CLINICAL REVIEW

Application Type	NDA 21-114 NDA 20-816
Submission Number	002
Submission Code	SE8
Letter Date	3/27/2006
Stamp Date	3/28/2006
PDUFA Goal Date	9/26/2006
Reviewer Name	Jennifer Harris, M.D.
Review Completion Date	7/20/06
Established Name	levobetaxolol hydrochloride ophthalmic suspension brinzolamide ophthalmic suspension
Trade Name	Betaxon 0.5% Azopt 1%
Therapeutic Class	beta-blocker carbonic anhydrase inhibitor
Applicant	Alcon Research, Ltd.
Priority Designation	P

Formulation	ophthalmic suspension
Dosing Regimen	Betaxon – one drop twice a day Azopt – one drop three times a day
Indication	treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Intended Population	pediatric patients less than 6 y.o.

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

NDA 21-114/SE8 [redacted] labeling revisions are made consistent with the recommendations listed in this review. The clinical study contained in this supplement [redacted] of levobetaxolol hydrochloride ophthalmic suspension in the pediatric population. [redacted].

NDA [redacted] 816/SE8 [redacted] revised labeling describing the failure of the b.i.d dosing regime. The clinical data generated in the amendment is not sufficient to establish the safety or efficacy of brinzolamide ophthalmic suspension in the pediatric population.

1.2 Recommendation on Postmarketing Actions

N/A – there are no recommendation on postmarketing actions

1.2.1 Risk Management Activity

N/A – there are no recommendations for risk management activity

1.2.2 Required Phase 4 Commitments

N/A – there are no recommended Phase 4 commitments

1.2.3 Other Phase 4 Requests

It is recommended that Azopt (brinzolamide ophthalmic suspension) 1% be studied in pediatric patients when dosed three times a day.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Clinical study C-00-17 was conducted to obtain needed pediatric information on Azopt (brinzolamide ophthalmic suspension), 1% and Betaxon (levobetaxolol hydrochloride ophthalmic suspension), 0.5% for the treatment of elevated intraocular pressure in children less than 6 years of age. This study was conducted in response to the Agency's Written Request of October 15, 1999, as amended November 17, 2000, [redacted]

(b) (4) for AZOPT 1%. It was also conducted in response to the Agency's Written Request of October 15, 1999, as amended November 17, 2000, (b) (4) for Betaxon 0.5%. This study was also conducted to fulfill the requirements of 21 CFR§314.55 for Betaxon. Deferred submission of pediatric data was granted in the approval letter for Betaxon dated February 23, 2000 and in the Agency's letter of May 26, 2004.

Study C-00-17 was designed to describe the safety and clinical response of AZOPT 1% and Betaxon 0.5% in patients 0 to 5 years of age with a clinical diagnosis of glaucoma or ocular hypertension. The clinical safety and efficacy of AZOPT 1% and BETAXON 0.5% have been established in adult and elderly patients with glaucoma or ocular hypertension in NDA 20-816 [Azopt (brinzolamide ophthalmic suspension), 1%] and NDA 21-114 [Betaxon (levobetaxolol hydrochloride ophthalmic suspension), 0.5%], respectively.

The pediatric clinical development plan for Azopt and for Betaxon included one safety/efficacy study (C-00-17). The objective of study C-00-17 was to describe the safety and IOP-lowering ability of Azopt 1% and Betaxon 0.5% in children less than 6 years of age with glaucoma or ocular hypertension.

This submission is based on data from a total of 32 pediatric patients exposed to Azopt and 48 exposed to Betaxon.

1.3.2 Efficacy

The purpose of the trial contained in this pediatric supplement was to demonstrate the safety of levobetaxolol HCL and brinzolamide when used in pediatrics patients below the age of six. The support for efficacy for both of these products was extrapolated from the adult trials. The limited clinical response data contained in the supplement demonstrates that levobetaxolol lowered IOP by approximately 1-2 mmHg while brinzolamide lowered IOP by approximately 0-2 mmHg.

