Investigators:

1. Prof. Dr. med. Boris M. Blochin
Russian State Medical University, Chair of Pediatrics, Policlinic No. 203, Moscow, 17513, Leninskij-Prospekt 113

2. Mrs. Dr. med. Olga N. Larina
63th Municipal Hospital, Allergology Department, Room 626, Moscow, ul. Durova 26, Building 5, 6th Floor

3. Dr. med. Vladimir D. Prokopenko
Institute of Immunology of the Ministry of Health of the Russian Federation Moscow, 115580
Kaschirskoe Chaussee 24, Build. 2

4. Doz. Mrs. Dr. med. Irina Sidorenko
Moscow Medical Academy "I. M. Seyenov", Chair of Clinical Immunology and Allergology, Moscow
ul. Bolschaja Pirogovskaja 2

5. Prof. Dr. med. Igor M. Vorontsov
Chair of Children's Diseases and Propedeutic at the Institute of Pediatrics, St. Petersburg, 194100

6. Dr. med. Jurij N. Petrovskij
International Allergology Centre of Sotschi, Sotschi, 354057
ul. Dagomysskaja 42a

7. Prof. Dr. med. Roman A. Chanferjan
Kuban State Medical Academy, Chair of Allergology and Clinical Immunology Krasnodar, 350640
ul. Sedina 4

8. Mrs. Prof. Dr. med. Lidija Sidorova
1st State Medical Institute of Novosibirsk, Chair of Internal Medicine, Novosibirsk, 630091
Krasnyj Prospekt 52

Centre	AZE	PLA	[redacted]	Σ
1	24	12	12	48
2	16	8	8	32
3	20	10	10	40
4	16	8	8	32
5	12	6	6	24
6	20	10	10	40
7	28	14	14	56
8	24	12	12	48
Σ	160	80	80	320

Demographics:

Parameter		Unit	AZE	PLA	[redacted]
Subjects evaluable		n	160	80	80
Gender	male	n	97	55	59
	female	n	63	25	21
Age	mean	years	9.2	8.8	8.8
	range	years	4-12	4-12	4-12
Race	Caucasian		159	78	80
	Unknown		1	2	0
Weight	mean	kg	32.9	31.8	31.3
	range	kg	17-58	15-60	15-58
Main Eye Symptoms	mean	points	6.9	6.9	7.0

Premature Terminations	AZE	[redacted]	VEH
Lack of efficacy	5	6	26
Non-compliance	6	7	4
Exclusion Criteria	1	2	3
Other	0	1	4

Subj ID	Group	Reason for premature termination	Treatment Duration
1/34	PLA	Inefficacy	9 days
1/36	[redacted]	efficacy	11 days
1/39	PLA	Inefficacy	6 days
1/48	PLA	Inefficacy	13 days
2/49	PLA	Inefficacy	4 days
2/50	PLA	occurrence of exclusion criteria (Dimedrol, Diazolin), non-compliance	4 days
2/54	AZE	Inefficacy	4 days
2/58	[redacted]	non-compliance	11 days
2/60	PLA	Inefficacy	4 days
2/61	[redacted]	Inefficacy	4 days
2/64	PLA	Inefficacy	4 days
2/66	PLA	Inefficacy	4 days
2/72	PLA	Inefficacy	4 days
2/306	PLA	Inefficacy	3 days
2/312	PLA	Inefficacy	7 days
3/75	AZE	non-compliance	15 days
3/76	AZE	non-compliance	14 days
3/79	[redacted]	non-compliance	14 days
3/81	PLA	non-compliance	14 days
3/82	AZE	non-compliance	14 days
3/83	[redacted]	non-compliance	14 days
3/84	[redacted]	non-compliance	14 days
3/86	AZE	non-compliance	15 days
3/90	[redacted]	non-compliance	1 day
3/102	AZE	non-compliance	15 days
3/105	[redacted]	non-compliance	14 days
4/113	[redacted]	other (familiar reasons)	6 days
4/118	[redacted]	Inefficacy	6 days
4/120	AZE	Inefficacy	6 days
4/122	[redacted]	inefficacy, occ. of exclusion criteria (Claritin, Sofradex)	5 days
4/130	AZE	non-compliance	4 days
4/313	PLA	Inefficacy	7 days
5/140	PLA	occ. of exclusion criteria (Tavegil)	9 days
5/143	PLA	Inefficacy	4 days
5/151	PLA	Inefficacy	4 days
5/157	PLA	occ. of exclusion criteria (Paralergin)	14 days
5/159	PLA	Inefficacy	4 days
6/161	PLA	Inefficacy	4 days
6/165	PLA	Inefficacy	7 days
6/171	AZE	Inefficacy	14 days
6/187	AZE	inefficacy, occ. of exclusion criteria (Suprastin)	15 days
7/206	[redacted]	non-compliance	14 days
7/207	PLA	Inefficacy	7 days
7/208	PLA	Inefficacy	3 days
7/214	PLA	Inefficacy	3 days
7/215	PLA	Inefficacy	16 days
7/219	PLA	Inefficacy	3 days
7/230	PLA	Inefficacy	4 days
7/232	PLA	Inefficacy	14 days
7/233	PLA	Inefficacy	14 days
7/234	[redacted]	Inefficacy	3 days
7/238	PLA	Inefficacy	3 days
7/242	AZE	Inefficacy	4 days
7/246	PLA	Inefficacy	14 days
7/252	[redacted]	Inefficacy	12 days
8/258	[redacted]	occurrence of exclusion criteria (Tavegil)	1 day

Average Number of Daily Applications by Treatment

Days	AZE			PLA			[redacted]		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
1-3	159	2.5	0.7	80	2.7	0.7	79	3.7	0.5
4-14	159	2.5	0.7	71	2.6	0.9	77	3.8	0.5
15-28	151	2.2	0.6	51	2.6	0.8	65	3.6	0.7

Per Protocol Results:

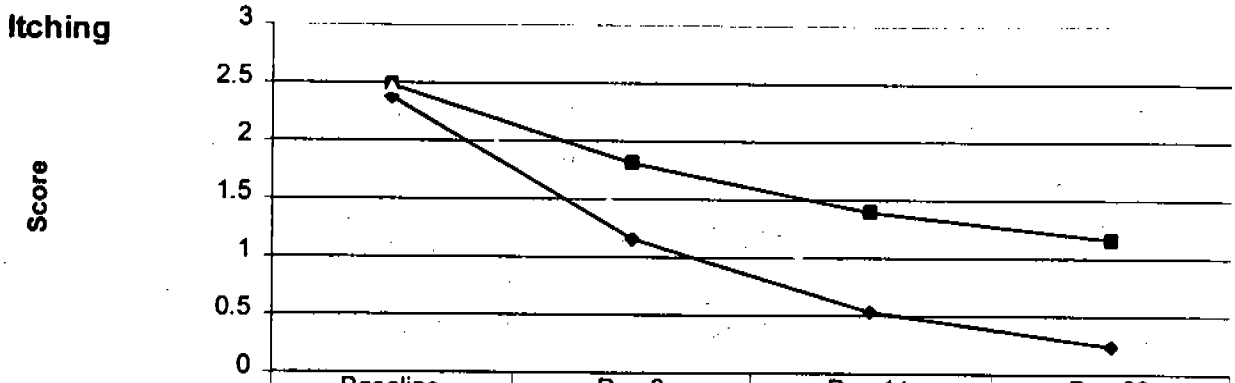
Symptoms of allergic conjunctivitis / rhinoconjunctivitis were rated by the investigators using a 4-point rating scale for severity (0 = none, 1 = mild, 2 = moderate, 3 = severe) on day 0, day 3, day 14 and day 28. The following symptoms were evaluated and summed up in the 2 sum scores:

- Main Eye Score (MES): itching of the eyes, conjunctival redness, flow of tears
- Total Eye Score (TES): itching of the eyes, conjunctival redness, flow of tears, soreness (burning) of the eyes, foreign-body sensation, photophobia, swollen eyelids, discharge / eyelids sticking together

The confirmatory hypotheses testing for the primary objective of this study was based on the MES.

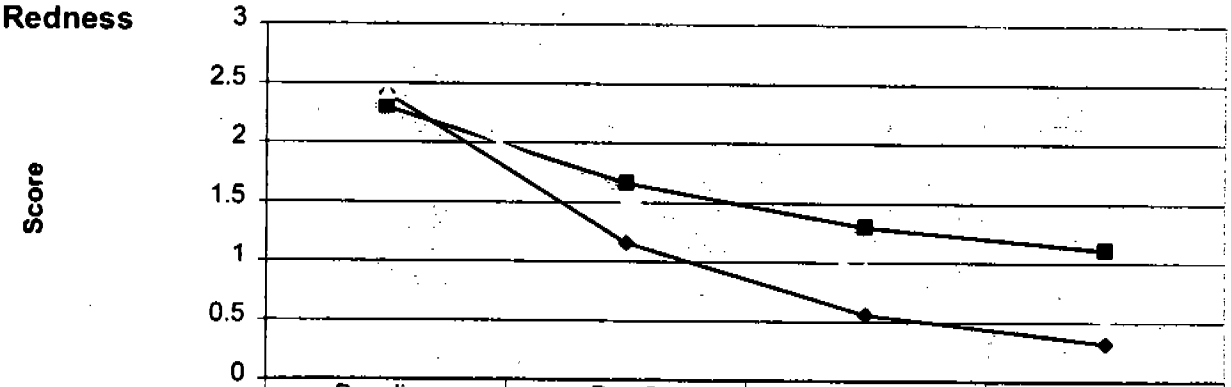
		Therapy Responders on Day 3		
Per-Protocol Analysis		**AZE**	**PLA**	[redacted]
Evaluable	n	160	80	79
Responders	n	128	27	41
	%	*80*	*34*	*52*
P-value vs. placebo	p	**< 0.01**		
		Therapy Responders on Day 14		
Per-Protocol Analysis		**AZE**	**PLA**	[redacted]
Evaluable	n	158	77	76
Responders	n	148	39	63
	%	*94*	*51*	*83*
P-value vs. placebo	p	< 0.01		
		Therapy Responders on Day 28		
Per-Protocol Analysis		**AZE**	**PLA**	[redacted]
Evaluable	n	149	76	68
Responders	n	142	47	61
	%	*95*	*62*	*90*
P-value vs. placebo	p	< 0.01		

	Results of the Main Eye Score								
	AZE			**PLA**			[redacted]		
	n	**Abs**	**chg**	**n**	**abs**	**chg**	**n**	**abs**	**chg**
Day 0	160	6.9	-	80	6.9	-	79	7.0	-
Day 3	160	3.0	-3.8	80	5.0	-1.9	79	4.0	-3.0
Day 14	160	1.4	-5.5	80	3.9	-3.0	79	2.5	-4.5
Day 28	160	0.7	-6.2	80	3.2	-3.6	79	1.5	-5.5
p-value	$p < 0.01$								
	Results of the Total Eye Score [redacted]								
	AZE			**PLA**			[redacted]		
	n	**abs**	**chg**	**n**	**abs**	**chg**	**n**	**abs**	**chg**
Day 0	160	12.6	-	80	12.7	-	79	12.8	-
Day 3	160	5.4	-7.3	80	9.0	-3.7	79	6.9	-5.8
Day 14	160	2.5	-10.1	80	7.4	-5.3	79	4.3	-8.5
Day 28	160	1.3	-11.3	80	6.2	-6.4	79	2.6	-10.1
p-value	$p < 0.01$								



	Baseline	Day 3	Day 14	Day 28
Azelastine	2.38	1.15	0.53	0.24
Vehicle	2.48	1.81	1.39	1.16
	2.46	1.39	0.82	0.58

Reviewer's Comments: *The differences are statistically significant on Days 3, 14 and 28.*



	Baseline	Day 3	Day 14	Day 28
Azelastine	2.41	1.16	0.56	0.32
Vehicle	2.3	1.66	1.3	1.11
	2.42	1.52	0.95	0.51

Reviewer's Comments: *The differences are statistically significant on Days 3, 14 and 28.*

Symptom Severity Means by Treatment and Assessment Day

	Baseline	Day 3	Day 14	Day 28
Itching				
Placebo (n=80)	2.48	1.81	1.39	1.16
AZE (n=160)	2.38	1.15	0.53	0.24
[redacted] (n=79)	2.46	1.39	0.82	0.58
p-value PLA v. AZE[a]	0.159	**<0.001**	**<0.001**	**<0.001**
p-value PLA v. [redacted][a]	0.809	**0.002**	**<0.001**	**<0.001**
Redness				
Placebo (n=80)	2.30	1.66	1.30	1.11
AZE (n=160)	2.41	1.16	0.56	0.32
[redacted] (n=79)	2.42	1.52	0.95	0.51
p-value PLA v. AZE[a]	0.128	**<0.001**	**<0.001**	**<0.001**
p-value PLA v. [redacted][a]	0.163	0.228	**0.010**	**<0.001**

[a] P-value from an independent samples t-test.

