1	0.2	0.7	0.2		
		MIN									
		MAX									
	PA	N	72	71	67	67	17	8	75		
		MEAN	-0.5	-1.0	-1.5	-1.6	-1.7	-1.6	-1.5		
		S.E.	0.1	0.1	0.1	0.1	0.2	0.3	0.1		
		MIN									
		MAX									
ANALYSIS OF MEAN RANK (V1-FINAL) OR MEAN (AUC) *****		D.F.									
	BASELINE	1									<.001
	TREATMENT	1	0.076	0.948	0.709	0.589	0.615	0.508	1.000	0.116	0.041
	INVESTIGATOR	7									0.018
	TRT X INVEST	7									0.393
ERROR		139									
EST. MEAN (LE-PA)											6.2
95% C.L. LOWER											0.2
UPPER											12.2
DISTRIBUTION OF CHANGE FROM BASELINE: N(%) *****	LE	>+2									
	WORSE--	+2									
		+1									
	UNCHANGED	0	33(45)	14(20)	10(17)	5(9)	4(21)	2(29)	16(20)		
		-1									
	BETTER--	-2									
		<-2									
	TOTAL		74	69	60	57	19	7	81		
	PA	>+2									
	WORSE--	+2									
		+1									
	UNCHANGED	0	31(43)	14(20)	6(9)	1(1)	0(0)	0(0)	2(3)		
		-1									
	BETTER--	-2									
		<-2									
	TOTAL										

Anterior Chamber Flare - Time to 0 Rating
Survival Function Estimates



A = Loteprednol etabonate 0.5% B = Prednisolone acetate 1%

Summary of IOP Changes

Baseline	n (patients)	Mean	S.E.
LE	81	15.0	0.6
PA	75	14.1	0.4 p = 0.181
Armaly		Each Visit (2-5)	Any Visit (2-5)
LE		4-9%	14%
PA		13-23%	35% p = 0.002
Stewart ($\Delta = \geq 10$ mm Hg)		Each Visit (2-5)	
LE		0-2%	
PA		0-5%	
Mean Changes	n (patients)	to Visit 5 (LOCF)	
LE	81	-0.2 mm Hg	
PA	75	+2.3 mm Hg	

Reviewer's Comments: *The IOP was higher in the prednisolone group than the loteprednol group, however, this could be due to more effective treatment of uveitis since uveitis is known to decrease IOP.*