1.3.3 Safety

- *The study in this NDA amendment is adequate to establish the safety of the use of levobetaxolol hydrochloride ophthalmic suspension in the pediatric population.*

- *The type of adverse events seen in patients treated with levobetaxolol are consistent with those seen in the adult population.*

- *There were no clinically relevant differences in the adverse event profile between the age group strata that were studied (i.e. 1 week to < 1 year, 1 year to < 2 years, 2 years to < 4 years, and 4 years to < 6 years.*

- *There was inadequate safety data gathered in this trial to support the use of Azopt in the pediatric population.*

1.3.4 Dosing Regimen and Administration

The dosage and administration in the pediatric population is identical to that which has been established in the adult population. The sponsor has not submitted data to support any change in the already established dose and frequency for either of these two products.

1.3.5 Drug-Drug Interactions

Drug/drug interaction analyses were not conducted for this trial.

1.3.6 Special Populations

There are no important considerations required for administering this product in special populations. The pediatric subpopulations analyzed were 1 week to < 1 year, 1 year to < 2 years, 2 years to < 4 years and 4 years to < 6 years of age. Adverse events and the safety profile for levobetaxolol hydrochloride and brinzolamide were consistent between these age groups.

2 INTRODUCTION AND BACKGROUND

See original NDA reviews for levobetaxolol HCL and brinzolamide

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

See original NDA reviews for levobetaxolol HCL and brinzolamide

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

See original NDA reviews for levobetaxolol HCL and brinzolamide

5 CLINICAL PHARMACOLOGY

See original NDA reviews for levobetaxolol HCL and brinzolamide

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor has not proposed to change the indication for levobetaxolol HCL or brinzolamide. The indication section of the package insert will remain unchanged. Both are currently indicated for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension. The results of the study conducted in this supplement have been used to add additional information to the Pediatric Use and Adverse Reactions sections of each products label.

6.1.1 Methods

The results of one trial, C-00-17 have been submitted for review in this NDA supplement to support the use of brinzolamide and levobetaxolol in the pediatric population. The trial was conducted in response with the pediatric written request issued by the Agency and was designed to address the safety of these two products. The support for efficacy in the pediatric population was extrapolated from the adult trials.

6.1.2 General Discussion of Endpoints

Study C-00-17 was designed to describe the safety of brinzolamide ophthalmic suspension 1% and levobetaxolol HCL ophthalmic suspension 0.5% in patients 0 – 5 years of age with a clinical diagnosis of glaucoma or ocular hypertension. Standard safety measurements were selected to evaluate those parameters associated with the use of topical ocular medications and to evaluate possible systemic side effects associated with brinzolamide ophthalmic suspension 1% and levobetaxolol hydrochloride ophthalmic suspension 0.5% in pediatric patients.

6.1.3 Study Design

Study C-00-17 was designed to describe the safety of brinzolamide ophthalmic suspension 1% and levobetaxolol HCL ophthalmic suspension 0.5% in pediatric patient less than six years of age with a clinical diagnosis of glaucoma or ocular hypertension. The patient population was subdivided into four age strata: 1 week to < 1 year; 1 year to < 2 years; 2 years to < 4 years; 4 years to < 6 years. At least five patients were enrolled per treatment group in the 1 week to < 1 year and 1 year to < 2 years age strata. At least 10 patients were enrolled per treatment group in the 2 years to < 4 years and 4 years to < 6 years age strata.

The study was a multi-center, randomized, double-masked, active-controlled, parallel comparison trial. It was conducted in two phases: a baseline phase and a treatment phase. The baseline phase consisted of Screening and Baseline visits. The treatment phase consisted of on-therapy visits at Weeks 2, 6, and 12 (exit).