Symptom Severity Means by Treatment and Assessment Day

	Days 1-3	Days 4-14	Days 15-28
Itching			
Placebo	2.05 (n=80)	1.49 (n=71)	0.56 (n=51)
AZE	1.59 (n=159)	0.81 (n=159)	0.30 (n=151)
[redacted]	1.83 (n=79)	1.05 (n=77)	0.46 (n=65)
p-value PLA v. AZE[a]	**<0.001**	**<0.001**	**0.001**
p-value PLA v. [redacted][a]	**0.027**	**<0.001**	0.301
Redness			
Placebo	1.91 (n=80)	1.44 (n=71)	0.65 (n=51)
AZE	1.65 (n=159)	0.82 (n=159)	0.39 (n=151)
[redacted]	1.83 (n=79)	1.08 (n=77)	0.40 (n=65)
p-value PLA v. AZE[a]	**0.003**	**<0.001**	**0.016**
p-value PLA v. [redacted][a]	0.386	**0.001**	**0.029**

[a] P-value from an independent samples t-test.

APPEARS THIS WAY
ON ORIGINAL

Summary of all Adverse Events by Treatment with Incidence Rate >2% for Azelastine

Randomized (N=320)	AZE (N=160)	PLA (N=80)	[redacted] (N=80)
All AEs[a]	53 (33.1)	15 (18.8)	23 (28.8)
WHO Preferred term			
Application Site Reaction	23 (14.4)	3 (3.8)	7 (8.8)
Coughing	22 (13.8)	8 (10.0)	10 (12.5)
Headache	6 (3.8)	1 (1.3)	2 (2.5)
Dyspnea	4 (2.5)	3 (3.8)	5 (6.3)
Pruritus	4 (2.5)	2 (2.5)	0 (0.0)

[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.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Study #9 Protocol 3034

Title: Assessment of the efficacy and safety of Azelastine eye drops in the treatment of 4 to 12 year old children suffering from allergic conjunctivitis or rhinoconjunctivitis

Design: Randomized, multicenter, placebo and active-controlled, parallel-group, partial double-blind, environmental study to evaluate the efficacy and safety of azelastine eye drops in pediatric patients aged 4-12 years with allergic conjunctivitis. Treatment response was defined as an improvement of 3 or greater on a scale of 0 (no symptoms) to 9 (severe symptoms), for the combined score of itching, redness and tearing in patients who had a baseline score of 6. Although the AZE and placebo medication bottles were indistinguishable (and thus blinded), it was not possible to blind the LEV bottles because they were distinguishable (different bottle size), and 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
Informed consent	•		
Medical history, including allergic Conjunctivitis	•		
Concomitant disease	•		
Concomitant medication	•	•	•
Vital signs	•	•	•
Symptoms assessed (by Investigator)	•	•	•
Eligibility criteria	•		
Randomization/1st application of study medication	•		
Adverse events	•	•	•
Study medication dispensed	•	•	
Patient Diary dispensed	•	•	
Beconase® dispensed[a]	•		
Patient Diary reviewed		•	•
Used study medication collected		•	•
Completed patient diaries collected		•	•
Final Status/termination			•

1. Dr. Sabbah
Coordinating Investigator
CHU d'Angers
F-49033 Angers Cedex 01

2. Dr. Amsellem-Nemni
14, Bd Emile Genevois
F-93230 Romainville

3. Dr. Anton
9, rue Kléber
F-44000 Nantes

5. Dr. Basset Stheme
59, Av. Gambetta
F-26000 Valence

6. Dr. Bertrac
6, rue des 11 Martyrs
F-29200 Brest

7. Dr. Billard
59, rue du Maconnais
F-73000 Chambery

8. Dr. Billet
9, Av. P. Semard
F-01100 Bourg en Bresse

9. Dr. Boidin
1, rue Platière
F-69001 Lyon

18. Dr. Dumoulin
6, rue des 11 Martyrs
F-29000 Brest

21. Dr. Grosclaude
226, Bd Ch. de Gaulle
F-07500 Guilherand Granges

22. Dr. Guerrier
53, rue Chatoun
F-69003 Lyon

24. Dr. Heurte
2, rue Bousaingault
F-29200 Brest

25. Dr. Houssel
73, Cours de Verdun
F-01100 Oyonnax

26. Dr. Jarsaillon
62, Av Victor Hugo
F-69160 Tassin-La-Demi-Lune

27. Dr. Lebeaupin
15, rue Louise Michel
F-44400 Reze

30. Dr. Noiret
21, quai Arloin
F-69003 Lyon

31. Dr. Partouche
31, Cours Vitton
F-69006 Lyon

33. Dr. Prince
8, Bd Gambetta
F-30100 Ales

34. Dr. Robert
63bis, rue de la République
F-69150 Decines Charpieu

36. Dr. Saint-Martin
Rue Henri Dunant
F-91140 Villebon Sur Yvette

37. Dr. Sanquer
34, rue de Douamenez
F-29000 Quimper

38. Dr. Taburet
19, rue du Château
F-29000 Brest

39. Dr. Taulelle
221, rue Claude Nicolas Ledoux
F-30900 Nimes

40. Pr. Verin
89, rue des Sablières
F-33077 Bordeaux Cedex

41. Dr. Wessel
3, rue de Gorges
F-44000 Nantes

Site	AZE	VEH	LEV
1	2	1	1
2	1	0	0
3	3	2	2
5	2	2	3
6	1	0	1
7	0	0	1
8	4	3	2
9	4	2	2
18	0	1	1
21	2	1	1
22	1	1	1
24	2	1	1
25	6	3	2
26	1	0	0
27	5	4	3
30	0	1	1
31	2	0	1
33	0	1	0
34	2	1	1
36	1	1	1
37	2	1	1
38	1	0	1
39	0	0	1
40	6	3	3
41	3	1	1

Premature Terminations	**AZE**	**LEV**	**VEH**
Lack of efficacy	3	3	5
Poor tolerability	1	0	1
Intercurrent illness	2	0	1
Non-compliance	2	0	0
Other	0	0	1
Adverse experience	4	0	2

The reasons for premature discontinuation as reported by the investigators are summarised in the following table:

Subj ID	Treat. Duration	Reason for Discontinuation	Investigator's Comments
1/3	11 days	non-compliance	Premature end of trial because climatic circumstances (rain) were not favourable to treatment (absence of symptoms)
3/10	4 days	non-compliance	
5/54	12 days	insufficient efficacy	1 day earlier, the 10th instead of 11/06/96, the study was finished regularly, assessment is consequently available
22/83	12 days	bad tolerability	The drug was not efficacious but induced an increase of ocular burning during instillation
25/96	3 days	intercurrent disease	Other: serious adverse event (hospitalisation for pollen asthma)
27/101	4 days	insufficient efficacy	Intake of Clarityne the 04/06/96 (worsening of conjunctivitis)
27/103	5 days	intercurrent disease	The treatment has been stopped because conjunctival infection and treatment by Tobrex eye drops prescribed by an ophthalmologist
37/143	12 days	insufficient efficacy	Tingling after each application of eye drops, intake of Primalan despite forbidding (self-medication)
3/9	4 days	insufficient efficacy	
9/35	11 days	insufficient efficacy	
22/81	2 days	other	Withdrawal of consent by father
25/169	4 days	insufficient efficacy	
27/104	9 days	intercurrent disease	Asthma attack with necessity of forbidden treatment intake, eye drops has been stopped the 16/06/96, he could not come back earlier
30/114	3 days	insufficient efficacy	Refusal to continue the study because the eye drops were not efficacious
33/125	3 days	bad tolerability	The patient has been met again and assessed at D4 instead of D2; he stopped the treatment for poor tolerability
36/138	5 days	insufficient efficacy	Necessity to prescribe Clarityne
6/21	6 days	insufficient efficacy	
36/137	6 days	insufficient efficacy	Treatment stopped the 11/06/96 for inefficacy and re-intake of corticoid treatment
38/145	7 days	insufficient efficacy	Concomitant asthma occurrence (no influence on study medication)

A summary of demographic and baseline characteristics is provided in the following table:

Parameter		Unit	AZE	PLA	LEV
Patients randomised		n	51	30	32
Sex:	male	n	32	22	21
	female	n	19	8	11
Age:	mean ± SD	years	8.6 ± 2.3	8.3 ± 2.4	8.2 ± 2.5
	range	years	4-12	4-12	4-12
Weight (all available data):	Patients	n	43	27	29
	mean ± SD	kg	31.1 ± 9.2	28.8 ± 7.7	27.7 ± 8.8
	range				
Main Eye Symptoms (PP)	mean ± SD	points	7.3 ± 1.2	6.9 ± 1.0	7.2 ± 1.0

Average Number of Daily Applications by Treatment

Days	AZE			PLA			LEV		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
1-3	49	2.0	0.6	29	2.0	0.4	32	2.1	0.6
4-14	49	2.1	0.5	25	2.1	0.5	32	2.2	0.7

Per Protocol Results:

Symptoms of allergic conjunctivitis/rhinoconjunctivitis were classified by the investigators using a 4-point rating scale for severity (0 = no, 1 = mild, 2 = moderate, 3 = severe symptoms) on day 0, day 3 and day 14. The following symptoms were evaluated and summed up in the different sum scores:

- Main Eye Score (MES): itching of the eyes, conjunctival redness, flow of tears
- Total Eye Score (TES): itching of the eyes, conjunctival redness, flow of tears, soreness (burning) of the eyes, foreign-body sensation, photophobia, swollen eyelids, discharge/eyelids sticking together

The hypothesis testing for the primary objective of this study was based on the MES.

