

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-127

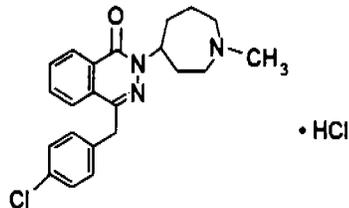
MEDICAL REVIEW

**Medical Officer's Review of NDA 21-127
Original**

NDA #21-127
M.O. Review #1

Submission: 8/3/1999
Review completed: 1/21/2000

Proposed trade name: **Optivar**
Generic name: **azelastine hydrochloride ophthalmic solution, 0.05%**



(±)4[(4-Chlorophenyl)methyl]-2(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone, monohydrochloride.

Pharmacologic Category: **Phthalazinone derivative, antihistamine**

Sponsor: **Asta Medical, Inc.
Tewksbury, MA**

Proposed Indication(s): **For the prevention and relief of the signs and symptoms of allergic conjunctivitis.**

Dosage Form(s)
and Route(s) of Administration: **Ophthalmic solution for topical ocular administration**

NDA Drug Classification: **3 S**

Related INDs/NDAs:

NDA 20-114	Astelin (Azelastine Hydrochloride) Nasal Spray	Wallace Laboratories
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Azelastine Hydrochloride Nasal Spray for the treatment of allergic rhinitis is also approved and marketed in many countries throughout the world. _____ has also conducted clinical studies in allergic rhinitis and asthma with Azelastine tablets. ASTA Medica AG has an _____ for azelastine tablets for the treatment of allergic dermatitis.

NDA 21-127 Optivar (azelastine hydrochloride ophthalmic solution)

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3 **Material Reviewed** NDA Volumes 1.33-1.101

4 **Chemistry/Manufacturing Controls**

Formulation		per mL
	Azelastine hydrochloride	0.5 mg
	Benzalkonium chloride	0.125 mg
	Hydroxypropylmethylcellulose	_____
	Disodium edetate dihydrate	_____
	Sorbitol solution (70%)	_____
	Sodium hydroxide (1N)	_____
	Water for Injection	_____

Regulatory Specifications

[Redacted content]

Reviewer's Comments: *Acceptable from a clinical prospective except that each unknown impurity should be no more than 0.1%*

5 **Animal Pharmacology/Toxicology**

Reviewer's Comments: *No specific issues identified.*

6 Clinical Background

6.2 Important information from related INDs and NDAs

The systemic action of azelastine hydrochloride is well known. Azelastine Hydrochloride Nasal Spray and Tablets are approved for the treatment of allergic rhinitis.

6.3 Foreign experience

Azelastine Eye Drops are approved in the countries listed below. Marketing was initiated in the United Kingdom in February 18, 1998. The following countries were included in the European Decentralized Procedure: Austria, Denmark, Finland, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden and the United Kingdom (as the Reference Member State (RMS)). In the Western European countries, France and Belgium, and in several Eastern European countries, national submissions were obtained. For Greece a second Decentralized Procedure (UK as RMS) will be started.

Countries in which Azelastine Eye Drops are Approved for Marketing

Country	Approval Date
Azerbaijan	01/07/98
Latvia	01/21/98
Georgia	02/12/98
United Kingdom	02/18/98
Belarus	03/25/98
Russia	05/19/98
Armenia	07/01/98
France	08/06/98
Ireland	08/28/98
Denmark	09/23/98
Austria	09/24/98
Netherlands	10/06/98
Belgium	10/21/98
Germany	10/23/98
Portugal	10/30/98
Sweden	11/06/98
Spain	11/18/98
Ukraine	12/04/98
Estland	12/11/98
Finland	12/21/98
Italy	02/10/99

So far, Azelastine Eye Drops had already been launched in the following countries: The United Kingdom, Russia, Germany, Belgium, Malta (on basis of the approval in UK), the Netherlands, Spain and Portugal.

Azelastine Eye Drops are submitted in the following countries: Brazil, Bulgaria, Hungary, Kazakhstan, Lithuania, Luxembourg, New Zealand, Poland, Romania, Slovak Republic, Switzerland and Uzbekistan. There is no country where the health authorities have rejected the product or ASTA Medica has withdrawn the application.

6.4 Human Pharmacology, pharmacokinetics, pharmacodynamics

Study 2983 was an efficacy study which included pharmacokinetic sampling. Patients dosed with one drop of AZE 0.05 in each eye twice-daily with increases in dosing frequency allowed up to four times a day as necessary to accommodate patients with more severe symptoms. Thus the total daily doses ranged from 0.060 mg to 0.12 mg of azelastine. A subset of 30 patients had plasma samples drawn after administration of AZE 0.050 or placebo. Since the study was blinded at the time blood was drawn, some placebo patients were inevitably included. Concentrations of AZE 0.050 and its metabolite DesAZE were assayed from blood samples collected from 20 patients enrolled in site 1 and 10 patients from site 4. The assay limit of quantification (LOQ) for azelastine was _____, and the limit of detection was _____. For each patient in site 1, single blood samples were collected prior to treatment, 4-5 hours after the second daily dose of AZE 0.050 after 14 days of treatment, and 12-15 hours after the last dose of AZE 0.050 after 8 weeks of therapy. For the patients in site 4, blood samples were collected after 8 weeks of therapy immediately prior to the last dose as well as 2 hours after the last dose.

Of the 30 patients who volunteered for blood sampling, 7 were found to be on placebo and 23 on the active treatment. Samples were obtained for 11 AZE 0.050 treated patients on Day 14 and for 10 AZE 0.050 treated patients on Day 56 at site 1. Samples were obtained for 9 AZE 0.050 treated patients on Day 56 at site 4.

Azelastine was detected in most patients, but quantified in only one patient. Patient 23 had a plasma concentration of 0.29 ng/mL of azelastine and 0.87 ng/mL of DesAZE after 14 days. No plasma concentrations for the parent drug or metabolite were quantifiable after 8 weeks of treatment in this patient. This same subject, however, had a DesAZE plasma concentration of 0.56 ng/mL prior to treatment, indicating that the samples from this patient may not provide valid information regarding the pharmacokinetics of AZE.

The results of this study indicate that systemic absorption of azelastine after ocular dosing must be very low since at an _____ plasma levels of azelastine were observed in only one patient. While metabolite levels were detected in 5 patients, one of the patients was treated with placebo. Given the low dose of AZE 0.050, it was expected that plasma levels of AZE and DesAZE would be correspondingly low.

Two studies evaluating the pharmacokinetics of azelastine nasal spray were performed. One of the studies evaluated the pharmacokinetics of single and multiple doses of azelastine nasal spray (1, 2 and 3 sprays/nostril bid (total daily dose of 0.56 mg, 1.12 mg and 1.68 mg, respectively)) in 39 healthy subjects over 29 days. Steady-state was achieved by day 15 and the mean values for C_{max} and AUC did not differ for 1 and 2 sprays. Significant differences in C_{max} values between the lower and higher doses were seen (C_{max} values were 264, 306 and 1195 pg/ml, respectively).

In an additional efficacy study, patients with a history of allergic rhinitis received 2 sprays/nostril once (0.56/total dose) or twice (1.12 mg/total dose) per day, oral chlorpheniramine maleate (12 mg bid), or placebo. After 2 weeks of treatment, mean plasma levels were double those reported for the healthy subjects after two weeks of treatment. In this study, mean plasma concentrations for the bid treatment group were double those reported for the qd treatment.

6.5 Other relevant background information

The *in vitro* protein binding of ^{14}C -azelastine to human plasma proteins was 88%. Protein binding determined *ex vivo* was found to range from 78 to 88%. The *in vitro* protein binding of ^{14}C -desmethylazelastine to human plasma proteins was 97%. The binding of blood radioactivity by erythrocytes *in vivo* was between 58% and 72% after intravenous administration and between 50% and 53% after oral administration.

The metabolites with known chemical structure account for 55% of the administered oral dose. The metabolites include DesAZE (18%) which is pharmacologically active, 6-hydroxy- and 7-hydroxy-azelastine (combined 7%), and open-ring metabolites D 19206 and D 19207 (combined 23%). DesAZE is the main metabolite in the feces whereas the open-ring metabolite D 19207 dominates in the urine. The main components found in the plasma were azelastine and the polar metabolites (probably D 19206 or D 19207).

Plasma concentrations of azelastine measured by means of clearly showed inter-and intra-individual fluctuation after single and multiple oral doses in 13 elderly subjects. The mean elimination half-life of azelastine was 20.7 h in the younger subjects, while the mean half-life in the elderly was 38.5 h. In this same study, steady state was achieved in 6 of the elderly patients after administration of twice daily 4.4 mg AZE for 7 days. Steady-state pharmacokinetic parameters were compared with data from healthy young subjects, and the results were similar for both age groups.

A single-dose study in patients with impaired renal or hepatic functions showed that hepatic dysfunction is without influence on the pharmacokinetics of azelastine and its main metabolite, DesAZE. In patients with impaired renal function (creatinine clearance <50 mL/min), increased plasma levels were found for both parent drug and the main metabolite. On average, the plasma levels were 70-75% higher compared to normal subjects.

6.6 Proposed Directions for Use

One drop instilled into each affected eye two times per day at an interval of 8-10 hours.

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7 Description of Clinical Data Sources
8 Clinical Studies

Number	Protocol	Study Design	Start/Stop Dates	Patients Exposed to Drug	Number of Sites	Length of Treatment	Study Treatments
1	400-301	Double blind Matched pair	3/98 – 8/98	80	1	2 x SD	AZE 0.050 + PLA
2	2967	Double blind Parallel group	1/95 – 2/95	20	1	1 Week	AZE 0.050 BID PLA BID
4	2982	Double blind Parallel group	4/95 – 9/95	144	26	2 Weeks	AZE 0.050 Variable BID PLA Variable BID DSCG QID
5	2983	Double blind Parallel group	4/95 – 11/95	277	4	8 Weeks	AZE 0.050 Variable BID PLA Variable BID
7	2985	Double blind Parallel group	4/95 – 9/95	290	7	2 Weeks	AZE 0.050 Variable BID PLA Variable BID
8	3021	Double blind Parallel group	4/96 – 10/96	320	8	4 Weeks	AZE 0.050 Variable BID PLA Variable BID DSCG QID
11	2966	Double blind Crossover	3/95 – 4/95 11/95 – 1/96	32	1	Single dose	AZE 0.050 PLA
3	2981	Double blind Parallel group	2/95 – 9/95	307	28	2 Weeks	AZE 0.050 Variable BID PLA Variable BID LEV Variable BID
6	2984	Double blind Parallel group	4/95 – 7/95	224	24	2 Weeks	AZE 0.050 Variable BID PLA Variable BID LEV Variable BID
9	3034	Double blind Parallel group	5/96 – 8/96	113	25	2 Weeks	AZE 0.050 Variable BID PLA Variable BID LEV Variable BID
10	3062	Double blind Parallel group	4/97 – 10/97	204	42	2 Weeks	AZE 0.050 Variable BID PLA Variable BID DSCG QID
14	2916	Double blind Parallel group	5/93 – 9/93	78	15	2 Weeks	AZE 0.025 BID AZE 0.050 BID AZE 0.100 BID PLA BID
13	2945	Double blind Parallel group	3/94 – 9/94	151	18	2 Weeks	AZE 0.025 BID AZE 0.050 BID PLA BID
12	2946	Double blind Parallel group	3/94 – 7/94	278	29	2 Weeks	AZE 0.025 BID AZE 0.050 BID PLA BID

Study Treatments: AZE 0.025 = Azelastine eye drops 0.025%; AZE 0.050 = Azelastine eye drops 0.05%;
AZE 0.100 = Azelastine eye drops 0.1%; DSCG = Disodium cromoglycate eye drops 2%;
LEV = Levocabastine eye drops 0.05%; PLA = Placebo (vehicle) eye drops; AZE 0.050 + PLA = AZE in one
eye and placebo in the other eye
Variable BID = BID, frequency could be increased up to QID if symptoms were severe

8.1 Indication # 1

8.1.1 Reviewer's Trial # 1 Sponsor's protocol # 400-301

Title: An evaluation of the efficacy of the investigational drug azelastine eye drops versus placebo in the treatment of allergic conjunctivitis using the conjunctival allergen provocation model

8.1.1.1 Objective/Rationale

1. To serve as a pivotal efficacy trial for AZE for the indication of allergic conjunctivitis using the conjunctival allergen provocation model
2. To evaluate the onset (visit 3) and duration of effect (visit 4) of azelastine eye drops (AZE) for the treatment of allergic conjunctivitis;

8.1.1.2 Design

Single-center, randomized, double-blind (matched-pair comparison), placebo-controlled study of the effects of a single-dose of azelastine eye drops versus placebo following allergen challenge in asymptomatic patients with a history of allergic conjunctivitis

Primary Investigator: Dr. Mitchell H. Friedlaender, Scripps Clinic, LaJolla, CA

8.1.1.3 Protocol

Eligibility was determined over a 2 week screening period (Day -14 to Day 0) that included a conjunctival provocation test (CPT) during visit 1 (Day -14) to establish the allergen threshold dose (ATD) and a second confirmatory CPT performed at visit 2 (Day -7). At visit 3 (Day 0), qualified patients were randomized to receive one drop of AZE in one eye and one drop of placebo in the other eye. Randomized patients underwent a CPT 20 minutes post administration of study drug (for evaluation of onset). During visit 4 (Day 7), qualified patients were randomized to either the 8 or 10 hour duration group and were randomized to receive one drop of AZE in one eye and one drop of placebo in the other eye. A CPT was performed either 8 or 10 hours post administration of study drug (for evaluation of duration). Allergic conjunctival symptoms were assessed by the investigator (conjunctival redness) and patient (itching) using a 5-point scale (0=none; 1+=mild; 2+=moderate; 3+=severe; 4+=very severe) immediately prior to CPT, and 3, 5 and 10 minutes post CPT. Adverse events were recorded at each visit. Physical examinations, pre-CPT ophthalmic examinations and vital sign evaluations were performed during visits 1 and 4.