General Study Design

Treatment Group	**Study phase**	
	Baseline Phase	**Treatment Phase**
	Screening and Baseline Visits	**Week 2, Week 6, and Week 12**
Brinzolamide ophthalmic suspension, 1%	Continue pre-study ocular hypotensive therapy or no dosing (if no prior therapy)	Brinzolamide ophthalmic suspension 1% BID (8am and 8pm)
Levobetaxolol HCL ophthalmic suspension, 0.5%	Continue pre-study ocular hypotensive therapy or no dosing (if no prior therapy)	Levobetaxolol HCl ophthalmic suspension 0.5% BID (8am and 8pm)

Reviewer's Comment:

Dosing of brinzolamide ophthalmic solution b.i.d is not consistent with the approved dosing frequency of brinzolamide in adults. The dosing frequency in this trial should have been t.i.d.

Investigators C-00-17

Investigator number	Principal Investigator	Location	Number of Subjects
3020	Allen Beck, M.D.	Atlanta, GA	2
3690[1] 4057	Luca Brigatti, M.D. Matthew Gearinger, M.D.	Rochester, NY	1
2909	Monte Del Monte, M.D.	Ann Arbor, MI	1
1637	Diana DeSantis	Wheat Ridge, CO	4
3666	John Frederick, M.D.	Davenport, IA	2
2908	Sharon Freedman, M.D.	Durham, NC	4
2910	Charlise Gunderson, M.D.	Galveston, TX	1
2912	David Johnson, M.D.	Wichita, KS	3
3068	Veronique Jotterand, M.D.	Long Beach, CA	1
3880	R. Krishnada, M.D.	India	3
826	Steven Lichtenstien, M.D.	Louisville, KY	1
3882	Anil Mandal, M.D.	India	4
3023	Stephen Mathias, M.D.	Danbury, CT	1
3614	Eric Packwood	Fort Worth, TX	2
3127	Evelyn Paysse, M.D.	Houston, TX	2
3292	David Plager, M.D.	Indianapolis, IN	4
3022	Stephen Prepas	Newport Beach, CA	1
2911	John Roarty	Detroit, MI	5
2906	Gary Rogers	Columbus, OH	3
3879	P. Sathyan, M.D.	India	6
2347	Paul Sidoti, M.D.	New York, NY	1
3902	Devindra Sood, M.D.	India	8
3881	Lingam Vijaya, M.D.	India	14
1909	Jess Whitson, M.D.	Dallas, TX	5
1641	Kenneth Wright, M.D.	Los Angeles, CA	1

[1]Matthew Gearinger, MD took over as principal investigator from Luca Brigatti, MD on October 18th, 2004.

Study Schedule

Activity	Screen	Baseline	Week 2 ± 1 day	Week 6 ± 1 day	Week 12 ± 3 days or early termination
Screen patients	X				
Informed consent	X				
Demographics	X				
Medical history	X				
Discontinue current glaucoma medication		X			
IOP[a]	X	X	X	X	X
alertness		X	X	X	X
Visual acuity (age-appropriate)[b]	X	X	X	X	X
Corneal diameter	X				
Ocular signs[d]	X	X	X	X	X
Resting pulse/blood pressure	X	X	X	X	X
Dilated fundus exam	X				X
In-office instillation of AM dose of meds	X	X	X	X	X
Dispense study meds		X	X	X	
Adverse event reporting			X	X	X
Collect study meds					X
Issue new contact len(s)[c]		X			X
Collect contact lenses[c]					X
Exit patients					X

[a] All IOPs were taken within 1 hr of 9AM. Screen and exit IOPs were taken from anesthetized patients if necessary. Goldmann or Perkins tonometer, or Tono-Pen were used for all IOPs
[b] Visual acuity measurements were taken using age-appropriate test. Patients had screening visual acuity taken with the most sophisticated test possible. Baseline, weeks 2, 6 and 12 exams used the same test as Screening.
[c] Aphakic patients wearing contact lenses were issued contact lenses for use during study. These lenses were collected at exit.
[d] Slit lamp or indirect ophthalmoscope and penlight.