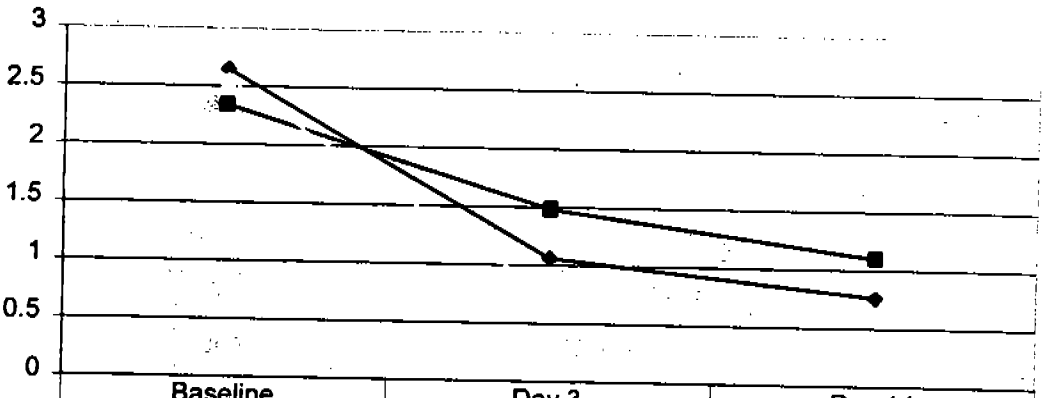
		Therapy Responders on Day 3		
Per-protocol Analysis		**AZE**	**PLA**	**LEV**
Evaluable	n	47	28	32
Responders	n	35	11	27
	%	*74*	*39*	*84*
p-value vs. placebo[a]	p	**< 0.01[b]**		
Intention-to-treat Analysis				
Evaluable	n	49	29	32
Responders	n	37	11	27
	%	*76*	*38*	*84*
p-value vs. placebo[a]	p	< 0.01[b]		

		Therapy Responders on Day 14		
Per-protocol Analysis		**AZE**	**PLA**	**LEV**
Evaluable	n	43	26	30
Responders	n	37	17	27
	%	86	65	90
p-value vs. placebo[a]	p	0.07[b]		

a - Fisher's Exact Test, 2-sided vs. placebo
b - analysed in an explorative sense

	Main Eye Score: Number of Observations and Means (completed cases, last value carried forward)								
	AZE			**PLA**			**LEV**		
	n	**abs**	**chg**	**n**	**abs**	**chg**	**n**	**abs**	**chg**
Day 0	47	7.3	-	28	6.9	-	32	7.2	-
Day 3	47	3.0	-4.3	28	4.2	-2.6	32	2.1	-5.1
Day 14	47	2.0	-5.4	28	3.4	-3.4	32	1.6	-5.6
p-value for group effect	$p < 0.01$								
	Total Eye Score: Number of Observations and Means (completed cases, last value carried forward)								
	AZE			**PLA**			**LEV**		
	n	**abs**	**chg**	**n**	**abs**	**chg**	**n**	**abs**	**chg**
Day 0	47	13.1	-	28	12.1	-	32	13.1	-
Day 3	47	5.4	-7.7	28	7.4	-4.7	32	3.9	-9.1
Day 14	47	3.5	-9.6	28	6.2	-5.8	32	2.8	-10.2
p-value for group effect	$p < 0.01$								

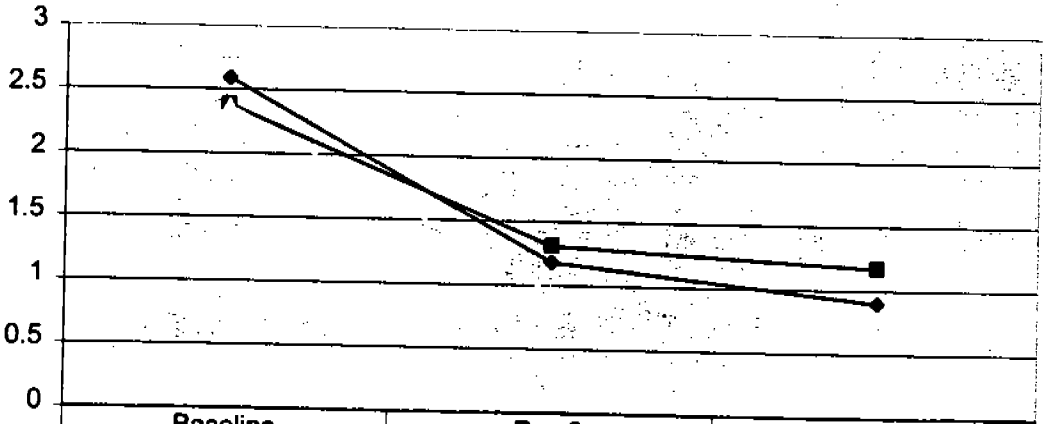
Itching



	Baseline	Day 3	Day 14
Azelastine	2.65	1.06	0.76
Vehicle	2.34	1.48	1.1
Levocabastine	2.56	0.75	0.59

Reviewer's Comments: *The differences between Azelastine and Vehicle are statistically significant at baseline only. The differences between Levocabastine and Vehicle are statistically significant at both day 3 and 14.*

Redness



	Baseline	Day 3	Day 14
Azelastine	2.59	1.18	0.9
Vehicle	2.38	1.31	1.17
Levocabastine	2.38	0.94	0.63

Reviewer's Comments: *Only the difference between Levocabastine and Vehicle is statistically significant and only at Day 14.*

Symptom Severity Means

	Day 0	Day 3	Day 14
Itching			
Placebo (n=29)	2.34	1.48	1.10
AZE (n=49)	2.65	1.06	0.76
LEV (n=32)	2.56	0.75	0.59
p-value PLA v. AZE[a]	**0.012**	0.072	0.103
p-value PLA v. LEV[a]	0.091	**0.003**	**0.026**
Redness			
Placebo (n=29)	2.38	1.31	1.17
AZE (n=49)	2.59	1.18	0.90
LEV (n=32)	2.38	0.94	0.63
p-value PLA v. AZE[a]	0.071	0.574	0.265
p-value PLA v. LEV[a]	0.976	0.127	**0.035**

(a) P-values on Day 0 from an independent samples t-test.

Symptom Severity Means by Treatment and Assessment Day

	Days 1-3	Days 4-14
Itching		
Placebo	1.84 (n=29)	1.24 (n=25)
AZE	1.62 (n=49)	1.00 (n=49)
LEV	1.42 (n=32)	0.88 (n=32)
p-value PLA v. AZE[a]	0.213	0.189
p-value PLA v. LEV[a]	**0.044**	0.096
Redness		
Placebo	1.74 (n=29)	1.21 (n=25)
AZE	1.59 (n=49)	1.13 (n=49)
LEV	1.45 (n=32)	1.11 (n=32)
p-value PLA v. AZE[a]	0.440	0.716
p-value PLA v. LEV[a]	0.179	0.660

[a] P-value from an independent samples t-test.

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

Randomized (N=113)	AZE (N=51)	PLA (N=30)	LEV (N=32)
All AEs[a]	30 (58.8)	13 (43.3)	14 (43.8)
WHO Preferred term			
Application Site Reaction	17 (33.3)	5 (16.7)	11 (34.4)
Coughing	5 (9.8)	1 (3.3)	3 (9.4)
Asthma	3 (5.9)	2 (6.7)	1 (3.1)
Pharyngitis	3 (5.9)	1 (3.3)	0 (0.0)
Headache	2 (3.9)	2 (6.7)	1 (3.1)
Heat Stroke	2 (3.9)	0 (0.0)	0 (0.0)
Taste Perversion	2 (3.9)	0 (0.0)	0 (0.0)

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

There were four adverse events of note in this study. Mild eye pain was reported by two patients (14 – site 3, AZE; 13 – site 3, placebo) after the initial administration of study drug. In both cases the event was considered to be related to study drug and persisted for minutes (14) or for days (13). Treatment was initiated for patient 13. This patient also reported photophobia (conjunctivitis) at this visit that persisted for minutes, was severe, and was related to study drug. No therapy was administered for this event.

Patient 138 – site 36 in the placebo group reported conjunctivitis (exacerbation of flow of tears) during the study that persisted for minutes, was moderate in severity and was of possible association with study drug. No therapy was administered.

An eye infection was reported by patient 103 – site 27 in the AZE group. This patient was prematurely discontinued from the study due to this event.

Conclusions Regarding Data

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

Study #10 Protocol 3062

Title: Azelastine Eye Drops in the Treatment of Children Suffering from Allergic Conjunctivitis or Rhinoconjunctivitis.

Design: The trial was designed as a randomized, placebo- and positive-controlled, double-blind versus placebo, open versus [redacted] (reference drug), multicentre trial with 3 parallel groups in children age 4 through 12. The treatment groups were:

Group	Dosing
AZE	1 drop of approx. 0.03 ml per eye twice daily; if complaints were severe this dose could be increased to 1 drop per eye 3 to 4 times daily
PLA	
[redacted]	1 drop of approx. 0.03 ml per eye four times daily

The visit schedule is outlined in the following table:

Item	Day 0	Day 3	Day 14
Written informed consent (parents)	x		
In-/exclusion criteria	x		
Demographic data	x		
Medical history, pre-treatments	x		
Concomitant diseases	x		
Prior medication	x		
Concomitant medication		x	x
Conjunctivitis/rhinoconjunctivitis symptoms, assessed by the investigators	x	x	x
Adverse events	(x)	x	x
Study medication provided	x	x	
Study medication returned		x	x
Patient's diaries provided	x	x	
Patient's diaries collected		x	x
Conjunctivitis symptoms from patients' diaries		d a i l y	
Global assessments of efficacy and tolerability			x

Site	Investigator	Country	Azelastine	Vehicle	Cromolyn
1	**Prof. Dr. Th. Zimmermann,** University Children's Hospital, Erlangen-Nürnberg, Loschgestraße 15, D-91054 Erlangen	Germany	0	0	0
7	Dr. R. Wiltfang, Ophthalmologist, Am Rathausplatz 2, D-85748 Garching	Germany		1	1
9	Dr. A. Zarth, Ophthalmologist, Bahnhofstraße 3, D-82211 Herrsching	Germany	5	2	3
11	Dr. J. Hungerland, Ophthalmologist, Sulinger Str. 11a, D-27211 Bassum,	Germany	3	1	1
13	Dr. F. Hurrelmann, General Practitioner, Kumpfmühlerstraße 64	Germany	1	0	1
14	Mr. L. Volgmann, Physician for internal medicine, pulmonal and bronchial medicine, Tulpenstraße 1, 30167 Hannover	Germany	2	0	0
15	Dr. A. Gandjour, Pediatrician, Wegsfeld 42, 30455 Hannover	Germany	2	0	0
16	**Docteur A. SABBAH*,** Laboratoire Fonctionnelle, d'Allergologie, Centre Hospitalier Universitaire, 49033 ANGERS CEDEX 01	France	3	2	2
17	Docteur M. ANTON, 11, rue Bertrand Geslin, 44000 NANTES	France	4	2	2
18	Docteur I. MOLLE, 15, rue Louise Michel, 44400 REZE	France	3	1	2
19	Docteur F. WESSEL, 3, rue de Gorges, 44000 NANTES	France	4	2	2
20	Docteur J.M. HOUSSEL, 73, Cours de Verdun, 01100 OYONNAX	France	4	2	2