8.1.1.3.1 Population

History of allergic conjunctivitis for at least 2 years, asymptomatic at study entry and throughout the study (no symptoms of redness, itching, chemosis or tearing), and redness and itching scores following CPT of at least moderate severity (2+) in both eyes at visits 1 and 2, ages 18 through 65 years old.

8.1.1.3.2 Endpoints Ocular Itching, Conjunctival Redness

8.1.1.4 Results

8.1.1.4.1 Populations enrolled/analyzed

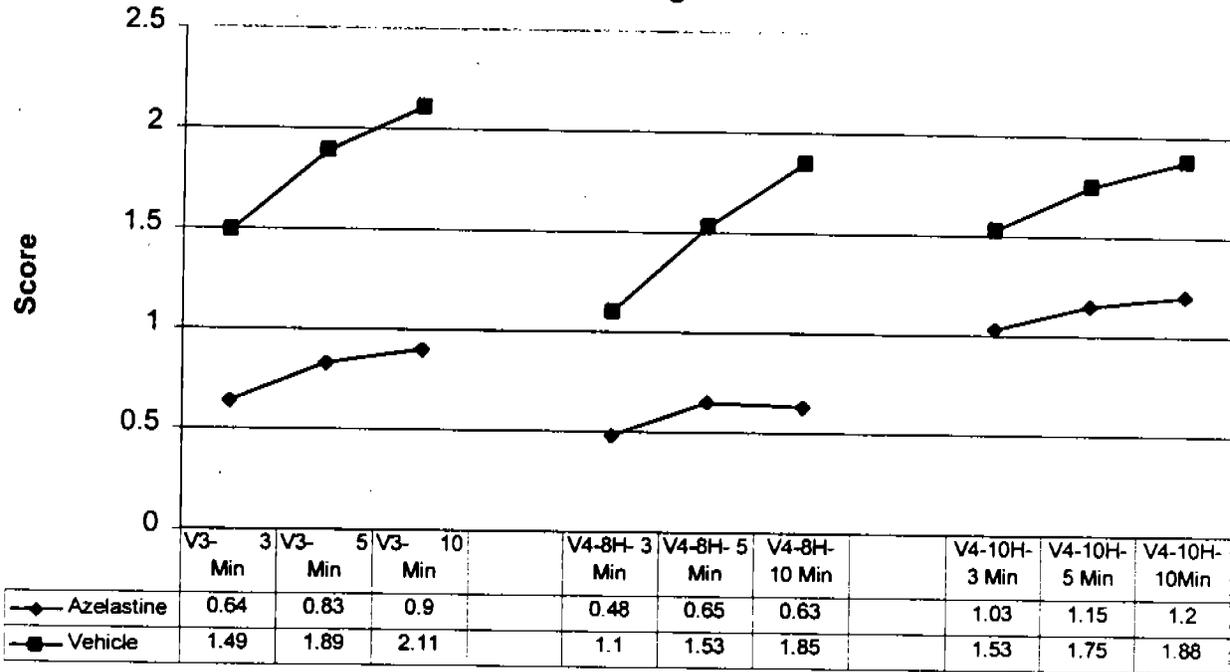
DEMOGRAPHICS FOR 8 AND 10 HOUR PATIENT SUBGROUPS AT VISIT 4

	<u>8 Hour Subgroup</u>	<u>10 Hour Subgroup</u>
<u>Gender</u>		
Male N(%)	12 (30%)	11 (28%)
Female N(%)	28 (70%)	29 (72%)
<u>Race</u>		
Caucasian N(%)	27 (68%)	32 (80%)
Black N(%)	3 (7 %)	2 (5%)
Asian N(%)	2 (5%)	2 (5%)
Hispanic N(%)	4 (10%)	4 (10%)
Other N(%)	4 (10%)	0 (0%)
<u>Iris Color</u>		
Blue N(%)	10 (25%)	12 (30%)
Green N(%)	5 (12%)	3 (8%)
Hazel N(%)	7 (18%)	5 (12%)
Brown N(%)	18 (45%)	20 (50%)
<u>Age (years)</u>		
N	40	40
Median	33.0	37.5
Mean	35.5	38.20
Standard Deviation	13.59	9.17
Minimum	18	20
Maximum	63	60
ALLERGEN REACTIVITY		
Grass	10 (25%)	17 (42.5%)
Ragweed	6 (15%)	6 (15%)
Cat Dander	24 (60%)	17 (42.5%)

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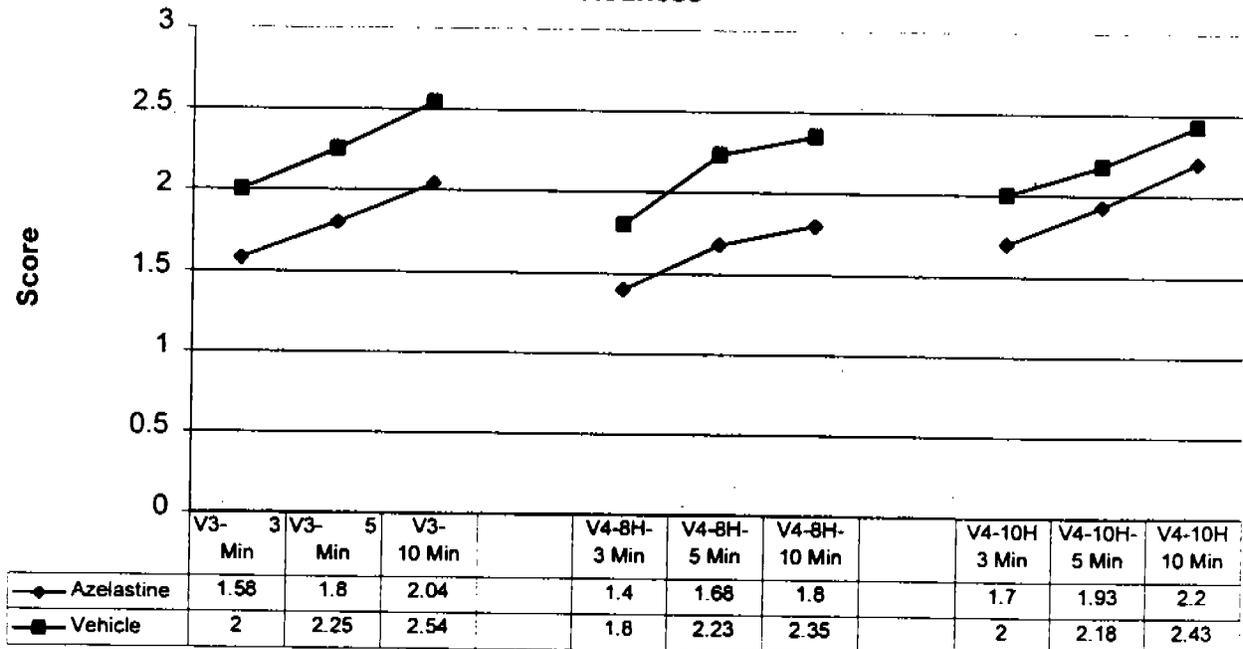
8.1.1.4.2 Efficacy endpoint outcomes

Itching



Reviewer's Comments: *A one unit difference between groups has been demonstrated at Visit 3. The effect appears to be wearing off at 10 hours.*

Redness



Reviewer's Comments: *A one unit change was not demonstrated at any observation period.*

8.1.1.4.3 Safety outcomes

Reviewer's Comments: *By design, this study is not adequate to properly evaluate safety.*

8.1.1.5 Conclusions Regarding Efficacy Data

The study demonstrates efficacy in the relief of itching lasting only up to 8 hours.

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8.1.2 Study #2 Protocol 2967

Title: Effect of azelastine eye drops on conjunctival allergen provocation

Objectives:

Part 1: To determine the onset of effect of azelastine eye drops (AZE) in comparison to placebo using a conjunctival allergen provocation model.

Part 2: To investigate the influence of azelastine eye drops on the number of inflammatory cells, evaluate ICAM-1 expression on epithelial cells, and evaluate the efficacy of AZE using a conjunctival allergen provocation model.

Study Design:

This was a placebo-controlled, double-blind, single-center, parallel-group study, where patients were randomized to receive either AZE or placebo. Eligibility was determined following a screening visit (Day -14 to -7) that included a conjunctival provocation test (CPT) to establish the allergen threshold dose (ATD). At study visit 2 (Day 0), a CPT using the ATD was performed on the right eye only with study drug administered in both eyes 20 minutes post CPT and symptom assessments were performed (right eye only), 5, 10, 20 and 30 minutes post drug. Patients administered study drug on a bid regimen between visits 2 and 3. At study visit 3 (Day 7), a CPT was performed (right eye only) 30 minutes following the last administration of study drug and symptoms were assessed 5, 10, 20 and 30 minutes post CPT (right eye only). Two independent investigators assessed patients' allergic conjunctivitis symptoms (including conjunctival redness) and patients assessed conjunctival itching using a 4-point scale. Conjunctival scrapings were performed at visit 1 (screening visit) and visit 3 prior to CPT and 30 minutes and 6 hours post CPT.

Population:

Asymptomatic, 18 through 50 year olds with a history of seasonal allergic conjunctivitis or rhinoconjunctivitis for at least 2 years and proof of a positive prick test (wheal diameter ≥ 3 mm) or radioallergosorbant test (RAST) (class ≥ 3) and a positive conjunctival reaction to an identified allergen during screening CPT with a score of ≥ 7 for redness, itching, tearing and eyelid swelling symptoms within 20 minutes after challenge at visit 1 and visit 2;

Coordinating investigator: Prof. Dr. Giorgio Walter Canonica, MD
Allergy and Immunology Service
Department of Internal Medicine (DIMI)
University of Genoa
Viale Benedetto XV, 6
I-16132 Genoa (Italy)

Clinical investigators: Dr. Giorgio Ciprandi, MD
Dr. Sandra Buscaglia, MD
Dr. Giampaola Pesce, BS
Dr. Antonella Catrullo, MD
Prof. Marcello Bagnasco, MD

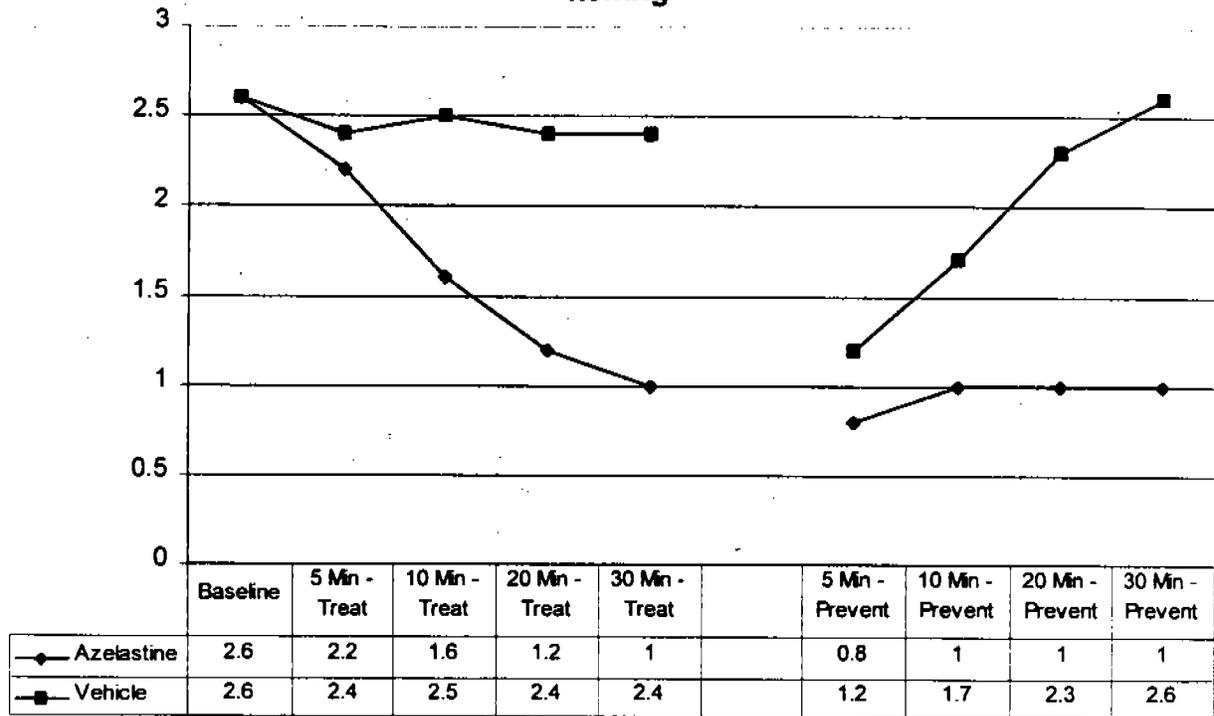
Allergy and Immunology Service
Department of Internal Medicine (DIMI)
University of Genoa
Viale Benedetto XV, 6
I-16132 Genoa (Italy)