Inclusion Criteria

1. Patients 1 week to < 6 years of age at screening, of either sex, of any race, diagnosed with glaucoma (congenital, associated with systemic or ocular abnormalities, or secondary to other ocular insults or conditions) or ocular hypertension, and either treated prior to the study with an ocular hypotensive medicine, or not undergoing prior treatment with ocular

hypotensive medications were eligible for enrollment.

2. Aphakic patients with contact lenses were eligible for enrollment. If study drops were to be instilled with lenses in eyes, the patient was to be provided with contact lenses to be used during the study.

3. Patients with conditions that required chronic treatment with glucocorticoids resulting in steroid induced glaucoma or with glaucoma secondary to uveitis that required steroid treatment were eligible for enrollment.

Exclusion Criteria

1. Children who were six years of age or older at the Screening Visit.
2. Children who at the time of the Screening Visit were less than one year of age (includes premature neonates) and were at or below the fifth (5th) percentile for body weight.
3. Patients who had clinically significant or progressive retinal disease such as retinal degeneration, diabetic retinopathy or retinal detachment in the study eye(s).
4. Any abnormality which would have prevented reliable tonometry of either eye.
5. Any eye with a history of penetrating keratoplasty.
6. History of any severe ocular pathology (including severe dry eye) in study eye(s) that would have precluded the administration of a topical beta blocker or carbonic anhydrase inhibitor.
7. Patients who had any amount of congenital optic atrophy in the study eye(s).
8. Intraocular surgery within the thirty (30) days of the Screening Visit in the study eye (if only one eye was operated on, the fellow eye was not excluded).
9. Patients that had fewer than 3 weeks stable dosing (prior to the Screening Visit) of the prestudy IOP-lowering medication(s) (unless there was no prestudy IOP-lowering medication).
10. History of severe or serious hypersensitivity to topical or systemic beta blockers, carbonic anhydrase inhibitors, sulfa drugs (sulfonamides), or any component of either of the study medications.
11. History of congenital cardiovascular anomalies or abnormalities which would preclude the safe administration of a selective topical beta blocker or carbonic anhydrase inhibitor. In the event that the effects of the study medications were unclear, the patient may have participated with written approval from the patient's pediatric cardiologist.
12. Patients with fewer than 3 weeks stable dosing (prior to the Screening Visit) of clonidine or other drugs for hyperkinesis which may have a cardiovascular effect.

Evaluability

All patients who received study drug were considered evaluable for the safety analysis. All patients who received study drug, had at least one on-therapy study visit were considered evaluable for the intent-to-treat analysis. All patients who received study drug, had at least one

on-therapy study visit, and satisfied inclusion and exclusion criteria were considered evaluable for the per protocol analysis. In addition, only those data points that satisfied protocol criteria were considered evaluable for the per protocol analysis.

Analysis

The primary objective of this study was to describe the safety and clinical response of BETAXON and AZOPT in patients 0 to 5 years of age with a clinical diagnosis of glaucoma or ocular hypertension.

The primary statistical objectives of this study were to:

- describe the IOP-lowering efficacy of BETAXON in pediatric patients 0 to 5 years of age relative to their baseline status.
- describe the IOP-lowering efficacy of AZOPT in pediatric patients 0 to 5 years of age relative to their baseline status.
- describe the IOP-lowering efficacy of BETAXON in pediatric patients 0 to 5 years of age relative to that of AZOPT in the same age cohort.

The primary efficacy parameter was an assessment of mean IOP from baseline at 9 AM. Study visits were planned at Week 2, Week 6, and Week 12. If only one of a patient's eyes was dosed, the dosed eye was selected for analysis. If both of a patient's eyes were dosed, the worse evaluable eye was selected for analysis. Worse eye was defined as the eye with the higher intraocular pressure at 9 AM averaged across the Screening and Baseline Visits. If both eyes were equal, then the right eye was selected for analysis.