21	Docteur P. COUTURIER, Immeuble « Le Victorien », 19, Av. V. Hugo, 26000 VALENCE	France	4	2	3
22	Docteur M. GROSCLAUDE, Centre Claude Bernard, 226, Boulevard Charles de Gaulle, 07500 GUILHERAND GRANGES	France	0	0	1
23	Docteur C. BOIDIN, 1, rue la Platière, 69001 LYON	France	3	2	2
24	Docteur J. ROBERT, 63 bis, rue de la République, 69150 DECINES CHARPIEU	France	4	2	2
25	Docteur Ph. PARTOUCHE, 31, Cours Vitton, 69006 LYON	France	0	1	1
26	Docteur E. BILLARD, 59, rue du Maconnais, 73000 CHAMBERY	France	6	3	3
27	Docteur RIOTTE-FLANDROIS, 6, rue Garillaud, 38550 LE PEAGE DU ROUSSILLON	France	4	1	1
28	Dr. F. Ansari, Pediatrician, Bahnhofstraße 9a, D-30890 Barsinghausen	Germany	1	0	0
29	Dr. F. Scheuplein, General Practicioner, Hammerweg 7, D-95659 Arzberg	Germany	2	2	2
30	Dr. G. Mahla, General Practicioner, Kirchenweg 7, D-82340 Feldafing	Germany	2	0	0
31	**Dr. D. J. Antonio Ojeda Casas***, Departm. of Pediatric Allergology, Hospital Universitario La Paz, Paseo de la Castellana n° 261, 28046 Madrid	Spain	2	1	1
34	Dr. D. Jesús Garde Garde, Departm. of Pediatric Allergology, Hospital General Universitario de Elche, Partida Huertos y Molinos s/n, 03203 Elche (Alicante)	Spain	6	3	3
35	Dra. Dª Mª Teresa Laso Borrego, Allergy Department, Hospital Infantil Niño Jesús Avda. Menéndez Pelayo 65, 28009 Madrid	Spain	1	0	0
38	Dr. D. E. Martí Guadaño, Departm. of Pediatric Allergology, Hospital Germans Trias y Pujol Carretera de Canyet s/n 08916 Badalona (Barcelona)	Spain	0	1	1
39	Dr. D. J. Ángel Porto Arceo, Departm. of Pediatric Allergology, Hospital General de Galicia, C / Galeras s/n 17705 Santiago de Compostela	Spain	4	2	2
41	**Dr. A. G. Wade***, Community Pharmacology Services, 11 Hume Street, Clydebank, Glasgow G81 1XL	Great Britain	2	0	0
42	Dr. Rafi Baghdjian, Chorley Health Centre, Collison Avenue, Chorley, Lancashire	Great Britain	1	1	0
44	Dr. N. Pinheiro, Acreswood Surgery, Coppull, Nr. Chorley, Lancashire PR7 5EJ	Great Britain	0	0	1
45	Dr. J. Zachariah, Central Milton Keynes Medical Centre, 1 North 6th Street, Central Milton Keynes MK9 2NR	Great Britain	2	1	1
46	Dr. D. G. Moran, The Coach House, 16 Chapman Street, Sheffield S9 1NG	Great Britain	2	1	1
48	Dr. P. J. Fell, Oxford Health Management Ltd., The Lodge, Acland Hospital, 25 Banbury Road, Oxford OX2 6PD	Great Britain	2	1	0
50	Dr. M. J. Rule, 110 Peartree Road, Welwyn Garden City, Herts	Great Britain	1	1	1
51	Dr. M. L. Campbell, Southbank Surgery, 17-19 Southbank Road, Kirkintilloch, Glasgow G66 1NH	Great Britain	3	1	2
52	Dr. A. Smithers, Bennetts Road Surgery, Keresley End, Coventry	Great Britain	4	2	1
53	Dr. T. Gooding, The Atherstone Surgery, 1 Ratcliffe Road, Atherstone, Warwickshire CV9 1EU	Great Britain	1	0	1
54	Dr. F. R. Cranfield, The Surgery, Oak Street Cwmbran, Newport, South Wales NP44 3LT	Great Britain	2	2	1
55	Dr. S. Crosbie, Bellevue Surgery, Courtybella Terrace, Newport, Gwent NP9 2WQ	Great Britain	6	3	2
58	Dr. Mokshad Kansagra, Fishermead Medical Centre, Fishermead Boulevard, Fishermead, Milton Keynes MK6 2LR	Great Britain	2	0	1
59	Dr. Simon Chatfield, The Surgery, Nevells Road, Letchworth, Herts. SG6 4TS	Great Britain	1	0	0
60	Dr. K. K. Garg, Croston Health Centre 30 Brookfield, Croston, Nr Preston, Lancs	Great Britain	2	2	1
66	Dr. Husselbee, Highland Surgery, Southend	Great Britain	2	1	1

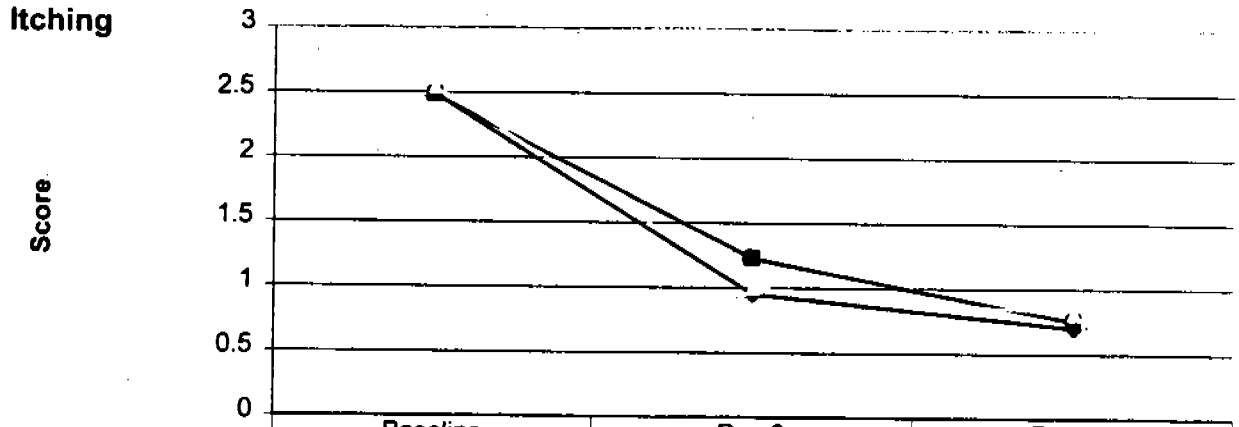
Parameter		Unit	AZE	PLA	[redacted]
All exposed patients (safety)		n	103	49	52
Sex	Male	n	68	33	36
	Female	n	35	16	16
Age	mean ± SD	years	8.5 ± 2.3	9.0 ± 2.1	8.2 ± 2.5
	Range	years	4 - 12	5 - 12	4 - 12
Weight	mean ± SD	kg	32.1 ± 11.7	32.4 ± 9.1	29.6 ± 10.2
	Range	kg	15 - 89	17 - 53	15 - 53
Main eye score	mean ± SD	points	6.9 ± 1.0	6.9 ± 0.9	6.8 ± 0.8
	Range	points	[redacted]		
Race	Caucasian		97	46	46
	Black		1	0	0
	Asian		1	0	0
	Arabian		2	2	4
	Mongolian		0	0	1
	Unknown		2	1	1

	Number of Patients		
	AZE	PLA	[redacted]
All exposed patients (safety)	103	49	52
Discontinued, all	18 (17%)	9 (18%)	9 (17%)
by reason (multiple answers possible)			
Due to lack of efficacy	6 (6%)	5 (10%)	5 (10%)
Due to poor tolerability	2 (2%)	-	1 (2%)
Due to intercurrent disease	2 (2%)	-	1 (2%)
Due to occurrence of exclusion criteria	2 (2%)	1 (2%)	-
Due to non-compliance	2 (2%)	-	-
Any other reasons	5 (5%)	4 (8%)	2 (4%)
Adverse experience	5 (5%)	-	2 (4%)

APPEARS THIS WAY
ON ORIGINAL

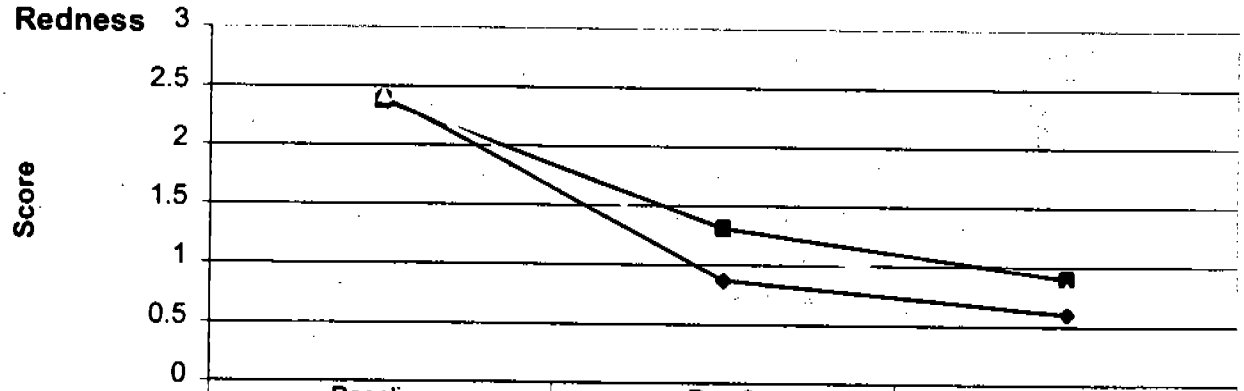
Subj ID	Treat Duration	Reason for Discontinuation	Investigator's Comments
09/162	9 days	Inefficacy	None
26/317	12 days	Inefficacy	Transient improvement then clear aggravation, preferring stop of the study
20/333	4 days	Inefficacy	Exit of the study because of inefficacy
18/339	12 days	Inefficacy	Insufficient improvement at visit 2, but the patient's mother wanted to go on – hoping on some efficacy
27/351	4 days	occurrence of exclusion criteria	Intercurrent disease: Infection, bronchitis and asthma with prescribed antiallergic treatment by the family doctor.
19/356	9 days	intercurrent disease	Stop for rhinitis/cough which require concomitant treatment
19/359	11 days	Other	Very good reaction (48h). Visit 3 on day 10 due to practical reasons.
21/368	1 day	Other	The father refused to continue the study after the first application (phone call on 29.05.97).
24/372	10 days	Other	9 days treatment - error in time schedule
24/373	9 days	Other	Error in the planning of the administration
34/526	11 days	intercurrent disease	Patient withdraw the study medication after 11 days due to the increase of nasal symptoms.
35/532	4 days	non-compliance	Study medication was applied only once a day.
39/565	2 days	Inefficacy	Patient was withdrawn from the study because main eye score had not been reduced at least one point between day 0 and day 3.
34/575	9 days	Other	Due to a mistake in the date of appointment.
54/707	15 days	poor tolerability (taste perversion, application site reaction)	Patient refused to have drops instilled after 19/6/97 due to 1) unpleasant taste 2) stinging of eye drops on instillation
52/753	once	non-compliance, lost for follow-up	Patient failed to return to visit 2, despite several attempts at contact
41/774	9 days	Inefficacy, occurrence of exclusion criteria	Withdrawn due to lack of efficacy on 9.7.97 by G.P. Use of not allowed concomitant medication (Clarityne)
58/798	3 days	poor tolerability (application site reaction, epistaxis)	Withdrawal from study due to adverse events.
16/302	4 days	Inefficacy	Conjunctivitis ++ → stop
17/311	4 days	Inefficacy	Stop of the study because of inefficacy
20/334	4 days	Inefficacy	None
26/364	8 days	Other	Treatment prematurely stopped, the father thought that the treatment has to be stopped as all symptoms were improved.
24/374	10 days	Other	Error in the planning of the administration
34/524	8 days	Inefficacy, occurrence of exclusion criteria	Due to the inefficacy of the study medication, the patient used fusidic acid to treat the eye symptoms (automedication)
42/716	12 days	Other	Visit 3 performed on day 11 because patient going on holiday
52/743	9 days	Inefficacy	None
54/784	1 day	Other	Parents withdrew consent
16/307	6 days	Inefficacy	Did not attend the visit planned on 30.05.97. Ongoing alternative treatment
17/313	11 days	Other	Patient lost the study medication
20/335	11 days	Inefficacy	Has taken a "forbidden" medication (Opticrom) on 8.6.97 at night, continued the next day. Good efficacy of this drug.
18/340	12 days	Intercurrent disease	Unconsciousness due to anaphylaxis to the water during a bath. No specific treatment. Study treatment stopped later.
27/348	12 days	Other	No treatment on 29th and 30th April. Marked improvement of the symptoms (rain). The mother did not think it was useful to continue the treatment, the child was well.
19/360	5 days	Inefficacy	First and second day good, then rhinitis symptoms increased. Patient need antihistamines.
26/376	4 days	Inefficacy	At visit 2 no improvement. The eye drops were given with a rescue prescription. This prescription was used the evening of visit 2, the study medication was not given.
20/385	8 days	Inefficacy	Took some forbidden medication: Clarityne than Levophta because of insufficient efficacy.
51/789	10 days	poor tolerability (application site reaction)	Patient complained at visit 3 that he could not tolerate the eye drops - stinging sensation.