Population: 20 recruited, 20 evaluable for safety and efficacy

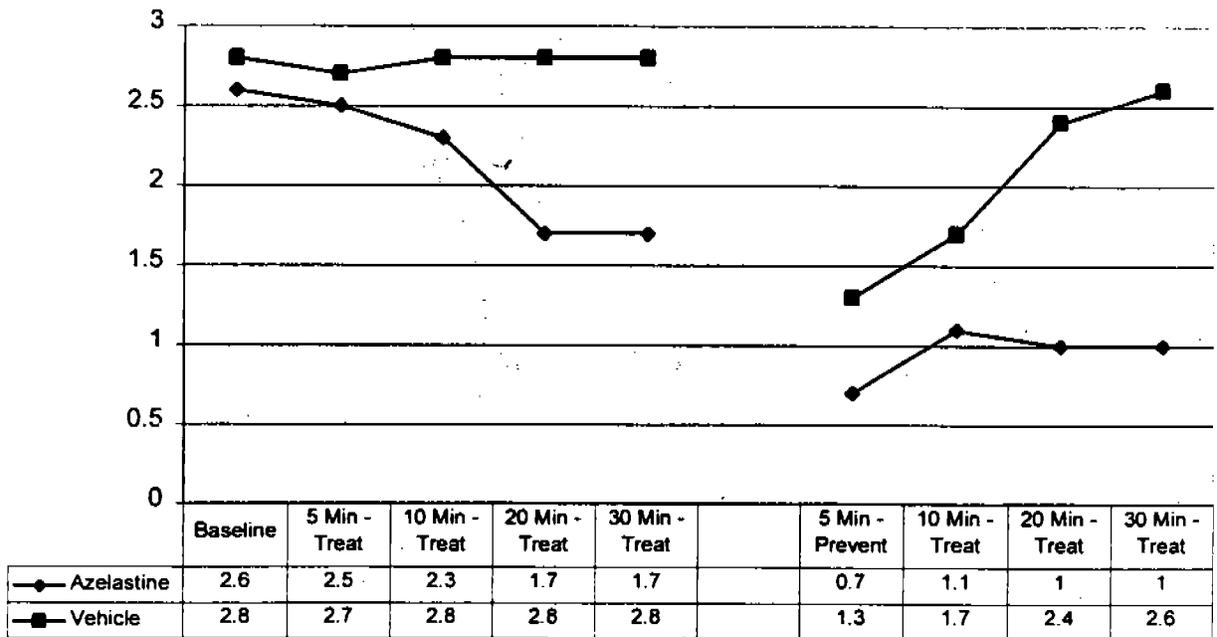
	Azelastine	Vehicle
Mean Age (years):	26.9	30.3
Age range (years):	23-49	18-48
Race		
Caucasian	10	10
Gender		
Male	4	5
Female	6	5

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Itching



Redness



Reviewer's Comments: *Efficacy was not established for either itching or redness because a one unit difference was not achieved in the majority of time points.*

NDA 21-127 Optivar (azelastine hydrochloride ophthalmic solution)

Safety Results:

Data of all 20 patients were included into the analysis of safety. No adverse events as well as no serious adverse events occurred within this study. No one died during the course of the study.

Conclusions Regarding Efficacy Data

Efficacy was not demonstrated in this study.

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8.1.2.5 8.1.2 Study #3 Protocol 2981

Title: Investigation of the efficacy and tolerability of Azelastine, Levocabastine and placebo eye drops in the treatment of patients with seasonal allergic conjunctivitis

Study Design: A randomized, multicenter, placebo and active-controlled, parallel-group, partial double-blind environmental study to evaluate the efficacy and safety of azelastine eye drops in adult patients with allergic conjunctivitis.

Population:

Patients 18 to 65 years of age with a history of seasonal allergic conjunctivitis or rhinoconjunctivitis for at least one year (eye symptoms to be predominant), confirmed by an acute allergic conjunctivitis/rhinoconjunctivitis by prick or radioallergosorbant test (RAST) or by slit-lamp examination and active symptomatology of allergic conjunctivitis, defined as a total sum score of 6 or greater for itching, redness and tearing.

Study Plan:

Patients were instructed to take the trial medication (one drop per eye) 2 times daily (azelastine, levocabastine or vehicle); if symptoms are severe, they could use medication 3 to 4 times daily. Furthermore, patients were required to enter daily assessments of conjunctivitis symptoms (in the evening) in their diary using both a 4-point verbal scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

During this 14-day period patients were required to visit the investigator on four different days (day 0, +3, +7, +14). On these days investigators assessed the patient's conjunctivitis/rhinoconjunctivitis symptoms (itching in the eyes, redness of conjunctiva, flow of tears, swollen eyelids, foreign body sensation, photophobia, soreness, discharge/eyelids sticking together, itching in the nose, sneezing, rhinorrhea, and stuffed nose) based on the scale previously mentioned. On day +14 or upon premature discontinuation, investigators made a global assessment of the test medication's efficacy and tolerability.

Reviewer's Comments: *For the purposes of this review, itching and redness will be considered the primary efficacy variables.*

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Investigators:

2	Beuing, H.;	D-35683 Dillenburg, Allergologist, pulmologist, Schlesische Str. 3
3	Bielicky, P	D-40545 Duesseldorf, Dermatologist, allergologist, Luegplatz 3
4	Brendt, P.	D-52428 Juelich, ENT specialist, allergologist, Grosse Ruhrstr. 38
6	Donhauser, G	D-81369 Muenchen, Dermatologist, allergologist, AlbertRosshaupterstr. 96
7	Dreesen, R.	D-13403 Berlin, Dermatologist, allergologist, Ollenhauerstr. 137/138
9	Gering, R.	D-47877 Willich, ENTspecialist, allergologist, Burgstr. 13
10	Goebels, W.	D-36037 Fulda, Ophthalmologist, Marktstr. 8
12	Henrich; Mrs.	D-97070 Wuerzburg, Ophthalmologist, Dominikanerplatz 7
13	Hornstein, M.	D-40472 Duesseldorf, Dermatologist, allergologist, Rotdornstr. 1
14	Janssen, E	D-67117 Limburgerhof, Internal practitioner, Burgunderplatz 18
16	Kolling	D-66763 Dillingen, Ophthalmologist, Odilienplatz 6
17	Kunkel, G.	D-13353 Berlin, Rudolf-Virchow-Krankenhaus, Asthmaklinik, Augustenburger Platz
18	Levi	D-63450 Hanau, ENTspecialist, Nuernbergerstr. 22
19	Lüdcke, H. J.	D-14480 Potsdam, Dermatologist, allergologist, Großbeerenstr. 301
21	Meyer, K. G.	D-10437 Berlin, Dermatologist, allergologist, Schoenhauser Allee 71
22	Meyer-Latzke, E	D-13505 Berlin, Allergologist, dermatologist, Berliner Str. 6
23	Ney, G.	D-66127 Klarenthal, Internal practitioner, Kreisstr. 30
24	Past, W	D-85250 Altomuenster, General practitioner, Kirchenstr. 13
25	Raddatz, C	D-55435 Gau-Algesheim, General practitioner, Bahnhofstr. 4
27	Schmidt, P	D-55571 Odernheim-Glan, General practitioner, Bahnhofstr. 2a
32	Strubel, H. B.	D-67117 Limburgerhof, General practitioner, Burgunder Platz 18
34	Walther, K. U	D-76133 Karlsruhe, General practitioner, Waldstr. 65
35	Wegler, C.	D-66333 Voelklingen, General practitioner, Poststr. 28
36	Weigl-Heider	D-81245 Gruenwald, Dermatologist, allergologist, Ludwig-Thoma- Str.39a
37	Westhoff	D-85748 Garching, Ophthalmologist, Am Rathausplatz 2
38	Zarth, A	D-88551 Kirchheim, Ophthalmologist, Am Gangsteig 5
39	Wendenburg	D-77815 Buehl, ENTspecialist, allergologist, Eisenbahnstr. 2
40	Holtemeyer	D-41061 Moenchengladbach, Ophthalmologist, Bismarckstr. 9

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Per Protocol Analysis					ITT Only	Safety only	Total
Centre	AZE	LEV	PLA	Σ			Total
2	2	2	2	6			6
3	1	2	1	4	2		6
4	1	1	2	4		1	5
6	2	1	2	5		1	6
7	3	4	4	11		1	12
9	3	3	3	9			9
10			1	1	1		2
12	2	2	1	5			5
13	6	6	6	18			18
14	1	1	1	3		1	4
16	1	2	1	4			4
17	17	17	18	52		2	54
18 ^a							
19 ^b					12		12
21	6	6	6	18			18
22			1	1			1
23	2	2	1	5	1		6
24	6	6	6	18			18
25	1	2	2	5			5
27	1	1	1	3		2	5
32	4	3	3	10			10
34	4	4	4	12			12
35		2	2	4		4	8
36	3	3	1	7	1		8
37	11	11	10	32			32
38	9	9	7	25	5		30
39	1	1	2	4		1	5
40	2	2	2	6			6
Σ	89	93	90	272	22	13	307

Premature Terminations

	<u>AZE</u>	<u>LEV</u>	<u>VEH</u>
Lack of efficacy	6	6	7
Poor tolerability	3	5	1
Intercurrent dx	1	1	1
Noncompliance	6	2	4
Other	3	4	6
Adverse Events	4	7	2

		AZE	LEV	VEH
		n=101	n=103	n=103
gender	male	40.6%	38.8%	40.8%
	female	59.4%	61.2%	59.2%
age (years)	mean	37.2	38.2	38.0
	range	18-64	18-69	17-66
Race	Caucasian	100	101	102
	Black	0	0	1
	Mongolian	1	2	0

Race Definitions: (*This and future studies in this review*)

Caucasian: White: American, European, Australian
 Black: Africa, South of Sahara, African-American
 Asian: India, Sri-Lanka, Pakistan
 Arabian: Middle East, North Africa, North of Sahara
 Mongolian: Indochina, China, Japan, South East Asia

Reviewer's Comments:

All results throughout this review are presented as an Intent to Treat Analysis with the last observation carried forward. A per protocol analysis was also reviewed and no significant differences were found.

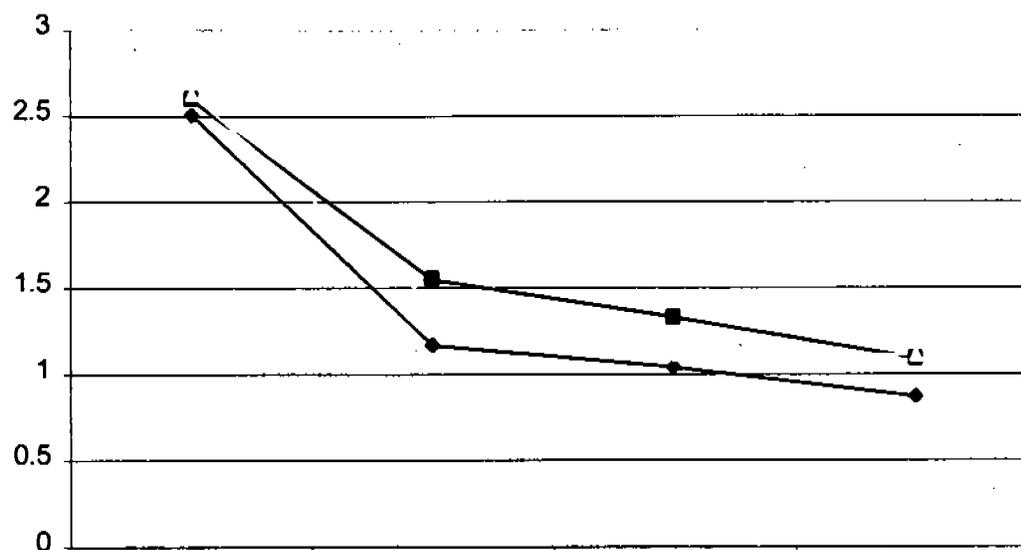
Nine (9) patients discontinued the study due to intolerability. For these patients the following ADRs were documented as (possible) reason for withdrawal:

AZE Patient 17/55: application site reaction (severe eye burning, not assessable)
 Patient 17/248: application site reaction (severe eye burning, likely)
 Patient 38/304: taste perversion (unpleasant bitter taste)

LEV Patient 6/37: application site reaction (severe eye burning, likely)
 Patient 17/35: headache (severe headache starting from the eyes, not assessable)
 Patient 17/136: eye pain (severe pressure like a sty, likely)
 Patient 38/350: headache (severe headache, not assessable)
 nausea (severe nausea, not assessable)
 Patient 39/316: application site reaction (severe eye burning, likely)

PLA Patient 17/36: application site reaction (severe eye burning, not assessable)