The mean IOP readings at the Screening and Baseline Visits were averaged to form the baseline IOP values for each patient. A repeated measures analysis of variance was used to describe the treatment differences with regard to mean IOP change from baseline. A two-sided 95% confidence interval for the treatment group difference at each visit and time point was constructed to describe the mean IOP change from baseline based on this repeated measures analysis of variance.

Descriptive statistics were calculated for IOP, IOP change from baseline, and IOP percent change from baseline.

6.1.4 Efficacy Findings

The primary efficacy parameter was an assessment of mean IOP change from baseline at 9 am. In this study, if anesthesia was required to obtain IOP at the screening visit and if IOP could not be obtained from the conscious child at subsequent visits (baseline, week 2, week 6), IOP assessment was not required at these visits. IOP was obtained under anesthesia at the week 12 visit if necessary.

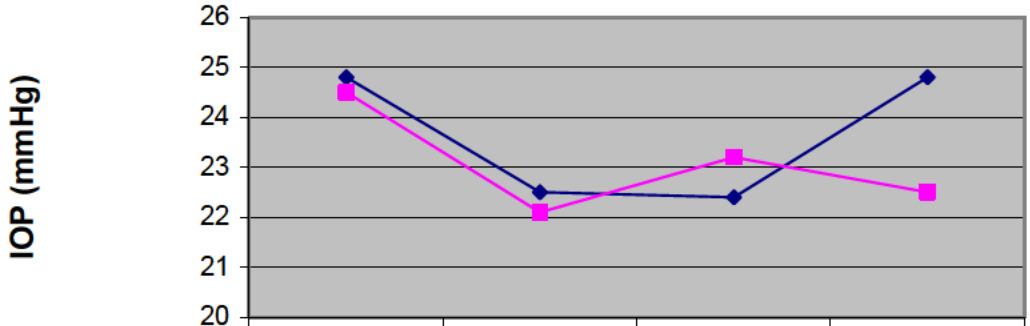
Status of IOP Data, Stratified By Use of Anesthesia at Screening Visit (Intent-to-Treat Data)				
	Anesthesia used at Screening		**Anesthesia not used at Screening**	
	Azopt	**Betaxon**	**Azopt**	**Betaxon**
Visit Status				
Screening IOP Collected	12	16	19	30
Baseline IOP Collected	3	6	19	28
Week 2 IOP Collected	4	7	17	26
Week 6 IOP Collected	2	8	17	23
Week 12 IOP Collected	9	14	17	25

Mean IOP

The determination of efficacy of both of these drugs cannot be established based on this trial design. IOP in this trial were only assessed at 9 am which was approximately 1 hour after patients received their morning dose. Proper determination of efficacy can only be determined by measuring the IOP throughout the day to capture the peak and trough effects of the drug under study. The maintenance of controlled IOP throughout the day is necessary in glaucoma patients to prevent damage from the disease. The purpose of including IOP measurements in this trial was to ensure that there was a clinical response present and to ensure the safety of patients in the trial by monitoring the control of their IOP.