Results



	Baseline	Day 3	Day 14
Azelastine	2.49	0.95	0.7
Vehicle	2.48	1.23	0.75
[redacted]	2.54	1	0.81

Reviewer's Comments: *None of the differences were statistically significant.*



	Baseline	Day 3	Day 14
Azelastine	2.42	0.87	0.6
Vehicle	2.37	1.31	0.9
[redacted]	2.42	1.12	0.81

Reviewer's Comments: *Only the differences on Day 3 were statistically significant.*

	Baseline	Day 3	Day 14
Itching			
Placebo (n=46)	2.48	1.26	0.76
AZE (n=99)	2.49	0.95	0.71
[redacted] (n=50)	2.54	0.98	0.80
p-value PLA v. AZE		0.067	0.735
p-value PLA v. [redacted]		0.124	0.838
Redness			
Placebo (n=46)	2.37	1.30	0.91
AZE (n=99)	2.42	0.88	0.62
[redacted] (n=50)	2.42	1.10	0.80
p-value PLA v. AZE		**0.006**	0.087
p-value PLA v. [redacted]		0.276	0.559

		Therapy Responders on Day 3		
Per-protocol Analysis		**AZE**	**PLA**	[redacted]
Evaluable	n	95	46	49
Responders	n	76	29	34
	%	80%	63%	69%
p-value vs. placebo	p	**p = 0.040**		
Intention-to-treat Analysis				
Evaluable	n	101	48	52
Responders	n	79	30	37
	%	78%	63%	71%
p-value vs. placebo	p	**p = 0.050**		
		Therapy Responders on Day 14		
Per-protocol Analysis		**AZE**	**PLA**	[redacted]
Evaluable	n	80	45	48
Responders	n	68	35	36
	%	85%	78%	75%
p-value vs. placebo	p	**p = 0.335**		

APPEARS THIS WAY
ON ORIGINAL

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

Randomized (N=204)	AZE (N=103)	PLA (N=49)	[redacted] (N=52)
All AEs[a]	62 (60.2)	27 (55.1)	26 (50.0)
WHO Preferred term			
Application Site Reaction	48 (46.6)	12 (24.5)	10 (19.2)
Coughing	9 (8.7)	7 (14.3)	6 (11.5)
Headache	6 (5.8)	4 (8.2)	4 (7.7)
Abdominal Pain	4 (3.9)	1 (2.0)	4 (7.7)
Conjunctivitis	4 (3.9)	2 (4.1)	0 (0.0)
Pharyngitis	4 (3.9)	2 (4.1)	3 (5.8)
Taste Perversion	4 (3.9)	0 (0.0)	0 (0.0)
Asthma	3 (2.9)	1 (2.0)	2 (3.8)

[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.

Study #11 **Protocol 2966**

Title: Protective effect of azelastine eye drops against conjunctival disorders induced by allergen challenge

Study Design: A Phase 2, randomized, single-center, placebo-controlled, crossover study to evaluate the duration of the protective effect and safety of azelastine eye drops in adult patients with asymptomatic allergic conjunctivitis using an allergen challenge model. There were four duration groups that were defined by the time that allergen challenges were to be performed (6, 8, 10, or 12 hours) following application of study medication. The 6 and 10 hour duration groups were originally planned in the protocol. Following an interim analysis, the 8 and 12 hour groups were added by amendment. A total of 32 patients were to be enrolled (8 patients in each duration group). Following confirmation of eligibility at visit 1 (including a positive CPT test), patients were randomized and treated with one dose of study medication (either AZE or placebo) at visits 2 and 3. A conjunctival provocation test (CPT) had to be performed between day -14 and day -7 for the determination of the allergen threshold dose. For inclusion into the study subjects had to have conjunctival redness and itching of the eyes of at least moderate intensity (performed separately for each eye) within 20 minutes after challenging.

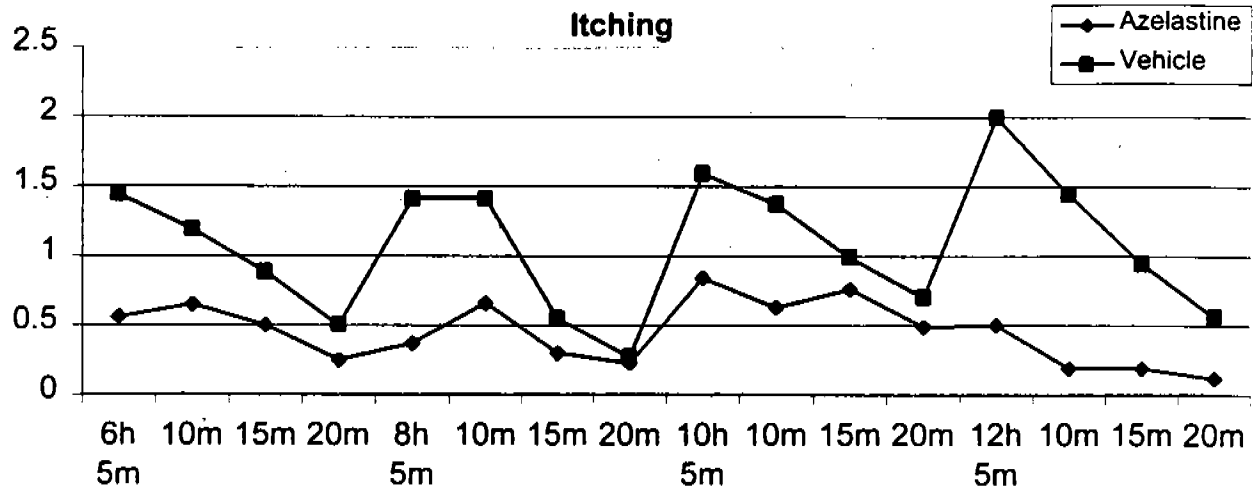
Primary Investigator: Dr. Andrea Leonardi, MD
Regional Centre for the Diagnosis and the
Treatment of Inflammatory Eye Diseases
Institute of Ophthalmology
University of Padova
via Giustiniani 2
I-35100 Padova (Italy)

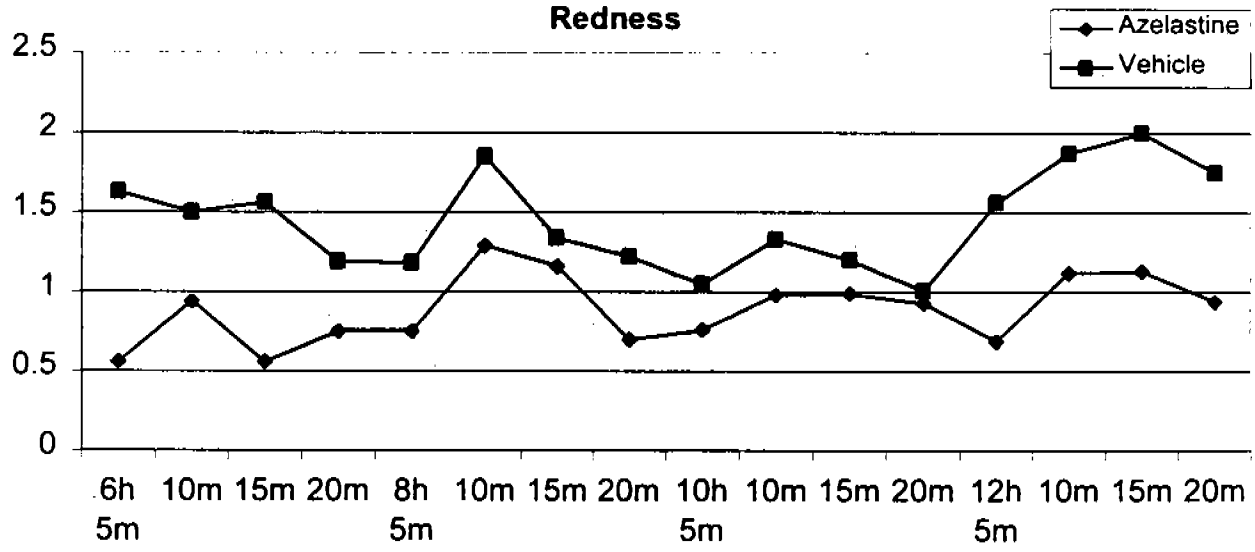
Protocol Deviation, Number (%) of Patients

Randomized (N= 32)	**AZE/PLA**
Eligibility Criteria Violation	4 (12.5)
Incorrect Treatment/dose	2 (6.3)
Study Non-Compliance	3 (9.4)

Multiple protocol deviations per patient were possible

Ages: Mean: 28.6 Range: 18-50
Gender: 18 Males, 14 Females
Race: 30 Caucasian, 1 Arabian, 1 Unknown.





Adverse Experiences	AZE	PLA
taste perversion	16 (50.0%)	1 (3.1%)
application site reaction	4 (12.9%)	2 (6.3%)
conjunctivitis	1 (3.2%)	1 (3.1%)

Conclusions Regarding Data

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

Study #12 **Protocol 2946**

Title of the Study: Investigation of the efficacy and tolerability of two different concentrations of azelastine eye drops in the treatment of patients suffering from seasonal allergic conjunctivitis/ rhinoconjunctivitis

Study Plan:

Randomized, multicenter, placebo-controlled, parallel-group, double-blind, environmental study to evaluate the efficacy and safety of two concentrations of AZE (0.025 and 0.050) in adult patients with allergic conjunctivitis. Approximately 225 patients were to be enrolled (75 patients in each treatment group) at a total of 35 sites with 6-12 patients per site. Following confirmation of eligibility and randomization, patients were treated with study medication for 14 days during which patients were required to make three visits (baseline, day 7 and 14) to their enrolling study site.