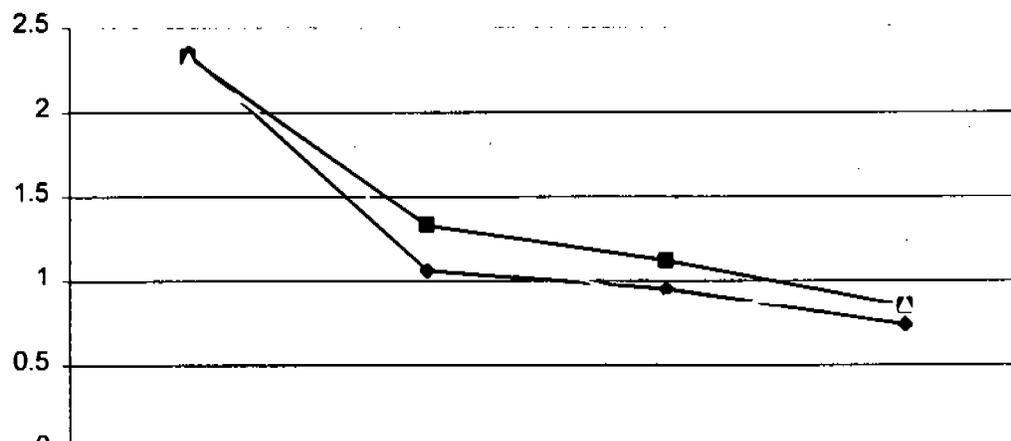
Itching



	Day 0	Day 3	Day 7	Day 14
◆ Azelastine	2.51	1.17	1.04	0.87
■ Vehicle	2.6	1.55	1.33	1.09
◆ Levocabastine	2.63	1.41	1.12	1.11

Reviewer's Comments: *There are statistically significant differences at Day 3 only.*

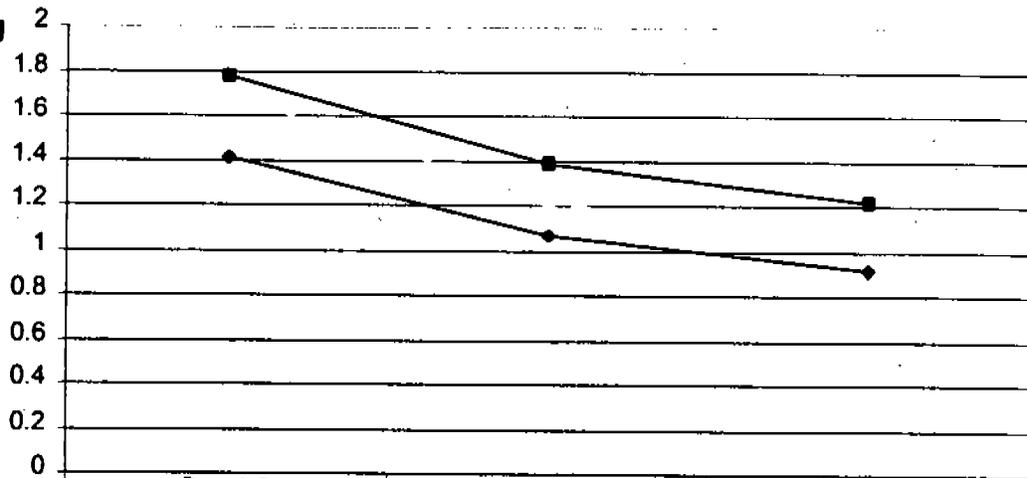
Redness



	Day 0	Day 3	Day 7	Day 14
◆ Azelastine	2.35	1.06	0.95	0.74
■ Vehicle	2.33	1.33	1.12	0.85
◆ Levocabastine	2.31	1.23	0.88	0.86

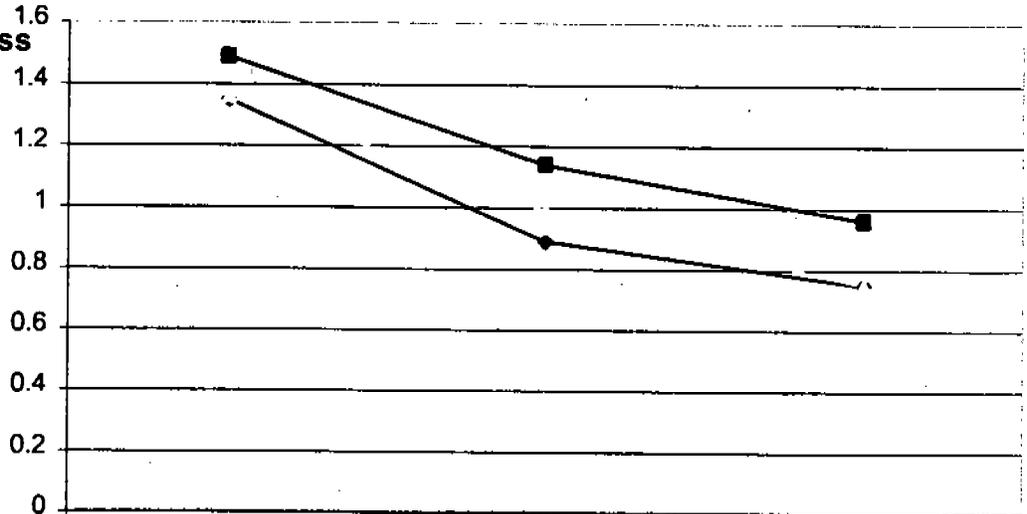
Reviewer's Comments: *There are statistically significant differences only at Day 3.*

Diary Itching



	Day 1-3	Day 4-7	Day 8-14
● Azelastine	1.41	1.07	0.92
■ Vehicle	1.78	1.39	1.22
○ Levocabastine	1.69	1.22	1.03

Diary Redness



	Day 1-3	Day 4-7	Day 8-14
● Azelastine	1.35	0.89	0.75
■ Vehicle	1.49	1.14	0.96
○ Levocabastine	1.36	0.99	0.75

Adverse Events, Number (%) of Patients by Treatment with Incidence Rate >2% for Azelastine

Randomized (N=307)	AZE (N=101)	PLA (N=103)	LEV (N=103)
All AEs ^a	54 (53.5)	38 (36.9)	44 (42.7)
<i>WHO Preferred term</i>			
Application Site Reaction	26 (25.7)	9 (8.7)	21 (20.4)
Headache	15 (14.9)	12 (11.7)	19 (18.4)
Taste Perversion	12 (11.9)	0 (0.0)	1 (1.0)
Dyspnea	7 (6.9)	5 (4.9)	2 (1.9)
Rhinitis	7 (6.9)	5 (4.9)	5 (4.9)
Coughing	5 (5.0)	3 (2.9)	5 (4.9)
Pharyngitis	4 (4.0)	3 (2.9)	3 (2.9)
Asthma	3 (3.0)	4 (3.9)	1 (1.0)
Conjunctivitis	3 (3.0)	2 (1.9)	1 (1.0)
Influenza-Like Symptoms	3 (3.0)	3 (2.9)	1 (1.0)
Vision Abnormal	3 (3.0)	1 (1.0)	0 (0.0)

^a Refers to all patients who had at least one adverse event

Conclusions Regarding Data

Minimal efficacy was demonstrated in this study and the safety profile was consistent with other studies.

APPEARS THIS WAY
ON ORIGINAL

Study #4 Protocol 2982

Title: Azelastine eye drops in the treatment of patients suffering from allergic conjunctivitis/rhinoconjunctivitis

Study Design: A randomized, multicenter, placebo and active-controlled, parallel-group, partial double-blind environmental study to evaluate the efficacy and safety in adults patients with allergic conjunctivitis

Population:

Patients 18 to 65 years of age with a history of seasonal allergic conjunctivitis or rhinoconjunctivitis for at least two years (eye symptoms to be predominant), confirmed by an acute allergic conjunctivitis/rhinoconjunctivitis by prick or radioallergosorbant test (RAST) or by slit-lamp examination and active symptomatology of allergic conjunctivitis, defined as a total sum score of 6 or greater for itching, redness and tearing.

Study Plan:

In this partly double-blind, standard- and placebo-controlled phase III trial, efficacy and safety of azelastine HCl eyedrops were investigated in patients with allergic conjunctivitis or rhinoconjunctivitis. One hundred forty-four patients (144 patients for safety analysis, 136 evaluable for per-protocol analysis) were recruited in 26 centres and were randomly allocated to receive either azelastine, or placebo eye drops during a 2 weeks treatment period. The dose regimen in the azelastine group was 1 drop into each eye twice a day which could be enlarged to up to 4 applications/day if necessary. One azelastine eye drop (0.05% solution) corresponds to approximately 0.015 mg of azelastine, giving a total daily dose of 0.06 mg for the intended bid application. In the DSCG group, the regimen was qid. Here, 1 DSCG eye drop (2% solution) corresponds to approximately 0.6 mg of DSCG, giving a total daily dose of 4.8 mg for the qid application. The appearance and application regimen of placebo eye drops was identical to azelastine eye drops.

Out-patients with an allergic conjunctivitis or rhinoconjunctivitis were recruited and were instructed to suspend all antiallergic eye medication. In case of nasal symptomatology the use of additional medication like a nasal steroid (Beconase® atomiser; supplied by ASTA Medica AG) and/or intranasal decongestants (α -sympathomimetics) were allowed.

The main efficacy criterion was the sum score of itching eyes, flow of tears and conjunctival redness documented by the investigator in the CRF. Each symptom was coded from 0 = none to 3 = severe. In case of at least 6 score points of the sum score patients were considered to be in an acute phase of their conjunctivitis/rhinoconjunctivitis and could be included into the study.

Centre	Per Protocol			Σ	ITT Only	Safety only	Total total
	AZE	<u> </u>	PLA				
1	6	6	7	19			19
2	0	1	0	1			1
3	2	2	2	6			6
4	1	1	1	3	2	1	6
5	3	5	4	12	1		13
7	3	3	2	8			8
8	1	1	1	3			3
9	0	1	1	2			2
10	0	0	1	1		1	2
12	0	0	1	1		1	2
13	2	1	3	6			6
14	1	1	2	4			4
15	0	1	1	2			2
16	2	3	3	8			8
17	1	0	1	2			2
18	3	3	2	8			8
19	2	2	2	6			6
20	0	1	1	2			2
21	2	1	1	4			4
22	2	3	2	7			7
23	2	2	2	6			6
24	2	2	2	6			6
25	2	2	2	6			6
26	2	2	2	6			6
27	1	2	2	5			5
28	1	1	0	2	2		4
Σ	41	47	48	136	5	3	144

Premature Terminations

Lack of efficacy

Poor tolerability

Noncompliance

Other

Adverse Events

AZE

0

1

1

3

1

3

2

2

4

3

VEH

5

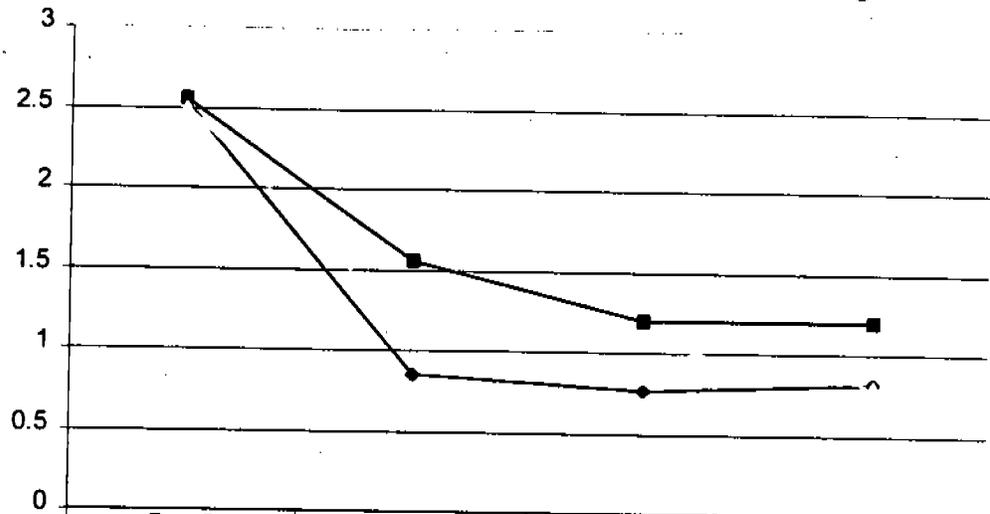
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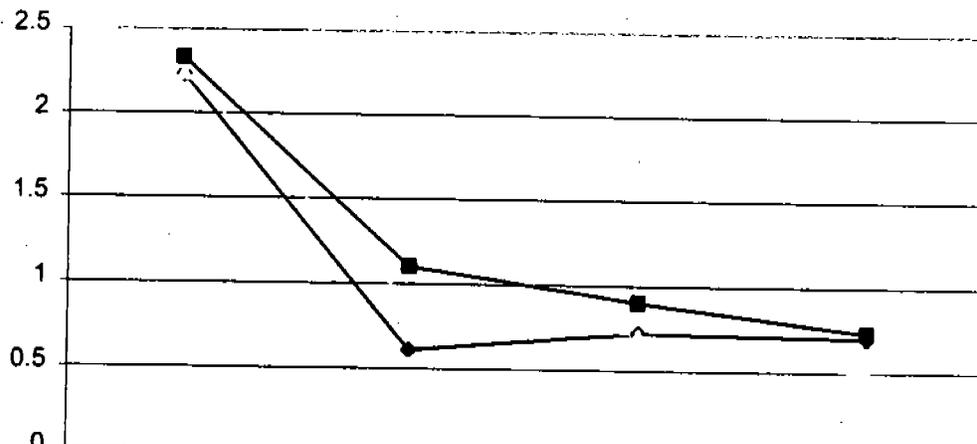
Itching