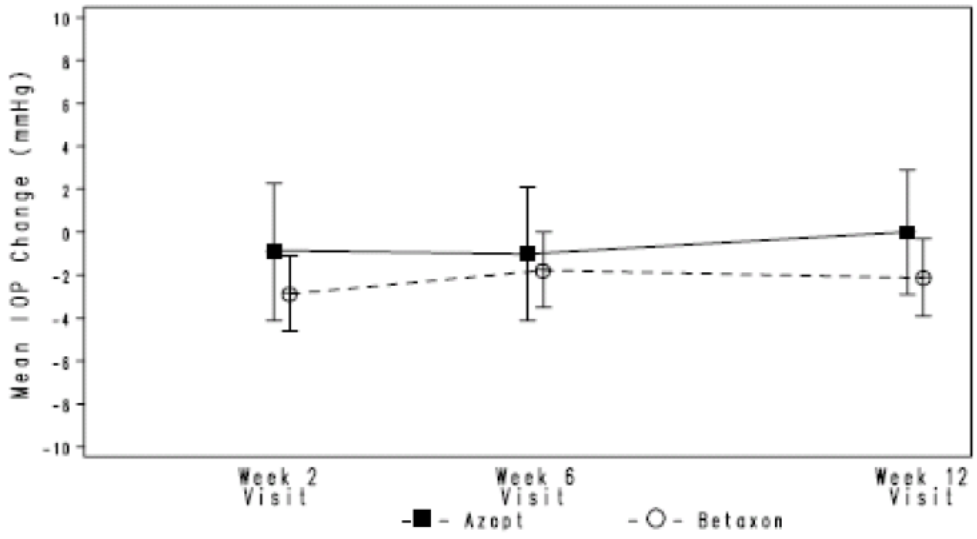
The limited clinical response data contained in the supplement demontrates that Betaxon lowered IOP by approximately 1-2 mmHg while Azopt lowered IOP by approximately 0-2 mmHg. The graphs for the mean IOP and change from baseline for Azopt and Betaxon are presented in this review for completeness. No conclusion can be drawn from these data to determine the efficacy of either product in the pediatric population.

Mean IOP (mmHg) - ITT

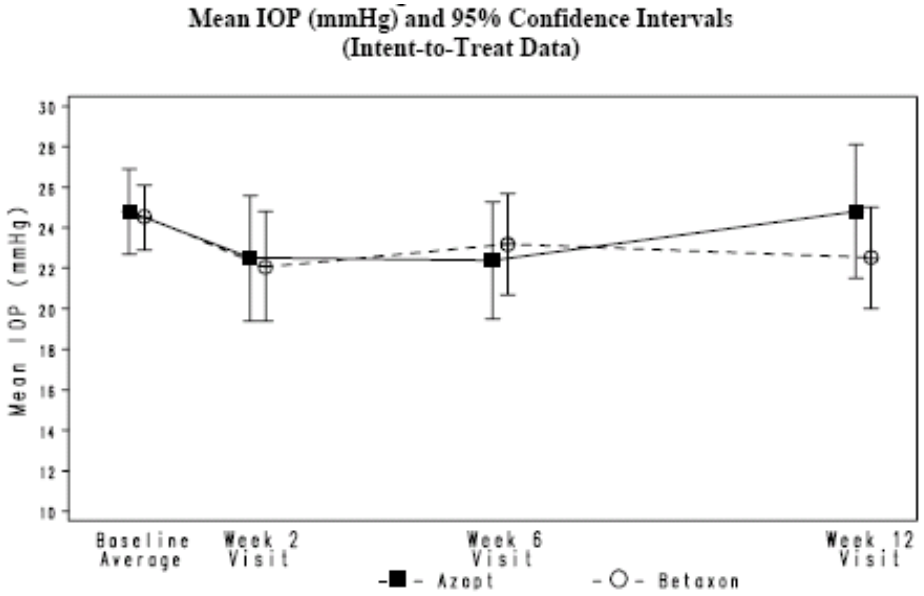


	baseline	week 2	week 6	week 12
Azopt	24.8	22.5	22.4	24.8
Betaxon	24.5	22.1	23.2	22.5

Mean IOP Change From Baseline (mmHg) and 95% Confidence Intervals (Intent-to-Treat Data)



Plotted data are descriptive means with 95% confidence intervals



Plotted data are descriptive means with 95% confidence intervals

6.1.5 Clinical Microbiology

N/A – this product is not an antimicrobial.