The reasons for discontinuation were as follows:

Treatment group	Inefficacy	Poor tolerability	Exclusion criteria	Others	Adverse experience
AZE 0.025	5	-	-	2	0
AZE 0.050	3	2	-	1	3
PLA	6	2	1	3	4

Protocol Deviation, Number (%) of Patients by Category

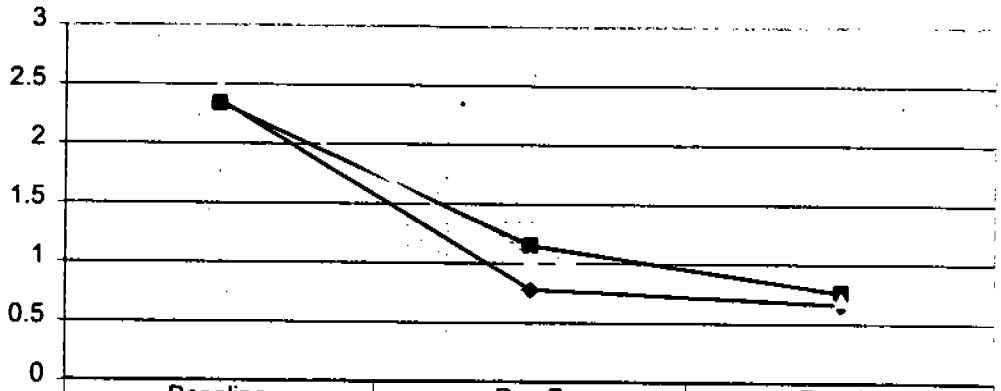
Randomized (N=278)	AZE 0.025 (N=92)	AZE 0.050 (N=92)	PLA (N=94)
Eligibility Criteria Violation	16 (17.4)	23 (25.0)	24 (25.5)
Incorrect Treatment/dose	0 (0.0)	0 (0.0)	0 (0.0)
Study Non-Compliance	0 (0.0)	2 (2.2)	1 (1.1)

Multiple protocol deviations per patient were possible

France	Number of Patients	
Centre 1	11	Prof. M. Perrin-Fayolle, MD (Principal Investigator France) Service de Pneumonologie, Centre Hospitalier Lyon Sud, F-69310 Pierre-Benite
Centre 2	18	Martine Grosclaude, MD, Centre Claude Bernard, 226, Bd General de Gaulle, F-07500 Guilherand-Granges
Centre 3	12	Philippe Partouche, MD, 31, cours Vitton, F-69006 Lyon
Centre 4	12	Michel Colas, MD, 18, avenue Loisy, F-69300 Caluire
Centre 5	12	Christine Boidin, MD, 1, rue Platiere, F-69001 Lyon
Centre 6	4	C. Favier, MD, 122, avenue Philippe Auguste, F-75011 Paris
Centre 7	2	T. Connault, MD, 15, rue Theodore Deck, F-75015 Paris
Centre 8	0	C. Lepetre, MD, 2, Rue de Narbonne, F-75007 Paris
Poland		
Centre 9	12	Prof. Krystyna Obtulowicz, MD (Principal Investigator Poland), Specjalista chorob

		wewnetrznych, alergolog, ul. Jagiellonska 9/5, PL-31-010 Krakow
Centre 10	0	I. Wroblewska, MD, ul. Danulowicza 13, PL-32-020 Wieliczka
Centre 11	12	B. Kacalska, MD, ul. M. Sklodowskiej-Curie 1, PL-33-100 Tarnow
Centre 12	6	T. Kotlinowska, MD, Osiedle Piastow 40, PL-30-211 Krakow - Nowa-Huta
Centre 13	11	J. Jakukowski + C. Palczynski, MD, ul. Bednarska 26 m 53, PL-90-950 Lodz
Centre 14	5	Prof. Janusz Kowalski, MD, Specjalista chorob pluc i fizjologii klinicznej, Klinika Pneumonologii AM, ul. Banacha 1A, PL-02-097 Warszawa
Centre 15	6	Andrzej Kazimierczak, MD, Institut Gruzliey i chorob pluc, ul. Plocka 26, PL-01-138 Warzawa
Centre 16	6	Aleksandra Frenkel, MD, Panska 5/47, PL-00-124 Warzawa
Centre 17	4	Ryszard Malinowski, MD, Jasna 19, PL-00-058 Warzawa
Centre 18	3	Wojciech Skowronski, MD, Specjalista chorob oczu, Klinika Okulistyczna WIML ul. Krasinskiego 54, PL-01-755 Warszawa
Centre 21	0	Adam Rybowski, MD, Specjalista chorob oczu, Sienkiewicza 68, PL-25-501 Kielce
Centre 22	2	Janusz Cieslik, MD, Specjalista chorob oczu, ul. Mala 17, PL-25-379 Kielce
Slovenia		
Centre 23	6	Prof. Ema Mivsek-Music, MD (Principal Investigator Slovenia) Institut za plucne bolezni Golnik, SL-64000 Golnik
Centre 24	6	Aleksandra Skralovnik-Stern, Klinicni center Pulmoloski odd., Zaloska 7, SL-61000 Ljubljana
Centre 25	21	Branko Meznar, MD, Zrdavstveni dom Celje, DPB in TBC, Gregorciceva 5, SL-63000 Celje
Centre 26	13	Mirko Birsa, Sonja Sunko-Korazija, Blanka Kreuh-Kuhta, MD, Oddelek z pljucne bolezni, Slivnisko Pohorje, SL-62000 Pohorje
Centre 27	7	Copi Borut, MD, Zdravstveni dom, Dispanzer za pljucne bolezni, Vojkovo nabrezje, SL-66000 Koper
Centre 28	12	Magda Lusic, MD, Bolnica Trbovlje, Ottroski odd., Rudarska 7, SL-61420 Trbovlje
Italy		
Centre 29	17	Prof. Secchi (Principal Investigator Italy) Clinica Oculistica, Policlinico Universitario, Via Giustiniani 2, I-35100 Padova
Centre 31	5	Bonifazi, MD, Servizio di Allergologia, Ospedale Regionale, Via Torrette, I-60100 Ancona
Centre 32	3	Prof. Brancato, MD, Divisione Oculistica, Ospedale San Raffaele Via Olgettina 60, I-20132 Milano
Centre 33	29	Prof. G. De Vizzi, MD, Divisione di Medicina, Ospedale "Cantu", Piazza Mussi 1, I-20081 Abbiategrasso (MI)
Centre 34	3	P. Zanon, MD, Divisione di Pneumologia, Ospedale di Circolo - U.S.S.L.8 P. le Solaro 3, I-21052 Busto Arsizio (VA)
Centre 35	18	Prof. G. D'Amato, MD, Div. Pneumologia e Allergologia, Ospedale "Cardarelli - U.S.L. 40, Via Cardarelli 9, I-80131 Napoli

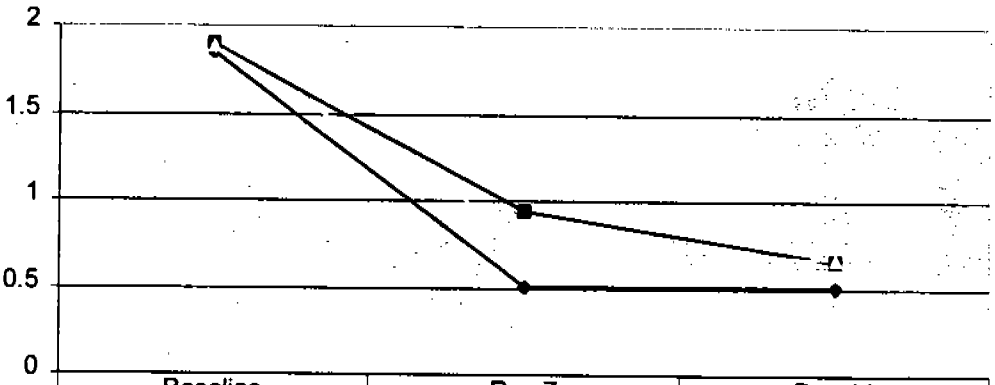
Itching



	Baseline	Day 7	Day 14
Azelastine 0.05%	2.36	0.78	0.66
Vehicle	2.34	1.15	0.76
Azelastine 0.025%	2.48	1.04	0.7

Reviewer's Comments: *Only the differences on Day 7 are statistically significant.*

Redness



	Baseline	Day 7	Day 14
Azelastine 0.05%	1.85	0.51	0.51
Vehicle	1.9	0.94	0.65
Azelastine 0.025%	1.88	0.79	0.67

Reviewer's Comments: *Only differences on Day 7 is statistically significant.*

Symptom Severity Means by Treatment and Assessment Day

	Baseline	Day 7	Day 14
Itching			
Placebo	2.34 (n=88)	1.15 (n=88)	0.76 (n=88)
AZE 0.025	2.48 (n=90)	1.04 (n=90)	0.70 (n=90)
AZE 0.050	2.36 (n=92)	0.78 (n=89)	0.66 (n=90)
p-value PLA v. AZE 0.025[a]	0.064	0.432	0.641
p-value PLA v. AZE 0.050[a]	0.804	**0.005**	0.424
Redness			
Placebo	1.90 (n=88)	0.94 (n=88)	0.65 (n=88)
AZE 0.025	1.88 (n=90)	0.79 (n=90)	0.67 (n=90)
AZE 0.050	1.85 (n=92)	0.51 (n=89)	0.51 (n=90)
p-value PLA v. AZE 0.025[a]	0.868	0.210	0.882
p-value PLA v. AZE 0.050[a]	0.684	**<0.001**	0.248

[a] P-value from an independent samples t-test.

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

Randomized (N=278)	AZE 0.025 (N=92)	AZE 0.050 (N=92)	PLA (N=94)
All AEs	19 (20.7)	38 (41.3)	27 (28.7)
WHO Preferred term			
Application Site Reaction	7 (7.6)	10 (10.9)	6 (6.4)
Taste Perversion	3 (3.3)	7 (7.6)	0 (0.0)
Headache	3 (3.3)	5 (5.4)	7 (7.4)
Conjunctivitis	3 (3.3)	3 (3.3)	6 (6.4)
Coughing	1 (1.1)	3 (3.3)	4 (4.3)
Dyspnea	0 (0.0)	3 (3.3)	2 (2.1)
Asthma	0 (0.0)	3 (3.3)	0 (0.0)
Rhinitis	0 (0.0)	3 (3.3)	0 (0.0)
Pharyngitis	2 (2.2)	2 (2.2)	1 (1.1)

Conclusions Regarding Data

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

Study #13 Protocol 2945

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

Study Design: A Phase III randomized, multicenter, placebo-controlled, parallel-group, double-blind, environmental study to evaluate the efficacy and safety of two concentrations (0.025% and 0.05%) of azelastine eye drops in adult patients with allergic conjunctivitis.

Table A - Study Procedures

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

Demographics:

		AZE 0.025%	AZE 0.05%	Vehicle
Age (years)	Mean	35.4	35.2	35.9
	Range	19-62	18-59	17-64
Gender	Male	22	18	26
	Female	25	34	26
Race	Caucasian	44	47	48
	Asian	0	1	0
	Arabian	0	0	2
	Other/Unknown	3	4	2

Names and addresses of investigators

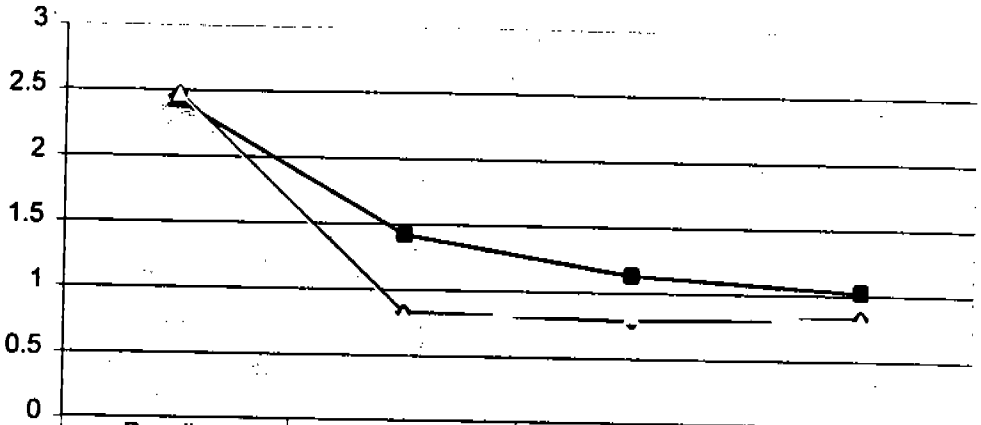
Principal Investigator:	Number of patients	
Centre 4	5	H. Beuing, MD, Schlesische Straße 3, D-35683 Dillenburg
Centre 5	18	P. Bielicky, MD, Luegplatz 3, D-40545 Düsseldorf
Centre 7	6	G. Donhauser, MD, Albert-Roßhaupter-Straße 96, D-81369 München
Centre 8	7	W.A. Eickstädt, MD, Albertusstraße 9-11, D-41061 Mönchengladbach
Centre 9	4	W. Goebels, MD / R. Handzel, MD, Marktstraße 8, D-36037 Fulda
Centre 11	2	S. Heilmann, MD, Biegenstraße 44, D-35037 Marburg
Centre 12	22	M. Hornstein, MD, Rotdornstraße 1, D-40472 Düsseldorf
Centre 14	22	A. Zarth, MD, Am Gangsteig 5, D-85551 Kirchheim-Heimstetten
Centre 15	3	W. Mayerhausen, MD, Freischützstraße 79, 81927 München
Centre 16	5	E. Meyer-Latzke, MD, Berlinerstraße 6, 13505 Berlin
Centre 17	15	H.J. Lüdcke, MD, Großbeerenstraße 301, D-14480 Potsdam
Centre 18	1	B. Schwarz, MD Jugenheimerstraße 48a, D-60528 Frankfurt/Main
Centre 19	6	P. Schmidt, MD, Bahnhofstraße 2a, D-55571 Odernheim/Glan
Centre 20	2	K. Schulz, MD, Bornheimer Landstraße 1, D-60528 Frankfurt/Main
Centre 22	1	T. Weber, MD, Therese-Giehse-Allee 70, D-81739 München
Centre 23	2	L. Weigl, MD, Ludwig-Thoma-Straße 39, D-81245 München
Centre 25	24	M. Westhoff, MD, Rathausplatz 2, D-85742 Garching
Centre 26	6	K.G. Meyer, MD, Schönhauser Allee 71, D-10437 Berlin