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Evaluations of IOP

		VISIT:	V1	V2	V3	V4	V5	V6	V7	VISIT
		DAY:	0	2-3	7	14	21	28	35	5
		REGIMEN:	----- 8 ----- --- 6 --- ----- 4 -----							(LOCF)
		(DOSE/DAY)								
		TREATMENT GROUP								
OBSERVED *****	LE	<10	13(16)	10(14)	4(6)	6(10)	3(5)	2(11)	0(0)	5(6)
	N(X)	[10 TO 20)	57(70)	49(68)	58(85)	47(80)	48(84)	16(84)	7(100)	65(80)
		>=20	11(14)	13(18)	6(9)	6(10)	6(11)	1(5)	0(0)	11(14)
	N		81	72	68	59	57	19	7	81
	MEAN		15.0	14.3	14.7	14.4	14.6	14.8	16.3	14.8
	S.E.		0.6	0.5	0.5	0.5	0.5	0.9	0.8	0.5
	MIN									
	MAX									
	PA	<10	8(11)	4(6)	1(1)	1(1)	0(0)	0(0)	0(0)	1(1)
	N(X)	[10 TO 20)	63(84)	62(86)	65(92)	58(87)	54(82)	14(93)	8(100)	62(83)
	>=20	4(5)	6(8)	5(7)	8(12)	12(18)	1(7)	0(0)	12(16)	
	N		75	72	71	67	66	15	8	75
	MEAN		14.1	14.7	15.2	16.1	16.4	14.8	15.5	16.4
	S.E.		0.4	0.4	0.4	0.5	0.5	0.8	1.0	0.4
	MIN									
	MAX									
CHANGE FROM BASELINE *****	LE	<6	68(94)	65(96)	54(92)	52(91)	19(100)	7(100)	75(93)	
	N(X)	[6 TO 10)	3(4)	3(4)	5(8)	4(7)	0(0)	0(0)	5(6)	
		>=10	1(1)	0(0)	0(0)	1(2)	0(0)	0(0)	1(1)	
	N		72	68	59	57	19	7	81	
	MEAN		-0.7	-0.1	-0.1	0.2	-0.8	0.4	-0.2	
	S.E.		0.5	0.4	0.5	0.6	1.1	1.6	0.5	
	MIN									
	MAX									
	PA	<6	63(88)	61(86)	53(79)	51(77)	12(80)	5(63)	58(77)	
	N(X)	[6 TO 10)	9(13)	7(10)	12(18)	12(18)	3(20)	2(25)	14(19)	
	>=10	0(0)	3(4)	2(3)	3(5)	0(0)	1(13)	3(4)		
	N		72	71	67	66	15	8	75	
	MEAN		0.5	1.1	2.2	2.4	1.1	3.4	2.3	
	S.E.		0.5	0.5	0.5	0.5	1.1	1.7	0.5	
	MIN									
	MAX									
ANALYSIS OF MEAN *****	BASELINE			<.001	<.001	<.001	<.001	<.001	0.063	<.001
	TREATMENT		0.181	0.343	0.359	0.036	0.036	0.812	0.247	0.047
	INVESTIGATOR		0.143	0.488	0.159	0.099	0.234	0.030	0.333	0.209
	TRT X INVEST		0.508	0.284	0.426	0.608	0.528	0.820	0.433	0.296
	EST. MEAN (LE-PA)		1.1	-0.6	-0.5	-1.5	-1.5	--	--	-1.3
	95% C.L. LOWER		-0.5	-2.0	-1.7	-2.8	-2.9			-2.6
	UPPER		2.8	0.7	0.6	-0.1	-0.1			-0.0
CHANGE FROM BASELINE RESPONSE: N(X)			ANY OF VISITS 2-5 *****							
CHANGE >=6	LE		11(14)	4(6)	3(4)	5(8)	5(9)	0(0)	0(0)	6(7)
	PA		26(35)	9(13)	10(14)	14(21)	15(23)	3(20)	3(38)	17(23)
	P (H0:LE=PA)		0.002	0.153	0.070	0.058	0.049	0.012	0.090	0.009
CHANGE >=10	LE		2(2)	1(1)	0(0)	0(0)	1(2)	0(0)	0(0)	1(1)
	PA		5(7)	0(0)	3(4)	2(3)	3(5)	0(0)	1(13)	3(4)
	P (H0:LE=PA)		0.216	0.317	0.102	0.206	0.396	0.396	0.564	0.292
SURVIVAL ANALYSIS: *****										
TIME TO 1ST CHANGE >=6			P=0.012 (Q1 TIME: LE=25 DAYS; PA=15 DAYS)							
TIME TO 1ST CHANGE >=10			P=0.399							

	Loteprednol (n=83)			Prednisolone (n=79)		
	Patients Reporting			Patients Reporting		
	At least once		Total	At least once		Total
ABNORMAL VISION (EYE/VIS)	28	34%	32	23	29%	31
OCULAR HYPERTENSION (EYE/IOP)	18	22%	23	33	42%	41
UVEITIS (EYE/UVE)	14	17%	14	3	4%	3
ITCHING, EYE (EYE/GEN)	7	8%	8	2	3%	2
KERATIC PRECIPITATE (EYE/COR)	7	8%	7	4	5%	4
FLARE, ANTERIOR CHAMBER (EYE/AH)	6	7%	6	1	1%	1
LACRIMATION DISORDER (EYE/GEN)	6	7%	6	1	1%	1
PHOTOPHOBIA (EYE/VIS)	5	6%	5	0	0%	0
CELLS, ANTERIOR CHAMBER (EYE/AH)	5	6%	7	1	1%	1
HEADACHE (HEAD)	5	6%	5	3	4%	3
KERATOCONJUNCTIVITIS (EYE/CON)	5	6%	5	3	4%	3
DISCOMFORT, EYE (EYE/GEN)	4	5%	4	3	4%	3
INFECTION (GEN)	4	5%	4	1	1%	1
EYE PAIN (EYE/GEN)	3	4%	3	3	4%	3
INJECTION (EYE/CON)	3	4%	3	0	0%	0
IRITIS (EYE/UVE)	3	4%	3	3	4%	3
DRY EYES (EYE/GEN)	2	2%	2	1	1%	1
NECK PAIN (NECK)	2	2%	2	0	0%	0
ERYTHEMA, EYELIDS (EYE/APP)	2	2%	2	0	0%	0
INFLAMMATION, ANTERIOR CHAMBER (EYE/AH)	2	2%	2	0	0%	0
SYNECHIA, ANTERIOR CHAMBER (EYE/AH)	2	2%	2	1	1%	1
DISCHARGE, EYE (EYE/GEN)	2	2%	2	2	3%	2
BACK PAIN (BACK)	2	2%	2	1	1%	1
FACE EDEMA (HEAD)	2	2%	2	0	0%	0
CHEMOSIS (EYE/CONJ)	1	1%	1	1	1%	1
CILIARY FLUSH (EYE/UVE)	1	1%	1	0	0%	0
CORNEAL ABNORMALITY (EYE/COR)	1	1%	1	1	1%	1
NAUSEA (GEN)	1	1%	1	2	3%	2
ACCIDENTAL INJURY (GEN)	1	1%	1	0	0%	0
ALLERGIC REACTION (GEN)	1	1%	1	1	1%	1
ASTHENIA (GEN)	0	0%	0	1	1%	1
FLU SYNDROME (GEN)	0	0%	0	2	3%	2
PAIN (GEN)	0	0%	0	1	1%	1