	Day 0	Day 3	Day 7	Day 14
● Azelastine	2.53	0.85	0.77	0.81
■ Vehicle	2.55	1.55	1.2	1.2
—	2.51	1.11	1.06	0.8

Reviewer's Comments: *The differences on Day 3 and Day 7 are statistically significant.*

Redness



	Day 0	Day 3	Day 7	Day 14
● Azelastine	2.23	0.61	0.72	0.7
■ Vehicle	2.33	1.1	0.9	0.73
—	2.24	0.89	0.71	0.49

Reviewer's Comments: *There are statistically significant differences only at Day 3.*

Adverse Events, Number (%) of Patients by Treatment with Incidence Rate >2% for Azelastine

Randomized (N=144)	AZE (N=45)	PLA (N=49)	PLA (N=50)
All AEs ^a	33 (73.3)	23 (46.9)	29 (58.0)
<i>WHO Preferred term</i>			
Application Site Reaction	16 (35.6)	7 (14.3)	12 (24.0)
Taste Perversion	14 (31.1)	3 (6.1)	2 (4.0)
Headache	11 (24.4)	8 (16.3)	12 (24.0)
Pharyngitis	2 (4.4)	2 (4.1)	6 (12.0)
Fatigue	2 (4.4)	1 (2.0)	0 (0.0)
Rhinitis	2 (4.4)	0 (0.0)	3 (6.0)
Conjunctivitis	2 (4.4)	0 (0.0)	1 (2.0)
Coughing	2 (4.4)	0 (0.0)	4 (8.0)
Migraine	2 (4.4)	2 (4.1)	1 (2.0)
Cystitis	1 (2.2)	0 (0.0)	0 (0.0)
Dizziness	1 (2.2)	0 (0.0)	0 (0.0)
Eye Abnormality	1 (2.2)	0 (0.0)	0 (0.0)
Gingivitis	1 (2.2)	0 (0.0)	0 (0.0)
Inflicted Injury	1 (2.2)	1 (2.0)	0 (0.0)
Influenza-Like Symptoms	1 (2.2)	0 (0.0)	1 (2.0)
Mouth Dry	1 (2.2)	1 (2.0)	1 (2.0)
Palpitation	1 (2.2)	0 (0.0)	0 (0.0)
Pruritus	1 (2.2)	0 (0.0)	0 (0.0)
Skin Dry	1 (2.2)	1 (2.0)	0 (0.0)
Tinnitus	1 (2.2)	0 (0.0)	0 (0.0)
Upper Resp Tract Infection	1 (2.2)	0 (0.0)	0 (0.0)

^a Refers to all patients who had at least one adverse event

Conclusions Regarding Data

Minimal efficacy was demonstrated in this study and the safety profile was consistent with other studies.

**APPEARS THIS WAY
ON ORIGINAL**

Study #5**Protocol 2983**

Title: Azelastine eye drops in the long-term treatment of patients suffering from seasonal allergic conjunctivitis/rhinoconjunctivitis

Objective: to investigate the tolerability and efficacy of azelastine eye drops in symptomatic patients with seasonal allergic conjunctivitis during a long-term treatment (8-weeks)

Design: Randomized, double-blind, placebo-controlled, parallel-group, multicentre study in patients with seasonal allergic conjunctivitis or rhinoconjunctivitis over an 8-weeks period. Main target of this study was to assess the tolerability under long-term treatment with azelastine eye drops. Therefore, allocation of the patients to the treatment groups (azelastine or placebo) was carried out in the ratio 3:1 in favour of azelastine. It was planned to include about 200 patients. Due to the fact that the recruitment of patients was not stopped after the inclusion of 200 patients, the total inclusion rate was much higher as originally planned in the trial protocol. The patients were recruited in 4 centres and randomly allocated to receive either azelastine or placebo eye drops.

Participating patients had to fulfill the following inclusion criteria: age between 18 and 65, a duration of disease of at least two years, proof of seasonal allergic conjunctivitis/rhinoconjunctivitis by means of ophthalmic evidence with the slit lamp or by allergological evidence by Prick test and necessity of treatment based on the sum score of three eye symptoms (itching of the eyes, tearing, conjunctival redness) coded 0 = none to 3 = severe, each. A minimum score of 6 points was the inclusion criterion. Furthermore, there had to be an expected need for antiallergic therapy over a period of at least 8 weeks. Patients with perennial allergy or urticaria were to be excluded. Pre-treatment with astemizole was to be stopped at least 4 weeks before inclusion. No concomitant treatment with ophthalmic agents, antihistaminic/antiallergic drugs, or corticosteroids was allowed.

For the evaluation of the systemic bioavailability of azelastine eye drops, it was planned to take plasma samples from patients in centres 1 and 4. In centre 1, samples were collected before start of treatment and after 14 as well as after 56 days of treatment. In centre 4, samples were taken at the end of the 56 days treatment, immediately before and 2 hours after the last administration. Plasma levels of azelastine and its main metabolite N-desmethyl-azelastine were determined.

Patients were instructed to take the trial medication (one drop per eye) 2 times daily; if symptoms were severe, patients could use the medication up to 3 or 4 times daily. Furthermore, patients were required to enter daily assessments of conjunctivitis symptoms (in the evening) in their diaries using a 4-point verbal scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) for each symptom as well as the frequency of administrations, additionally used medical treatment and other clinical symptoms.

During this 8-weeks period patients were required to visit the investigator on six different days (day 0, +3, +14, +35, +56, and day +63). Between days +56 and +63, no study medication was used. On each study day, investigators assessed the patient's conjunctivitis/rhinoconjunctivitis symptoms (itching of the eyes, redness of conjunctiva, flow of tears, swollen eyelids, foreign-

body sensation, photophobia, burning of the eyes, discharge/eyelids sticking together, itching in the nose, sneezing, rhinorrhoea, and stuffed nose) based on the scale previously mentioned. On day +63 or upon premature discontinuation, investigators made a global assessment on efficacy (allergologist) and the local (ophthalmologist) as well as the general tolerability (allergologist) of the test medication.

All those patients were regarded as therapy responders, whose sum score for the three symptoms "itching of the eyes", "conjunctival redness" and "flow of tears" (assessed by the physician) decreased by at least 3 score points between day 0 and day +3 provided a baseline value of at least 6 was found on day 0. Patients who terminated the study prematurely due to lack of efficacy are considered as "non-responders" on all visits.

Local tolerability was assessed by different ophthalmological examinations. They were performed prior to inclusion (screening visit), on day 0 (visit 1) prior to the first administration of the eye drops, and on day +14 and day +56 of treatment (visits 3 and 5).

	prior to season	day 0 visit 1	day +3 visit 2	day +14 visit 3	day +35 visit 4	Day +56 visit 5	day +63 visit 6
	screening	8-week treatment					one week follow-up
Information and consent		X					
medical history, clinical exam		X					
Demographic data		X					
blood pressure, pulse		X	X	X	X	X	X
Conjunctivitis symptoms		X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	X
ophthalmic examinations	X	X		X		X	X*
plasma sampling (facultative)		X		X		X	
adverse events		X	X	X	X	X	X
global evaluation of efficacy and tolerability							X**

*only in case of pathological findings on day +56

**or at premature termination

The stated criteria for the assessment on efficacy were:

- response rates on day +3 (target parameter for confirmatory analysis);
- response rates on days +14, +35 and +56;
- time course of the individual conjunctivitis/rhinoconjunctivitis symptoms;
- main eye score (itching of the eyes, flow of tears and conjunctival redness);
- time course of the total eye score (sum of all 8 eye symptoms);
- application frequency;
- investigator's global assessment on efficacy at the end of the investigation, also in case of premature end.

Investigators:

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3	1 PETROVSKIJ, J. N.; Dr. 2 REZNIKOV, J. E.; MD 3 RYBALOV, V. P.; MD	RU-354057 Sotschi RU-354057 Sotschi RU-354057 Sotschi	International allergological center of ul. Dagomysskaja 42a Municipal hospital of Sotschi ul. Dagomysskaja 42 Municipal hospital of Sotschi ul. Dagomysskaja 42
4	1 CHANFERJAN, R. A.; Prof. 2 NARTENKO, T. M.; MD 3 SOSNOVIKOVA, L. J.; MD 4 MUGU, M. A.; MD 5 NOVAK, L. S.; MD 6 DERJUGIN, I. L.; MD 7 MAMIEVA, O. J.; MD 8 EREMENKO, A.I.; MD 9 MALYSEV, A.V.; MD 10 SUNDATOVA, TV; Prof. MD	RU-350640 Krasnodar RU-350007 Krasnodar RU-350640 Krasnodar RU-350640 Krasnodar RU-350007 Krasnodar RU- Krasnodar RU-350007 Krasnodar RU- Krasnodar RU- Krasnodar RU-350640 Krasnodar	Cuban State Medical Academy: Chair o ul. Sedina 4 Center of Allergology ul. Recnaja 8 Cuban State Medical Academy: Chair o ul. Sedina 4 Cuban State Medical Academy: Chair o ul. Sedina 4 Center of Allergology ul. Recnaja 8 Municipal Center of Allergology Center of Allergology ul. Recnaja 8 Cuban Medical Academy: Chair of Ophth Clin. Hospital of Krasnodar Cuban State Medical Academy: Chair o ul. Sedina 4

The trial was performed between April and November 1995 at 4 Russian centres recruiting 277 out-patients as follows:

Centre	azelastine	placebo	Σ
1	30	10	40
2	52	18	70
3	43	12	55
4	82	30	112
Σ	207	70	277

		azelastine (n = 207)	placebo (n = 70)
Gender	male	85	29
	female	122	41
Age (years)	mean	35.7	32.5
	range	18 - 64	18 - 63
Race	Caucasian	207	69
	Unknown	0	1

Discontinuations

	<u>AZE</u>	<u>VEH</u>
Lack of efficacy	16	21
Poor tolerability	4	1
Intercurrent condition	2	1
Exclusion criteria	1	0
Other	5	1
Adverse Events	6	3

patient	Reason for premature termination	Treatment Duration
1/2 (p)	Insufficient efficacy	35 days
1/5 (a)	Insufficient efficacy	4 days
1/8 (p)	Insufficient efficacy	15 days
1/9 (a)	Insufficient efficacy	17 days
1/19 (a)	Other	15 days
1/20 (p)	Insufficient efficacy	14 days
1/22 (a)	Insufficient efficacy	14 days
1/27 (a)	Other (business trip)	15 days
1/28 (a)	Insufficient efficacy	25 days
1/39 (a)	Other (business trip)	21 days
2/62 (p)	Insufficient efficacy	37 days
2/81 (a)	Insufficient efficacy	55 days
2/96 (a)	Insufficient efficacy	14 days
2/100 (a)	Intercurrent disease (acute respiratory virus infection, bronchitis and otitis)	35 days
2/102 (a)	Insufficient efficacy	35 days
2/106 (p)	Insufficient efficacy	31 days
3/121 (a)	Insufficient efficacy	4 days
4/156 (a)	Insufficient efficacy	3 days
4/158 (a)	Insufficient efficacy	3 days
4/163 (p)	Insufficient efficacy	3 days
4/167 (p)	Insufficient efficacy	3 days
4/170 (p)	Other	15 days
4/171 (a)	Insufficient efficacy	4 days
4/175 (a)	Insufficient efficacy	14 days
4/181 (a)	non-compliance, lost for follow-up	unknown
4/188 (p)	Insufficient efficacy	3 days
4/196 (p)	Poor tolerability (burning, headache, impairment of accommodation, impairment of co-ordination, numbness in the face and on the thumb, paraesthesia and vertigo)	3 days
4/200 (a)	Insufficient efficacy, intercurrent disease (cough)	35 days
4/204 (p)	Insufficient efficacy	14 days
4/206 (p)	Insufficient efficacy	14 days
4/209 (p)	Insufficient efficacy	3 days
4/216 (p)	Insufficient efficacy	27 days
4/217 (a)	Other (business trip)	35 days
4/221 (a)	Poor tolerability (burning, swollen eyelids, bitter taste, sleepiness)	17 days
4/222 (p)	Insufficient efficacy	18 days
4/225 (a)	Insufficient efficacy, poor tolerability (burning)	14 days
4/227 (p)	Insufficient efficacy	20 days
4/229 (p)	Intercurrent disease (cough)	30 days
4/236 (p)	Insufficient efficacy	15 days
4/238 (a)	Insufficient efficacy	13 days
4/240 (p)	Insufficient efficacy	2 days
4/244 (p)	Insufficient efficacy	14 days
4/245 (p)	Insufficient efficacy	15 days
4/246 (a)	Insufficient efficacy, poor tolerability (burning, eye pain, oedema on the eyelid)	3 days
4/272 (p)	Insufficient efficacy	14 days
4/275 (a)	Poor tolerability (burning)	1 day

4/280 (p)	Insufficient efficacy	3 days
4/281 (p)	Insufficient efficacy	3 days

Results:

Protocol Defined Results:

response		azelastine	placebo	p-value
Day +3	per-protocol	132/202 = 65%	33/68 = 49%	p = 0.02
	intention-to-treat	134/206 = 65%	35/70 = 50%	p = 0.03
Day +14	per-protocol	159/200 = 80%	39/67 = 58%	p < 0.01
Day +35	per-protocol	167/197 = 85%	39/64 = 61%	p < 0.01
Day +56	per-protocol	176/195 = 90%	41/64 = 64%	p < 0.01

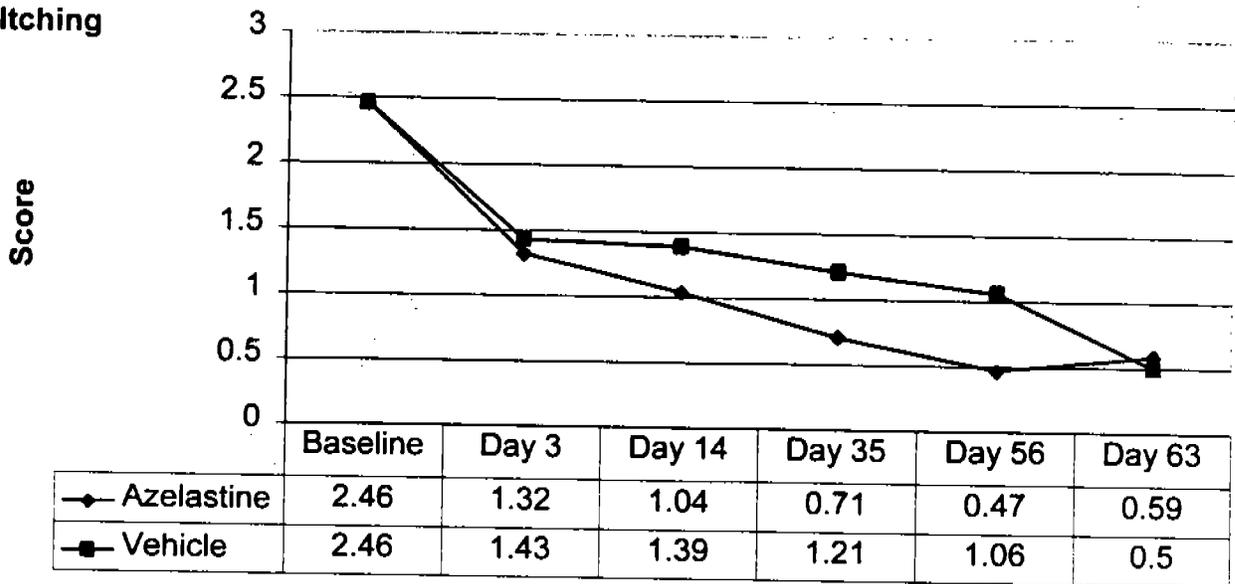
main eye score	Azelastine (n = 202)	placebo (n = 68)	p-value
day 0	6.9 ± 0.9	7.0 ± 1.1	
Difference day +3 - day 0	-3.4 ± 2.1	-2.8 ± 2.4	0.051
Difference day +14 - day 0	-4.3 ± 2.3	-3.3 ± 2.9	0.004
Difference day +35 - day 0	-5.0 ± 2.5	-3.6 ± 3.1	< 0.001
Difference day +56 - day 0	-5.0 ± 2.4	-4.0 ± 3.4	0.008

A separate analysis of the main eye score was done within each study centre. The results (mean values, completed cases, last values carried forward) are listed below:

Main eye score	centre 1		centre 2		centre 3		centre 4	
	AZE n = 30	PLA n = 10	AZE n = 52	PLA n = 18	AZE n = 43	PLA n = 12	AZE n = 77	PLA n = 28
day 0	6.3	7.6	6.9	6.6	7.2	6.8	7.0	7.1
Difference day +3 - day 0	-2.5	-3.7	-3.4	-2.2	-2.8	-2.7	-4.0	-2.9
Difference day +14 - day 0	-3.2	-4.2	-4.5	-3.2	-5.0	-5.1	-4.1	-2.3
Difference day +35 - day 0	-4.4	-4.8	-5.0	-3.9	-6.3	-6.2	-4.6	-1.8
Difference day +56 - day 0	-4.6	-5.2	-5.3	-4.8	-6.5	-6.3	-5.7	-2.0
p-value for group effect	p = 0.34		p = 0.04		p = 0.88		p < 0.01	

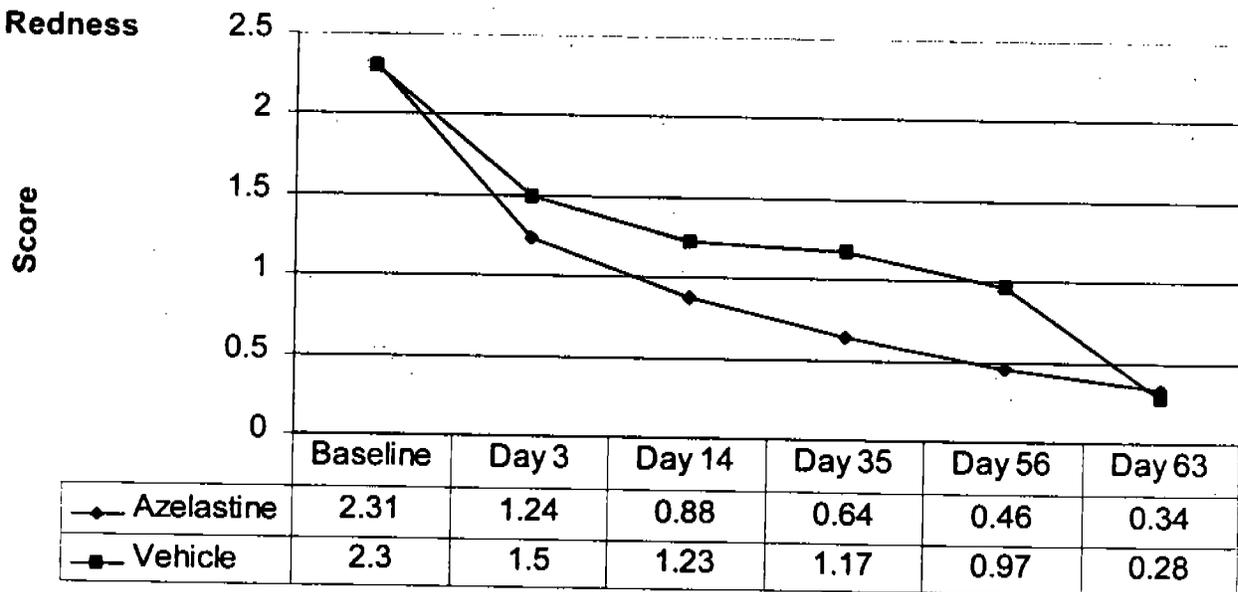
total eye score	Azelastine (n = 202)	placebo (n = 68)	p-value
day 0	13.5 ± 3.1	13.1 ± 3.5	
Difference day +3 - day 0	-6.5 ± 4.1	-4.9 ± 5.1	0.01
Difference day +14 - day 0	-8.7 ± 4.8	-6.5 ± 5.9	0.002
Difference day +35 - day 0	-9.9 ± 5.2	-6.7 ± 6.7	< 0.001
Difference day +56 - day 0	-11.0 ± 5.3	-7.4 ± 7.3	< 0.001

Itching



Reviewer's Comments: *The differences at Days 14, 35 and 56 are statistically significant.*

Redness



Reviewer's Comments: *The differences at Days 3, 14, 35 and 56 are statistically significant.*

	Baseline	Day 3	Day 14	Day 35	Day 56	Day 63 ^(b)
Itching						
Placebo (n = 70)	2.46	1.43	1.39	1.21	1.06	0.50 (n = 40)
AZE (n = 206)	2.46	1.32	1.04	0.71	0.47	0.59 (n = 164)
p-value PLA v. AZE ^(a)	0.991	0.311	0.010	0.001	<0.001	0.461
Redness						
Placebo (n = 70)	2.30	1.50	1.23	1.17	0.97	0.28 (n = 40)
AZE (n = 206)	2.31	1.24	0.88	0.64	0.46	0.34 (n = 164)
p-value PLA v. AZE ^(a)	0.935	0.024	0.021	0.001	0.002	0.531

^(a) P-value from an independent samples t-test.

^(b) Day 63 was one week after treatment was discontinued.

Dairy Symptom Severity Means by Treatment and Assessment Day

	Days 1-3	Days 4-14	Days 15-35	Days 36-56	Days 57-63 ^(b)
Itching					
Placebo	2.04 (n = 70)	1.39 (n = 62)	0.99 (n = 56)	0.56 (n = 47)	0.48 (n = 40)
AZE	1.83 (n = 205)	1.12 (n = 202)	0.77 (n = 193)	0.42 (n = 184)	0.50 (n = 164)
p-value ^(a)	0.006	0.005	0.034	0.194	0.859
Redness					
Placebo	1.95 (n = 70)	1.18 (n = 62)	0.91 (n = 56)	0.52 (n = 47)	0.28 (n = 40)
AZE	1.75 (n = 205)	1.05 (n = 202)	0.71 (n = 193)	0.39 (n = 184)	0.33 (n = 164)
p-value ^(a)	0.018	0.203	0.092	0.244	0.606

^(a) P-value from an independent samples t-test.

^(b) Treatment was discontinued between days 57-63

Systemic bioavailability

For the evaluation of the systemic bioavailability of azelastine eye drops, plasma samples from patients in centres 1 and 4 were collected. In centre 1, samples were collected before start of treatment (n = 20) and under steady state conditions on day +14 (n = 16) and day +56 (n = 15) of the study. The time between the last administration of the eye drops and the collection of samples was 4 to 5 hours on day +14 (visit 3) and 12 to 15 hours on day +56 (visit 5), respectively. In centre 4, samples were taken at the end of the 8-weeks treatment (n = 10), immediately before and 2 hours after the last administration of the eye drops under the supervision of the investigator (2nd addendum). Plasma levels of azelastine were not detectable (<0.02 ng/mL) or below the limit of quantification (0.25 ng/mL) in all tested samples except one (Patient 1/23: 0.29 ng/ml); plasma levels of the main metabolite N-desmethyl-azelastine were detected in 2/11 patients in centre 1 (patient 23, 24) and in 2/9 patients in centre 4 (patient 230, 232). There is no difference between the centres and also no conditional on time distance for collecting samples. It can be concluded that systemic bioavailability of azelastine eye drops is none to very poor even after administration over an 8-weeks period. Therefore, any adverse events related to systemic plasma levels of the compound are unlikely to occur.

Reviewer's Comments: *Most levels were detectable, but not quantifiable (i.e., between 0.02 and 0.25 ng/mL).*

Randomized (N=277)	AZE (N=207)	PLA (N=70)
All AEs ^(a)	117 (56.5)	29 (41.4)
<i>WHO Preferred term</i>		
Application Site Reaction	59 (28.5)	5 (7.1)
Headache	36 (17.4)	11 (15.7)
Coughing	30 (14.5)	14 (20.0)
Dyspnea	19 (9.2)	9 (12.9)
Rhinitis	13 (6.3)	3 (4.3)
Conjunctivitis	10 (4.8)	4 (5.7)
Taste Perversion	9 (4.3)	0
Pruritus	5 (2.4)	2 (2.9)
Somnolence	5 (2.4)	1 (1.4)
Angina Pectoris	5 (2.4)	0
Dyspepsia	4 (1.9)	0
Hypertension	4 (1.9)	0
Urticaria	4 (1.9)	0
Asthenia	3 (1.4)	1 (1.4)
Dizziness	3 (1.4)	1 (1.4)
Toothache	3 (1.4)	1 (1.4)
Nausea	3 (1.4)	0
Upper Respiratory Infection	3 (1.4)	0

^(a)Refers to all patients who had at least one adverse event

Conclusions Regarding Data

Efficacy was demonstrated in this study and the safety profile was consistent with other studies.

Title: Assessment of the efficacy and safety of azelastine eye drops in the treatment of adult patients suffering from allergic conjunctivitis or rhinoconjunctivitis

Study Plan:

Partly double-blind (vs PLA) , positive- and placebo-controlled phase III trial, efficacy and safety of azelastine eye drops were investigated in patients with allergic conjunctivitis or rhinoconjunctivitis. Patients were randomly allocated to receive either azelastine, levocabastine or placebo eye drops during a 2 weeks treatment period. Depending on their randomization group patients received a box containing a 10 ml bottle (AZE, PLA) or a 3 ml bottle (LEV) on visit 1 and visit 2 each. The dose regimen was 1 drop into each eye bid which could be increased to 4 applications/day if necessary. The composition of placebo eye drops was identical to azelastine eye drops but without any active substance.

The main efficacy criterion was the sum score of itching eyes, tearing eyes and redness documented by the investigator. Each symptom was coded from 0 = none to 3 = severe. In case of at least 6 score points of the sum score patients were considered to be in an acute phase of their conjunctivitis/rhinoconjunctivitis and could be included into the study. Target parameter of efficacy was the response rate, response being defined as an improvement of at least 3 score points in the above cited eye sum score between day 0 and day +3. Patients who discontinued the study due to inefficacy were regarded as non-responders.