Premature Terminations:	**AZE 0.025%**	**AZE 0.05%**	**Vehicle**
Lack of efficacy	1	1	3
Poor tolerability	0	0	1
Intercurrent illness	3	0	0
Non-compliance	0	1	1
Exclusion Criteria	2	0	0
Other	2	3	1
Adverse experiences	3	0	2

Protocol Deviation, Number (%) of Patients by Category

Randomized (N=151)	AZE 0.025 (N=47)	AZE 0.050 (N=52)	PLA (N=52)
Eligibility Criteria Violation	6 (12.8)	5 (9.6)	9 (17.3)
Incorrect Treatment/dose	0 (0.0)	0 (0.0)	0 (0.0)
Study Non-Compliance	5 (10.6)	7 (13.5)	9 (17.3)

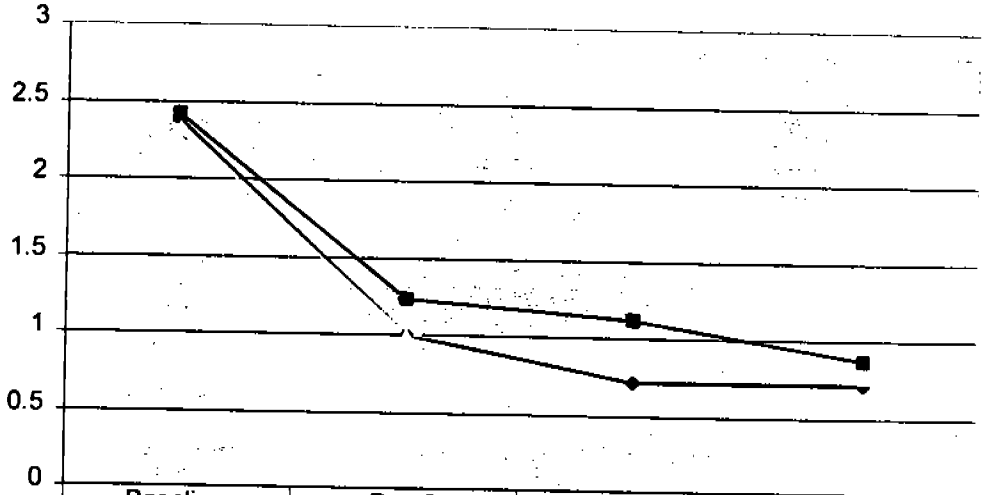
Itching



	Baseline	Day 3	Day 7	Day 14
Azelastine 0.05%	2.48	0.83	0.79	0.83
Vehicle	2.42	1.42	1.13	1.02
Azelastine 0.025%	2.47	0.8	0.83	0.81

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

Redness



	Baseline	Day 3	Day 7	Day 14
Azelastine 0.05%	2.38	1	0.71	0.71
Vehicle	2.42	1.23	1.12	0.87
Azelastine 0.025%	2.32	1	0.89	0.77

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

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

Randomized (N=151)	AZE 0.025 (N=47)	AZE 0.050 (N=52)	PLA (N=52)
All AEs	20 (42.6)	35 (67.3)	21 (40.4)
WHO Preferred term			
Application Site Reaction	10 (21.3)	20 (38.5)	6 (11.5)
Headache	5 (10.6)	12 (23.1)	7 (13.5)
Taste Perversion	4 (8.5)	6 (11.5)	0 (0.0)
Eye Pain	2 (4.3)	4 (7.7)	2 (3.8)
Conjunctivitis	2 (4.3)	2 (3.8)	4 (7.7)
Epistaxis	1 (2.1)	2 (3.8)	0 (0.0)
Influenza-Like Symptoms	3 (6.4)	2 (3.8)	1 (1.9)
Rhinitis	1 (2.1)	2 (3.8)	0 (0.0)
Dyspnea	2 (4.3)	1 (1.9)	0 (0.0)
Vision Abnormal	2 (4.3)	1 (1.9)	0 (0.0)
Pruritus	2 (4.3)	0 (0.0)	0 (0.0)
Circulatory Failure	1 (2.1)	0 (0.0)	0 (0.0)
Eczema	1 (2.1)	0 (0.0)	0 (0.0)

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 #14 **Protocol 2916**

Title: Investigation of the efficacy and tolerability of three different concentrations of azelastine eye drops in the treatment of patients suffering from seasonal allergic conjunctivitis/rhinoconjunctivitis

Study Design: A Phase 3 randomized, multicenter, placebo-controlled, parallel-group, double-blind, environmental study to evaluate the efficacy and safety of three concentrations of azelastine eye drops in adult patients with allergic conjunctivitis. Same as Study #13.

Investigators

2. Dr. med. R.N. Bartelt, Albanusstraße 22, D-65929 Frankfurt
4. Dr. med. P. Bielicky, Luegplatz 3, D-40545 Düsseldorf
5. Dr. med. M. Butscher, Ringstraße 80, D-66953 Pirmasens
6. Dr. med. H. Deuker, Heidelberger Landstraße 221, D-64297 Darmstadt
7. Joint practice of Dr. med. W. Goebels, Dr. med. R. Handzel, Marktstraße 8, D-36037 Fulda
9. Dr. med. A. Heiligenhaus, Dr. med. J. Bautista, Universitäts-Augenklinik, Hufelandstraße 35 D-45147 Essen
10. Dr. med. M. Hornstein, Rotdornstraße 1, D-40472 Düsseldorf
11. Dr. med. R. Koch, Wolfsschlucht 6 ½, D-34117 Kassel
12. Dr. med. R. Lehmann, Albertusstr. 9-11, D-41061 Mönchengladbach
13. Dr. med. W. Ottmar, Königsplatz 55, D-34117 Kassel
14. Dr. med. K. Schulz, Bornheimer Landstraße 1, D-60316 Frankfurt
18. Dr. med. S. Heilmann, Biegenstraße 44, D-35037 Marburg
19. Dr. med. H. Beuing, Schlesische Straße 3, D-35683 Dillenburg
20. Dr. med. F. Rohr, Bahnhofstraße 47, D-55234 Framersheim
21. Dr. med. P. Schmidt, Bahnhofstraße 2A, 55571 Odernheim-Glan

Site	AZE 0.025%	AZE 0.05%	AZE 0.1%	Vehicle
2	0	1	1	0
4	1	1	1	2
5	0	2	1	0
6	0	0	0	1
7	1	1	1	0
9	1	1	0	1
10	5	5	6	5
11	3	3	3	3
12	5	4	4	4
13	0	1	1	0
14	1	0	1	1
18	0	1	1	0
19	1	1	1	1
20	0	0	0	1
21	1	0	0	0

15 patients (8 of them in centre 12) discontinued the study prematurely due to following reasons:

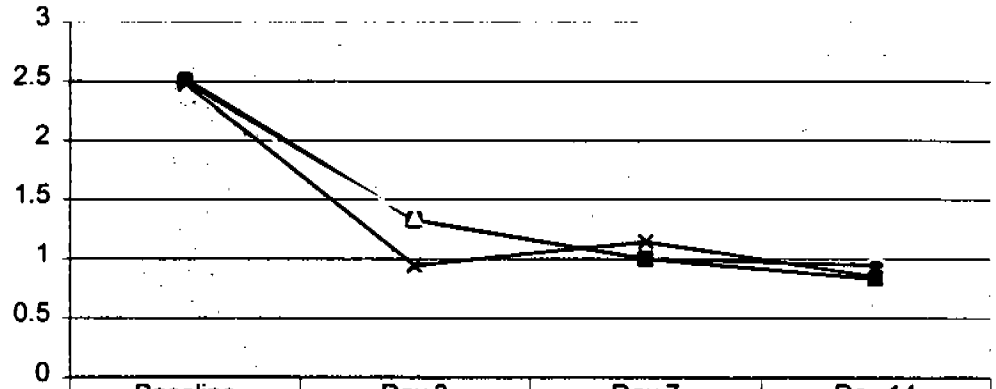
reason	AZE 0.025	AZE 0.050	AZE 0.100	PLA
inefficacy	4/33, 12/140, 12/191	2/13, 12/137	13/146; 12/136	
intolerability			5/56	10/115
inefficacy / intolerability			4/36	
non-compliance	14/158		5/56	12/141
intercurrent disease	12/144			
other reasons	12/135			12/139
Adverse experience	12/144		4/36	10/115

Demographics

		Vehicle	AZE 0.025%	AZE 0.05%	AZE 0.1%
Age (years)	Mean	39.4	37.1	35.5	40.0
	Range	21-64	19-67	18-59	21-64
Gender	Male	4	9	6	7
	Female	14	9	15	14
Race	Caucasian	17	18	19	20
	Black	0	0	1	0
	Asian	0	0	0	1
	Other/Unknown	1	0	1	0

APPEARS THIS WAY
ON ORIGINAL

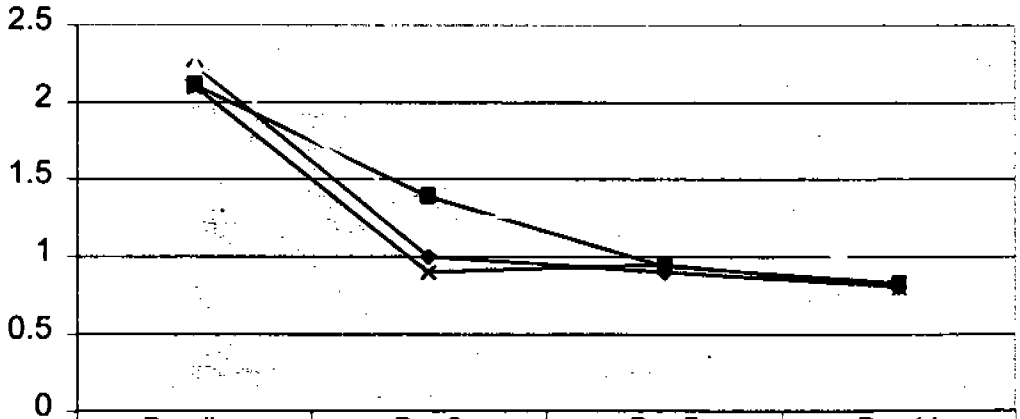
Itching



	Baseline	Day 3	Day 7	Day 14
Azelastine 0.05%	2.52	1.33	1	0.95
Vehicle	2.5	1.33	1	0.83
Azelastine 0.025%	2.41	1.35	1.29	1.06
Azelastine 0.1%	2.48	0.95	1.15	0.85