6.1.6 Efficacy Conclusions

The efficacy of Betaxon and Azopt has been extrapolated from the adult studies submitted in each of the respective original NDAs. This trial has not been designed to support efficacy in the pediatric population. The limited clinical response data contained in the supplement demonstrates that Betaxon lowered IOP by approximately 1-2 mmHg while Azpot lowered IOP by approximately 0-2 mmHg.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The review of safety for Azopt and Betaxon in pediatric patients is based on the results of a single trial. C-00-17 enrolled a total of 80 patients with 32 exposed to Azopt and 48 exposed to Betaxon for 12 weeks. Standard safety measurements were selected to evaluate those parameters associated with the use of topical ocular medications and to evaluate possible systemic side effects. Safety assessments included the following: evaluation of patient alertness,

measurement of corneal diameter, slit-lamp and dilated fundus exam, IOP measurements, pulse/blood pressure measurement and adverse event reporting.

In the review of the safety data, it is important to note that the dosing of Azopt in this trial was only twice a day. The labeled dosing frequency of Azpot is three times a day. Therefore, the safety data gathered during this pediatric study was based on dosing at a level below the therapeutic dose.

7.1.1 Deaths

N/A – no deaths were reported during this study.

7.1.2 Other Serious Adverse Events

Serious Adverse Events

Patient	Age (years)	Sex	Treatment	Adverse Event
7522	3	M	Azopt	Surgical/Medical Procedure[a]
1021	3	M	Betaxon	Surgical/Medical Procedure[b]
6032	4	M	Betaxon	Surgical/Medical Procedure[c]

[a]open stamm gastrostomy
[b]plastic surgery for neurofibromatosis
[c]planned hospitalization for immune work-up and second opinion for recurrent fevers and neutropenia

7.1.3 Dropouts and Other Significant Adverse Events

N/A – no patient discontinued participation in the study due to an adverse event.

7.1.3.1 Overall profile of dropouts

Patient Status (Safety Population)

	N	Completed Study
Azopt	32	26 (81.3%)
Betaxon	48	40 (83.3%)

Reasons for Study Discontinuation (Safety Population)

	Azopt (N=32)	**Betaxon (N=48)**
Inadequate Control of IOP	5 (15.6%)	6 (12.5%)
Parent's Decision [a]	1 (3.1%)	0
Other		2 (4.2%) [b]

[a] unrelated to an adverse event
[b] patient did not meet inclusion/exclusion criteria (elevated IOP), dispensed expired medication

Patients discontinued from Study

Principal Investigator No.	**Patient No.**	**Treatment**	**Reason for Discontinuing Treatment**
826	5531	Azopt	Inadequate IOP control
3292	602	Azopt	Inadequate IOP control
3292	603	Azopt	Inadequate IOP control
3879	121	Azopt	Inadequate IOP control
3881	301	Azopt	Inadequate IOP control
3881	713	Azopt	Parents decision
1637	1521	Betaxon	Inadequate IOP control
2908	3021	Betaxon	Inadequate IOP control
2910	3501	Betaxon	Inadequate IOP control
3614	1221	Betaxon	Protocol violation – patient did not meet inclusion/exclusion criteria
3666	5111	Betaxon	Inadequate IOP control
3666	5121	Betaxon	Inadequate IOP control
3879	111	Betaxon	Protocol Violation – dispensed expired medication
3881	333	Betaxon	Inadequate IOP control

Reviewer's Comments:
There were no patients that discontinued this study due to an adverse event. The percentage of patients that discontinued due to inadequate IOP control is equivalent between the treatment groups.

7.1.3.2 Adverse events associated with dropouts

N/A – there were no patients in this study that discontinued prematurely due to an adverse event.

7.1.3.3 Other significant adverse events

N/A –There were no other significant adverse events.