Study Procedures

Study Procedure Completed	Visit 1 Day 0	Visit 2 Day 3	Visit 3 Day 14
Informed consent	•		
Medical history, including allergic conjunctivitis	•		
Concomitant disease	•		
Concomitant medication	•	•	•
Vital signs	•	•	•
Symptoms assessed (by Investigator)	•	•	•
Eligibility criteria	•		
Randomization/1 st application of study medication	•		
Adverse events	•	•	•
Study medication dispensed	•	•	
Patient Diary dispensed	•	•	
Patient Diary reviewed		•	•
Used study medication collected		•	•
Completed patient diaries collected		•	•
Final Status/termination			•

Investigators:

1.	Dr. Anton	9 Rue Kléber, 44000 Nantes
2.	Dr. Basset-Stheme	59, Av. Gambetta, 26000 Valence
3.	Prof. Bloch-Michel	168, Rue de Grenelle, 75007 Paris
4.	Dr. Boidin	1, Rue Platière, 69001 Lyon
5.	Prof. Bousquet	Hôpital A. de Villeneuve, Av. Doyen G. Giraud, 34295 Montpellier Cedex 5
6.	Dr. Castel	19, Bd. Winston Churchill, 44800 St Herblain
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9.	Dr. Couturier	59, Av. Gambetta, 26000 Valence
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21.	Dr. Severac	Centre Médical "Le Rabelais", 3, Av. d'Oc, 34500 Beziers
22.	Dr. Taulelle	221, Rue Claude Nicolas Ledoux, 30900 Nantes
23.	Dr. Verin	Centre J. Abadie, 89, Rue des Sablières, 33077 Bordeaux
24.	Dr. Wessel	3, Rue de Gorges, 44000 Nantes

Centre	AZE	LEV	PLA	Σ
1	6	6	6	18
2	3	1	3	7
3	2	1	2	5
4	4	4	3	11
5	1	1	2	4
6	0	0	1	1
7	1	0	0	1
8	4	4	4	12
9	3	5	4	12
10	3	3	3	9
11	2	2	2	6
12	7	7	7	21
13	3	2	3	8
14	5	5	5	15
15	2	2	1	5
16	4	4	4	12
17	4	4	4	12
18	0	1	1	2
19	4	3	4	11
20	3	4	4	11
21	2	2	1	5
22	2	2	2	6
23	4	4	4	12
24	6	6	6	18
Σ	75	73	76	224

		AZE	LEV	PLA
		n = 75	n = 73	n = 76
Gender	male	44.0%	42.5%	43.3%
	female	56.0%	57.5%	56.6%
Age (years)	mean	34.3	33.9	33.8
	range	18-62	18-64	13-64
Race	Caucasian	64	67	67
	Black	3	1	3
	Asian	5	5	5
	Arabian	1	0	0
	Mongolian	2	0	1
	Other	1	1	0

Average Number of Daily Applications by Treatment

Days	AZE			PLA			LEV		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
1-3	74	2.3	0.7	76	2.3	0.6	70	2.4	0.9
4-14	72	2.6	0.7	73	2.6	0.8	68	2.6	0.9

Discontinuations:

The reasons for discontinuation were as follows:

Group	Inefficacy	Intolerability	Intercurrent disease	Non-compliance	Other	Adverse event
AZE	4	1	1	0	1	2
LEV	3	0	2	1	4	2
VEH	7	1	0	0	2	1

**APPEARS THIS WAY
ON ORIGINAL**

Per Protocol Definitions

A patient was considered to be a responder if an improvement of at least 3 score points in the sum score of itching, redness and tearing was observed between baseline and day +3. Patients who discontinued the study due to inefficacy were analyzed as non-responders with no regard to the day of discontinuation.

per-protocol group	response		
	ratio	95%-confidence limit	p-value versus PLA*
AZE	53/73 = 72.6%	60.9 - 82.4%	1.000
LEV	55/67 = 82.1%	70.8 - 90.4%	0.310
PLA	54/73 = 74.0%	62.3 - 83.6%	-

* 2-sided FISHER test

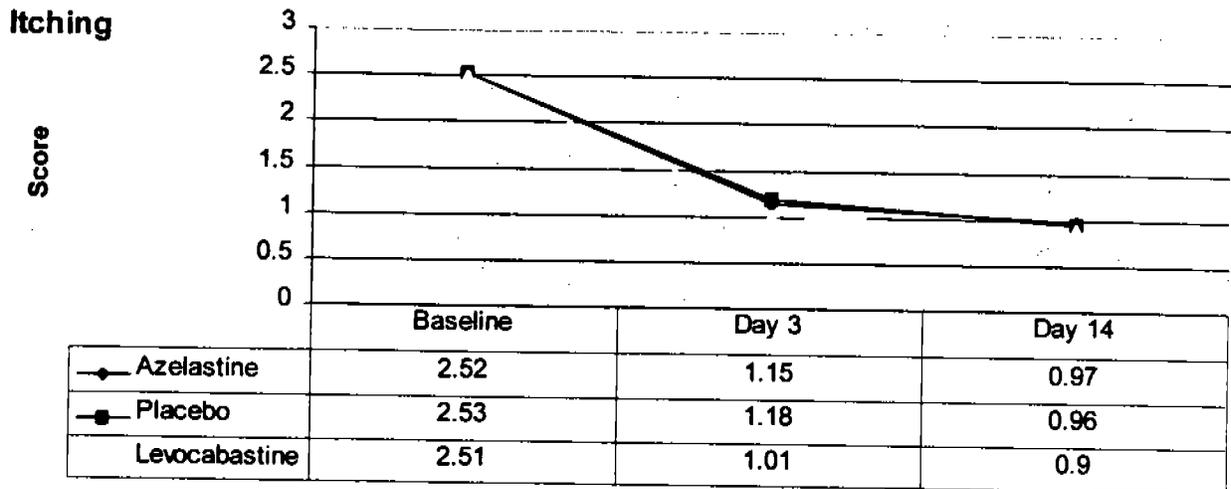
ITT group	response		
	ratio	95%-confidence limit	p-value versus PLA*
AZE	55/75 = 73.3%	61.9 - 82.9%	1.000
LEV	56/70 = 80.0%	68.7 - 88.6%	0.435
PLA	56/76 = 73.7%	62.3 - 83.1%	-

* 2-sided FISHER test

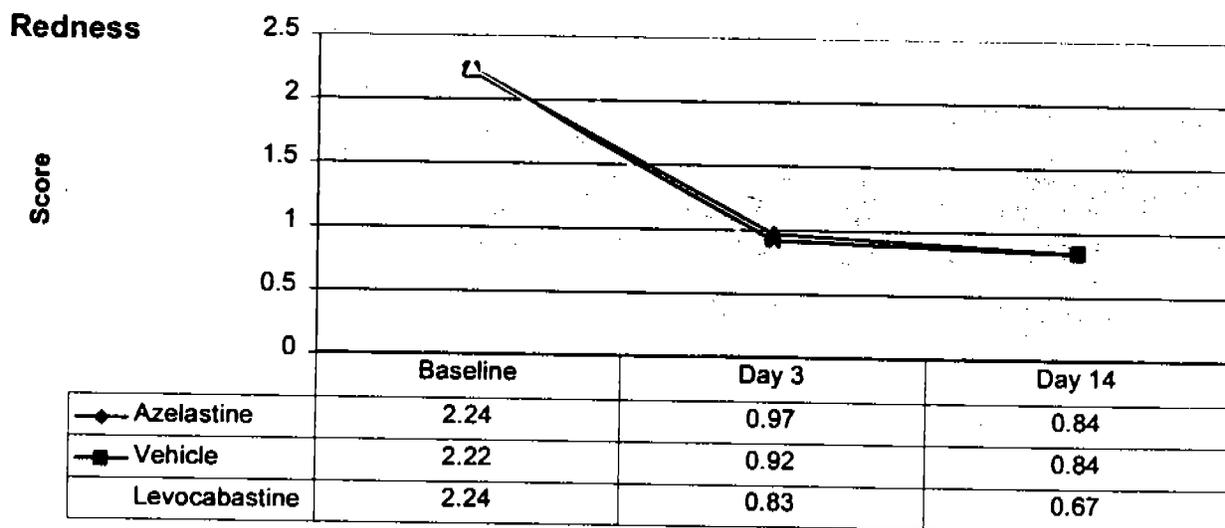
Agency Criteria:

	Baseline	Day 3	Day 14
<i>Itching</i>			
Vehicle (n=76)	2.53	1.18	0.96
AZE (n=75)	2.52	1.15	0.97
LEV (n=70)	2.51	1.01	0.90
p-value VEH v. AZE		0.797	0.935
p-value VEH v. LEV		0.252	0.696
<i>Redness</i>			
Vehicle (n=76)	2.22	0.92	0.84
AZE (n=75)	2.24	0.97	0.84
LEV (n=70)	2.24	0.83	0.67
p-value VEH v. AZE		0.708	0.989
p-value VEH v. LEV		0.489	0.244

P-value from an independent samples t-test.



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



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

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The most frequently reported adverse drug reactions were listed in the following table:

Incidence Rate > 2% for Azelastine

Randomized (N=224)	AZE (N=75)	PLA (N=76)	LEV (N=73)
All AEs ^(a)	40 (53.3)	26 (34.2)	27 (37.0)
<i>WHO Preferred term</i>			
Application Site Reaction	26 (34.7)	9 (11.8)	17 (23.3)
Taste Perversion	7 (9.3)	1 (1.3)	0 (0.0)
Asthma	4 (5.3)	1 (1.3)	0 (0.0)
Dyspnea	3 (4.0)	0 (0.0)	0 (0.0)
Headache	3 (4.0)	7 (9.2)	6 (8.2)

^(a) Refers to all patients who had at least one adverse event

Other adverse drug reactions following AZE treatment were "dizziness" and "increase of conjunctival symptoms" (1 patient each). Whereas "dizziness" was regarded to be a chance finding, the "increase of conjunctival symptoms" seemed to be more likely an insufficient efficacy than an adverse drug reaction. Five patients who were treated with PLA reported 11 adverse drug reactions (dizziness, headache, paraesthesia, dry mouth, thirst, rhinitis, asthma, face oedema and chest pain). Additionally adverse drug reactions following LEV treatment were "headache" (1 patient) and "vision abnormal" (3 patient). "Vision abnormal" was the preferred term for "blurred vision". This reaction was mentioned subjectively by the patients; no measurement of the visual acuity had been performed.

Conclusions Regarding Data

No efficacy was demonstrated in this study and the safety profile was consistent with other studies.

APPEARS THIS WAY
ON ORIGINAL

Study #7 Protocol 2985

Title: Azelastine eye drops in the treatment of patients suffering from seasonal allergic conjunctivitis/rhinoconjunctivitis

Study Plan:

Phase III randomized, multicenter, placebo-controlled, parallel-group, double-blind, environmental study to evaluate the efficacy and safety of AZE in adult patients with allergic conjunctivitis.

Study Procedures

Study Procedure Completed	Visit 1/ Day 0	Visit 2/ Day 3	Visit 3/ Day 7	Visit 4/ Day 14
Informed consent	•			
History of allergic conjunctivitis	•			
Concomitant disease	•			
Concomitant medication	•	•	•	•
Vital signs	•	•	•	•
RAST test /slit lamp examination	•			
Symptoms assessed (by Investigator)	•	•	•	•
Eligibility criteria	•			
Randomization/1 st application of study medication	•			
Adverse events	•	•	•	•
Study medication dispensed	•		•	
Patient Diary dispensed	•		•	
Patient Diary reviewed		•	•	•
Used study medication collected			•	•
Completed patient diaries collected			•	•
Final Status/termination				•

Patients were instructed to apply one drop (0.03 ml containing vehicle or 0.015 mg AZE) of study medication to each eye two times a day in both treatment groups (for a total dose of 0.06 mg AZE). If symptoms were perceived as more severe by any patient, dosing could be increased to three to four times daily (to a maximum dose of 0.12 mg). The AZE and placebo medication bottles were indistinguishable.