Reviewer's Comments: *None of the differences are statistically significant.*

Redness



	Baseline	Day 3	Day 7	Day 14
Azelastine 0.05%	2.24	1	0.9	0.81
Vehicle	2.11	1.39	0.94	0.83
Azelastine 0.025%	2.24	1.29	1.18	0.94
Azelastine 0.1%	2.1	0.9	0.95	0.8

Reviewer's Comments: *None of the differences are statistically significant.*

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

Randomized (N=78)	AZE 0.025 (N=18)	AZE 0.050 (N=21)	AZE 0.100 (N=21)	PLA (N=18)
All AEs	9 (50.0)	14 (66.7)	16 (76.2)	7 (38.9)
WHO Preferred term				
Application Site Reaction	3 (16.7)	7 (33.3)	10 (47.6)	5 (27.8)
Taste Perversion	2 (11.1)	6 (28.6)	2 (9.5)	0 (0.0)
Headache	3 (16.7)	3 (14.3)	5 (23.8)	3 (16.7)
Conjunctivitis	0 (0.0)	1 (4.8)	4 (19.0)	0 (0.0)
Dyspnea	1 (5.6)	1 (4.8)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)
Influenza-Like Symptoms	2 (11.1)	1 (4.8)	0 (0.0)	0 (0.0)
Palpitation	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)
Pharyngitis	0 (0.0)	1 (4.8)	1 (4.8)	1 (5.6)
Pruritus	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)
Tooth Ache	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)
Coughing	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)
Dyspepsia	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)
Eye Pain	0 (0.0)	0 (0.0)	2 (9.5)	0 (0.0)
Mouth Dry	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)
Sinusitis	1 (5.6)	0 (0.0)	1 (4.8)	0 (0.0)

Conclusions Regarding Data

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

9 Overview of Efficacy

Itching

Study	Antigen Challenge	Day 3	Day 7	Day 14	Day 28/35
1	+				
2	-				
3		+	-	-	
4		+	+	-	
5				+	+
6		-		-	
7		+	-	-	
8		+		+	+
9		-		-	
10		-		-	
11	-				
12			+	-	
13		+	-	-	
14		-	-	-	

Redness

Study	Antigen Challenge	Day 3	Day 7	Day 14	Day 28/35
1	-				
2	-				
3		+	-	-	
4		+			
5		+		+	+
6		-		-	
7		+	-	+	
8		+		+	+
9		-		-	
10		-		+	
11	-				
12			+	-	
13		-	+	-	
14		-	-	-	

Reviewer's Comments: *Azelastine is never inferior to vehicle. It is superior on the days listed above. Taken as a whole, evidence has been demonstrated that the drug product will have an effect on both itching and redness, but only with qid dosing. Bid dosing will support a claim of itching associated with allergic conjunctivitis.*

10 Overview of Safety

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

Reviewer's Comments: *None that appear to be related to product use.*

10.1.2 Other Significant/Potentially Significant Events

Reviewer's Comments: *None beyond those included in ADR tables.*

10.1.3 Overdose Experience

Reviewer's Comments: *Levels not expected to reach typical oral dosing.*

10.2.2 Laboratory Findings, Vital Signs, ECGs

Reviewer's Comments: *No particular findings.*

10.2.6 Drug-Drug Interactions

Reviewer's Comments: *None for ophthalmic use.*

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables

	2981	2982	2983	2984	2985	3021	3034	3062	2946	2945	2916
Application site reaction	26%	36%	28%	35%	27%	15%	33%	47%	11%	38%	33%
Headache	15%	24%	17%	4%	3%	4%	4%	6%	5%	23%	14%
Taste Perversion	12%	31%	4%	9%	5%		4%	4%	8%	11%	29%
Dyspnea	7%		9%	4%	4%	2%			3%	2%	5%
Rhinitis	7%	4%	6%						3%	4%	
Coughing	5%	4%	14%		7%	14%	10%	9%	3%		
Pharyngitis	4%	4%			3%		6%	4%	2%		
Asthma	3%			5%			6%	4%	3%		
Conjunctivitis	3%	4%	5%		7%			4%	3%	4%	5%
Influenza-like symptoms	3%	2%								4%	5%
Vision abnormal	3%									2%	
Fatigue/Somnolence		4%	2%								5%
Pruritis		2%	2%			2%					5%
Eye pain										8%	

Reviewer's Comments:

The most frequent adverse experience was application site reactions which occurred approximately 30-40% of the time.

This was followed by headaches and taste perversion which occurred in 10-30% of the patients.

The other events, asthma, conjunctivitis, coughing, decreased vision, dyspnea, eye pain, fatigue, influenza-like symptoms, pharyngitis, pruritis and rhinitis occurred in 1-10% of patients.

4 page(s) of revised draft labeling has been redacted from this portion of the review.

12 Conclusions

Safety and efficacy has been demonstrated for Optivar (azelastine hydrochloride ophthalmic solution), 0.05% in adequate and well controlled studies for the prevention of allergic conjunctivitis.

13 Recommendations

It is recommended that NDA 21-127, Optivar (azelastine hydrochloride ophthalmic solution) be approved for the prevention of allergic conjunctivitis with the revised labeling identified in this review.

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: HFD-550
HFD-340
HFD-550/Proj Mgr/Rodriguez
HFD-830/CHEM/Rodriguez
HFD-550/PHARM/ZChen
HFD-550/MO/Chambers

Medical Officer's Review of NDA 21-127
Safety Update

NDA #21-127
M.O. Review #2

Submission: 11/29/1999
Review completed: 4/20/2000

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

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

Submitted: Safety Update
Updated safety tables and the final reports for studies 3112 and 3075.

Reviewer's Comments:

The submitted safety update is consistent with the information submitted in the original application. Review of this information does not alter the conclusions from the previous Medical Officer's Review.

Financial Disclosure Information

Reviewer's Comments:

The information reported in the Financial disclosure of the original application has been reviewed. It does not alter the conclusions or recommendations from the previous Medical Officer's Review.

/S/

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

cc: HFD-550
HFD-340
HFD-550/Proj Mgr/Rodriguez
HFD-830/CHEM/Rodriguez
HFD-550/PHARM/ZChen
HFD-550/MO/Chambers

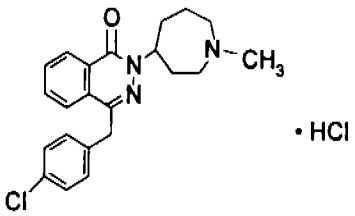
Medical Officer's Review of NDA 21-127
Original

NDA #21-127
M.O. Review #3

Submission: 4/27/2000
Review completed: 5/ 8/2000

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

9 Overview of Efficacy

Itching

Study	Antigen Challenge	Day 3	Day 7	Day 14	Day 28/35
1	+				
2	-				
3		+	-	-	
4		+	+	-	
5				+	+
6		-		-	
7		+	-	-	
8		+		+	+
9		-		-	
10		-		-	
11	-				
12			+	-	
13		+	-	-	
14		-	-	-	

Redness

Study	Antigen Challenge	Day 3	Day 7	Day 14	Day 28/35
1	-				
2	-				
3		+	-	-	
4		+			
5		+		+	+
6		-		-	
7		+	-	+	
8		+		+	+
9		-		-	
10		-		+	
11	-				
12			+	-	
13		-	+	-	
14		-	-	-	

10.2.1 ADR Incidence Tables

	2983	3021	2985	3062	2981	2946	2984	3034	2945	2982	2916
	N=207	N=160	N=146	N=103	N=101	N=93	N=75	N=51	N=53	N=45	N=21
Application site reaction	28%	14%	27%	47%	26%	11%	35%	33%	38%	36%	33%
Burning	28%	14%	27%	19%	23%	4%	23%	23%	40%	2%	29%
Stinging				16%				2%		36%	
Tingling				1%	2%		15%	12%			
Irritation				2%		2%					
Itching				10%	2%						5%
Headache	17%	4%	3%	6%	15%	5%	4%	4%	23%	24%	14%
Taste Perversion	4%		5%	4%	12%	8%	9%	4%	11%	31%	29%
Bitter Taste Complaint	4%		1%	2%	7%	3%	7%	4%	7%	9%	29%
Other Taste Complaint			4%	2%	6%	4%	3%		2%	27%	
Dyspnea	9%	2%	4%		7%	3%	4%		2%		5%
Rhinitis	6%				7%	3%			4%	4%	
Coughing	14%	14%	7%	9%	5%	3%		10%		4%	
Pharyngitis			3%	4%	4%	2%		6%		4%	
Asthma				4%	3%	3%	5%	6%			
Conjunctivitis	5%		7%	4%	3%	3%			4%	4%	5%
Influenza-like symptoms					3%				4%	2%	5%
Vision abnormal					3%				2%		
Fatigue/Somnolence	2%									4%	5%
Pruritis	2%	2%								2%	5%
Eye pain	1%	1%	1%		1%	1%		2%	8%		

Reviewer's Comments:

The most frequent adverse experience was application site reactions which occurred approximately 30% of the time.

This was followed by headaches and bitter taste which occurred in 5-20% of the patients.

The other events, asthma, conjunctivitis, coughing, decreased vision, dyspnea, eye pain, fatigue, influenza-like symptoms, pharyngitis, pruritis and rhinitis occurred in 1-10% of patients.

4 page(s) of revised draft labeling has been redacted from this portion of the review.

12 Conclusions

Safety and efficacy has been demonstrated for Optivar (azelastine hydrochloride ophthalmic solution), 0.05% in adequate and well controlled studies for the prevention of allergic conjunctivitis.

13 Recommendations

It is recommended that NDA 21-127, Optivar (azelastine hydrochloride ophthalmic solution) be approved for the prevention of allergic conjunctivitis with the revised labeling identified in this review.

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: HFD-550
HFD-340
HFD-550/Proj Mgr/Rodriguez
HFD-830/CHEM/Rodriguez
HFD-550/PHARM/ZChen
HFD-550/MO/Chambers

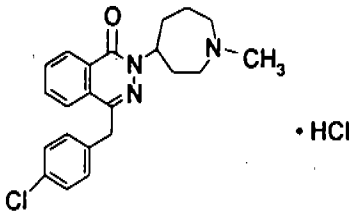
Medical Officer's Review of NDA 21-127
Original

NDA #21-127
M.O. Review #4

Submission: 5/16/2000
Review completed: 5/19/2000

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 treatment of itching of the eye associated with allergic conjunctivitis.

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

NDA Drug Classification: 3 S

Submitted: Revised labeling based on agency comments of earlier drafts.

4 page(s) of revised draft labeling has been redacted from this portion of the review.

Conclusions

Safety and efficacy has been demonstrated for Optivar (azelastine hydrochloride ophthalmic solution), 0.05% in adequate and well controlled studies for the treatment of itching of the eye associated with allergic conjunctivitis.

Recommendations

It is recommended that NDA 21-127, Optivar (azelastine hydrochloride ophthalmic solution) be approved for the treatment of itching of the eye associated with allergic conjunctivitis.

/S/

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: HFD-550
HFD-340
HFD-550/Proj Mgr/Rodriguez
HFD-830/CHEM/Rodriguez
HFD-550/PHARM/ZChen
HFD-550/MO/Chambers