Reviewer's Comments:

The differences in abnormal vision, ocular hypertension, uveitis, keratic precipitate and flare are all suggestive of a more effective steroid in the form of prednisolone.

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Study #4 Conclusions: -

1. Prednisolone acetate has demonstrated superiority over loteprednol in the treatment of anterior uveitis.
2. Both products have an acceptable safety profile, however, individual adverse experiences may need to be re-coded/classified.
3. There were no significant differences with respect to age, race or eye color (data not shown).
4. The applicant's claim that the US population behaves differently than the British population cannot be validated in this study because there is not a sufficient number of subjects in each group to perform an adequate evaluation.

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8.4 Additional Studies

8.4.1 Reviewer's Trial # 5 Sponsor's protocol # 114

Title: Safety and efficacy of loteprednol etabonate in seasonal allergic conjunctivitis

Objective:

This study was designed to evaluate the safety and efficacy of loteprednol etabonate (LE) 0.5% in reducing the ocular signs and symptoms accompanying seasonal allergic conjunctivitis.

Study Design:

This study was a prospective, double-masked, randomized, placebo-controlled, parallel-group comparison of LE 0.5% to its vehicle (placebo).

Number and Description of Volunteers:

Nine adults with active signs and symptoms of seasonal allergic conjunctivitis were enrolled and evaluated in this study. This study was planned for 80 subjects. The study was stopped after the enrollment of nine subjects for reasons related to poor enrollment and financial considerations.

Test Drug Schedule:

Subjects were randomly assigned to masked test drug treatment with either 0.5% LE or placebo and instructed to instill one drop into each eye up to eight times daily during the first two days of treatment and then four times daily for the next twelve days. Follow-up examinations were scheduled on Days 1, 2, 6 and 12 of therapy.

Results:

The average age of all subjects was 36 years, with an approximately equal distribution between males and females, and all subjects were Caucasian. Prior to treatment, the LE treatment group had a mean primary composite score (itching and bulbar injection) of 4.8 ± 0.3 units (mean $\pm$ s.e.), and the placebo group had a mean of 4.4 ± 0.3 units ($p = 0.434$). Fifteen minutes after treatment, there was a mean decrease to 2.6 units in the LE group. The severity of this composite continued to decrease until Day 12, at which the score was 0.5, or a mean decrease of 4.3 units. In the placebo treatment group, there were mean decreases of up to 3.0 units. At none of these visits did the difference between the two treatment groups reach statistical significance. Similar treatment effects were observed in the secondary composite score (bulbar chemosis, tearing, discharge and erythema), individual subjective measures (itching, tearing, discomfort, foreign body sensation, and burning/stinging) and individual objective measures (bulbar injection, palpebral injection, discharge, chemosis, corneal disease, and erythema). The physician global assessment mean values ranged from 0.0 to 0.8 units in the LE group, and from 1.8 to 1.4 in the placebo group. This difference reached statistical significance on day 12 ($p = 0.040$).

One placebo-treated subject left the study because of uncontrolled ocular signs and symptoms on Visit 3 (Day 2). The remaining eight subjects all completed the study. There were no differences between treatment groups in mean intraocular pressure during the study. There were no adverse experiences other than complaints of headache or ocular discomfort, both of which were observed in both LE- and placebo-treated subjects.

Conclusions:

LE was numerically, although generally not statistically, more effective than PL in the treatment of seasonal allergic conjunctivitis in this small subject population. There were no safety concerns over a two week period in these subjects.

Reviewer's Comments: *This study did not have a sufficient number of subjects from which to make any definitive conclusions.*