**APPEARS THIS WAY
ON ORIGINAL**

Investigators:

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- 2 Mrs. Dr. med. V. V. Aldonina Russian State Medical University, Chair of Pediatrics, Polyclinic No. 203, Moscow
- 3 Prof. Dr. med. Y. B. Belousov Russian State Medical University, Chair of Clinical Pharmacology, Moscow
- 4 Prof. Dr. med. L. A. Gorjackina Russian Medical Academy of Postgraduate Advanced Training, Chair of Allergology, Moscow
- 5 Dr. med. N. A. Didkoskij Research Institute of Physico-Chemical Medicine 7th Municipal Hospital, Laboratory of Clinical Immunology, Moscow
- 6 Dr. med. V. D. Prokopenko Institute of Immunology of the Ministry of Health of the Russian Federation, Moscow
- 7 Prof. Dr. med. L. D. Sidorova Novosibirsk Medicinal Institute, Medical Academy of Sciences, Novosibirsk

The trial was performed between April and September 1995 at 7 Russian centres recruiting out-patients as follows:

Centre	Azelastine	Vehicle	Σ
1	28	32	60
2	23	22	45
3	5	3	8
4	20	20	40
5	14	16	30
6	30	27	57
7	26	24	50
Σ	146	144	290

		Azelastine (n = 146)	Vehicle (n = 144)
Gender	male	61	53
	female	85	91
Age (years)	mean	34.5	33.1
	range	18-64	17-63
Race	Caucasian	146	143
	Mongolian	0	1

Average Number of Daily Applications by Treatment

Days	Azelastine			Vehicle		
	N	Mean	SD	N	Mean	SD
1-3	140	2.6	0.7	143	2.8	0.7
4-7	137	2.7	0.8	134	2.9	0.8
8-14	131	2.5	0.8	125	2.7	0.8

Premature Terminations

	<u>AZE</u>	<u>VEH</u>
Lack of efficacy	10	18
Poor tolerability	3	1
Intercurrent illness	1	0
Non-compliance	7	0
Exclusion criteria	1	1
Other	4	5
Adverse event	5	4

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patient	reason for premature termination	Treatment duration
1/3 (p)	Insufficient efficacy	4 days
1/14 (p)	insufficient efficacy	3 days
1/19 (p)	insufficient efficacy	3 days
1/20 (p)	insufficient efficacy	4 days
1/21 (p)	insufficient efficacy	4 days
1/32 (a)	non-compliance, lost for follow up	once (?)
1/35 (p)	insufficient efficacy	8 days
1/41 (a)	insufficient efficacy	8 days
1/48 (p)	insufficient efficacy, bad tolerability (headache)	3 days
1/50 (p)	insufficient efficacy, occurrence of exclusion criteria	12 days
1/242 (p)	insufficient efficacy	12 days
1/245 (a)	insufficient efficacy, bad tolerability (severe conjunctivitis symptoms)	9 days
1/246 (p)	Insufficient efficacy	8 days
1/250 (p)	Insufficient efficacy	5 days
4/125 (p)	Insufficient efficacy	3 days
4/131 (p)	Insufficient efficacy	9 days
4/132 (p)	Insufficient efficacy	6 days
4/136 (a)	Insufficient efficacy	6 days
4/138 (p)	Insufficient efficacy	6 days
4/139 (a)	Insufficient efficacy	7 days
4/140 (a)	Insufficient efficacy	6 days
4/146 (a)	Insufficient efficacy	7 days
4/147 (p)	Insufficient efficacy	8 days
4/150 (a)	Insufficient efficacy	8 days
4/151 (a)	Insufficient efficacy	8 days
4/156 (p)	Insufficient efficacy	4 days
4/157 (a)	Insufficient efficacy	4 days
5/162 (a)	Other (pain in the eye)	1 day
5/168 (p)	Insufficient efficacy	7 days
5/180 (a)	Non-compliance	9 days
5/188 (a)	Insufficient efficacy, bad tolerability (increased symptoms)	1 day
6/107 (a)	Intercurrent disease (intensification of atopic dermatitis, ketotifen treatment)	8 days
6/112 (p)	Other (klaritine treatment)	2 days
6/192 (a)	Other (good efficacy)	12 days
6/194 (a)	Bad tolerability (increased conjunctivitis symptoms)	1 day
6/196 (p)	Other (increased conjunctivitis symptoms)	1 day
6/204 (p)	Other (severe eye-burning)	1 day
6/208 (p)	Other (severe rhinoconjunctivitis)	2 day
6/210 (p)	Other (increased conjunctivitis symptoms)	3 day
6/216 (a)	Non-compliance, lost for follow up	once (?)
6/217 (a)	Non-compliance, lost for follow up	once (?)
6/223 (a)	Non-compliance, lost for follow up	once (?)
6/232 (a)	Non-compliance	4 days
6/235 (a)	Non-compliance, lost for follow up	once (?)

Per Protocol Results:

A main eye score of ≥ 6 on day 0 (itching in the eyes, flow of tears and conjunctival redness) was necessary for inclusion. As specified in the protocol, the main variable for efficacy is the response rate on day +3. A patient is defined as "responder" if there is a reduction in the main eye score of at least 3 points from day 0 to day +3 (for individual data see table C2). All patients who terminated the study prematurely due to insufficient efficacy (judgement of the investigator at the final assessment) are considered as non-responders on all visits. Confirmatory group comparisons were done between azelastine and placebo with the exact FISHER test (two-sided).

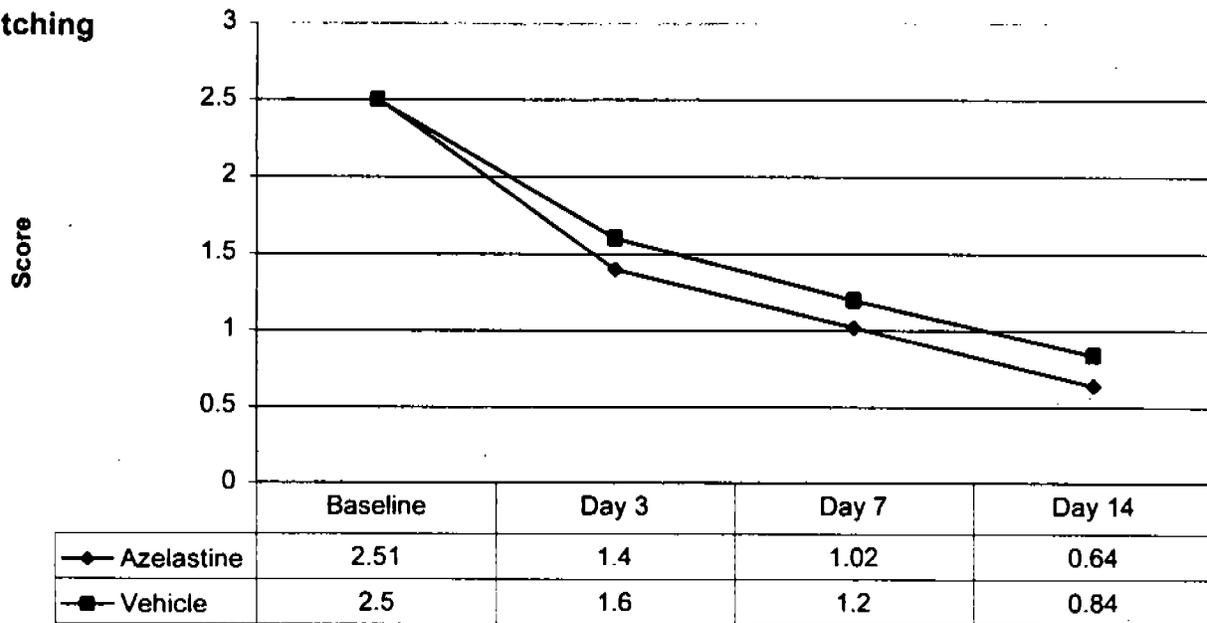
Protocol defined response		Azelastine	Vehicle	p-value
day 3	per-protocol	93/137 = 68%	65/139 = 47%	p < 0.01
	Intention-to-treat	94/141 = 67%	66/144 = 46%	p < 0.01
day 7	per-protocol	102/134 = 76%	93/138 = 67%	p = 0.14
day 14	per-protocol	120/132 = 91%	109/136 = 80%	p = 0.02

total eye score (range: 0 - 24)	azelastine (n = 137)	Placebo (n = 139)
day 0	13.4 \pm 3.7	14.0 \pm 3.5
difference day 3 - day 0	-6.5 \pm 4.5	-5.4 \pm 4.6
difference day 7 - day 0	-8.5 \pm 4.9	-7.7 \pm 5.3
difference day 14 - day 0	-10.5 \pm 5.2	-9.6 \pm 5.5
p-value for group effect	p = 0.11	

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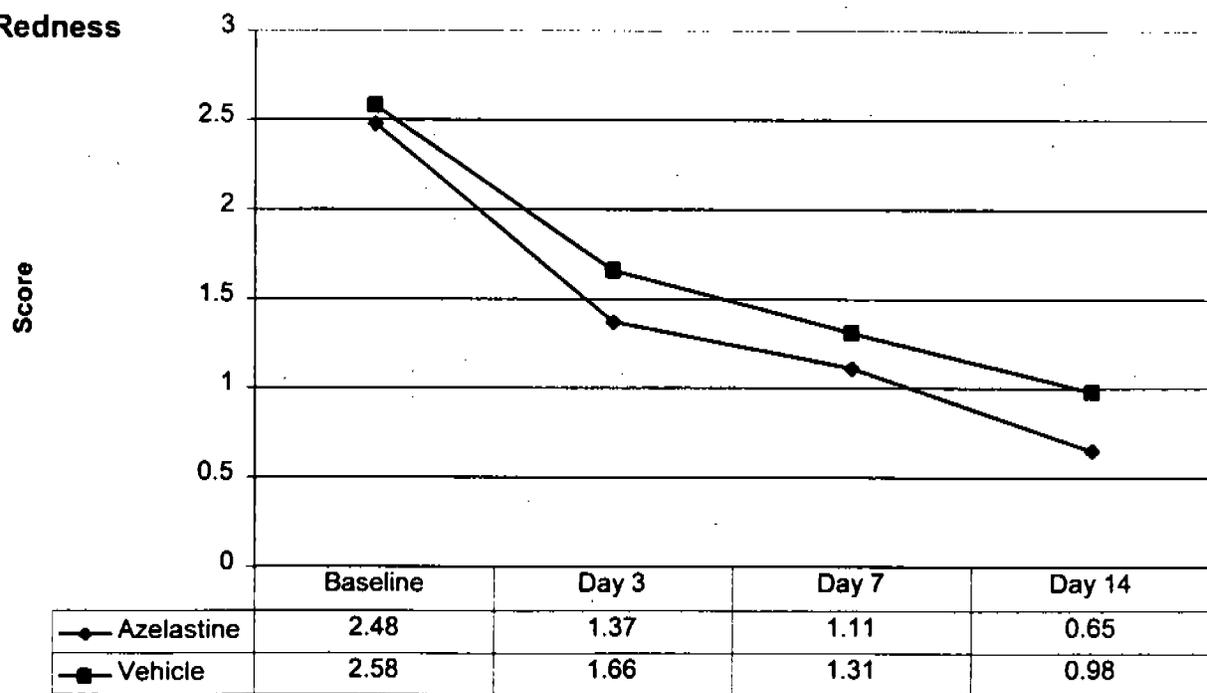
Agency Analysis:

Itching



Reviewer's Comments: *Only the difference on Day 3 is statistically significant.*

Redness



Reviewer's Comments: *The differences on Days 3 and 14 are statistically significant.*

Symptom Severity Means by Treatment and Assessment Day

	Baseline	Day 3	Day 7	Day 14
<i>Itching</i>				
Placebo (n=143)	2.50	1.60	1.20	0.84
AZE (n=141)	2.51	1.40	1.02	0.64
p-value PLA v. AZE ^(a)	0.872	0.039	0.084	0.053
<i>Redness</i>				
Placebo (n=143)	2.58	1.66	1.31	0.98
AZE (n=141)	2.48	1.37	1.11	0.65
p-value PLA v. AZE ^(a)	0.119	0.003	0.056	0.002

^(a) P-value from an independent samples t-test.

Summary of Adverse Events, Number (%) of Patients with Incidence Rate > 2% for Azelastine

Randomized (N=290)	AZE (N=146)	PLA (N=144)
All AEs ^(a)	62 (45.2)	30 (20.8)
<i>WHO Preferred term</i>		
Application Site Reaction	39 (26.7)	4 (2.8)
Conjunctivitis	11 (7.5)	5 (3.5)
Coughing	10 (6.8)	7 (4.9)
Taste Perversion	7 (4.8)	0 (0.0)
Dyspnea	6 (4.1)	6 (4.2)
Headache	4 (2.7)	7 (4.9)
Pharyngitis	4 (2.7)	4 (2.8)

^(a) Refers to all patients who had at least one adverse event

Conclusions Regarding Data

Minimal efficacy was demonstrated in this study and the safety profile was consistent with other studies.

APPEARS THIS WAY
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Study #8 Protocol 3021

Title: Clinical investigation of the efficacy and tolerability of Azelastine eye drops, _____ eye drops and placebo in the therapy of children with seasonal allergic conjunctivitis/rhinoconjunctivitis

Study Design: Placebo-controlled, partial double-blind, multicenter parallel-group study with a 2:1:1 ratio, where patients were randomized to receive AZE, _____ cromoglycate eye drops _____ or placebo over a 28 day treatment period. During each of the 4 study visits (Days 0, 3, 14 and 28), investigators assessed patients' allergic conjunctivitis symptoms (including itching and conjunctival redness) using a 4-point scale (0=none; 1=mild; 2=moderate; 3=severe symptoms). Although the AZE and placebo medication bottles were indistinguishable (and thus blinded), it was not possible to blind the _____ treatment group because of the different bottle size and dosing regimen. Thus the active control treatment arm was not blinded to either the investigators or to the patients.

Study Procedures

Study Procedure Completed	Visit 1 Day 0	Visit 2 Day 3	Visit 3 Day 14	Visit 4 Day 28
Informed consent	•			
History of allergic conjunctivitis	•			
Concomitant disease	•			
Concomitant medication	•	•	•	•
Vital signs	•	•	•	•
RAST test/Prick test or ophthalmic diagnosis	•			
Symptoms assessed (by Investigator)	•	•	•	•
Eligibility criteria	•			
Randomization/1 st application of study medication	•			
Adverse events	•	•	•	•
Study medication dispensed	•		•	
Patient Diary dispensed	•		•	
Patient Diary reviewed		•	•	•
Used study medication collected			•	•
Completed patient diaries collected			•	•
Final Status/termination				•