7.1.4 Other Search Strategies

N/A – no additional search strategies were conducted

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were obtained as solicited comments from study patients (including parents and/or guardians) and as observations by the study investigator. Adverse events were defined as any change (expected or unexpected) in a patient's ophthalmic and/or medical health that occurred after initiation of study treatment. Adverse events were collected for changes in concomitant medications due to a new medical diagnosis or a worsening in preexisting/prestudy intercurrent illness. Adverse events were also collected for any clinically relevant changes in visual acuity (age-appropriate test), ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens, vitreous), dilated fundus parameters (retina/macula/choroid, optic nerve, disc pallor, cup/disc ratio), corneal diameter, alertness, and cardiovascular parameters (pulse, systolic and diastolic blood pressure).

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All adverse events were coded using a modified COSTART dictionary and received independent causality assessments from the study investigator and medical monitor. A review of the verbatim terms and the associated COSTART terms was conducted. The applicant appears to have appropriately categorized the reported adverse events. However, due the limited terms associated with ophthalmic disorders, some of the associated COSTART terms are not representative of the actual adverse event. For example corneal enlargement gets coded as corneal disorder NOS under the COSTART system. This translation minimizes the actual importance of this adverse event.

7.1.5.3 Incidence of common adverse events

See section 7.1.5.4

7.1.5.4 Common adverse event tables

Overall Frequency and Incidence of Adverse Events Occurring at Rates ≥ 1%

Adverse Event	**Azopt (N=32)**	**Betaxon (N=48)**
Ocular		
Hyperemia Eye	3 (9.4%)	3 (6.3%)
Discomfort Eye	2 (6.3%)	1 (2.1%)
Corneal Disorder	2 (6.3%)	0
Photophobia	1 (3.1%)	2 (4.2%)
Cataract	1 (3.1%)	0
Cornel Haze	1 (3.1%)	1 (2.1%)
Discharge Eye NOS	1 (3.1%)	1 (2.1%)
Edema Conjunctival	1 (3.1%)	0
Edema Corneal	1 (3.1%)	0
Keratitis	1 (3.1%)	0
Tearing	1 (3.1%)	0
Conjunctivitis	0	1 (2.1%)
Edema Lid	0	1 (2.1%)
Erythema Lid	0	1 (2.1%)
Foreign Body Sensation	0	1 (2.1%)
Hordeolum	0	1 (2.1%)
Irritation Eye	0	1 (2.1%)
Pruritus eye	0	1 (2.1%)
Visual Acuity Decreased	0	1 (2.1%)
Non-ocular		
Body As A Whole		
Cold syndrome	3 (9.4%)	5 (10.4%)
Infection	1 (3.1%)	5 (10.4%)
Surgical/Medical procedure	1 (3.1%)	3 (6.3%)
Fever	1 (3.1%)	2 (4.2%)
Fatigue	1 (3.1%)	0
Headache	1 (3.1%)	0
Abscess	0	1 (2%)
Pain	0	1 (2.1%)
Cardiovascular system		
Bradycardia	1 (3.1%)	1 (2.1%)
Cardiovascular disease	1 (3.1%)	0
Digestive system		
Gastroenteritis	1 (3.1%)	1 (2.1%)
Diarrhea	1 (3.1%)	0

Monilia Oral	0	1 (2.1%)
Toothache	0	1 (2.1%)
Nervous system		
Attention Defecit/Hyperactivity	0	1 (2.1%)
Irritability	0	1 (2.1%)
Respiratory system		
Cough increased	1 (3.1%)	4 (8.3%)
Asthma	1 (3.1%)	0
Epistaxis	1 (3.1%)	0
Lung Disease	1 (3.1%)	0
Pharyngitis	1 (3.1%)	0
Rhinitis	0	1 (2.1%)
Wheezing	0	1 (2.1%)
Skin and Appendages		
Dermatitis	1 (3.1%)	0
Special Senses		
Otitis media	3 (9.4%)	2 (4.2%)

Reviewer's Comments:
The most common ocular adverse events identified in both treatment groups are consistent with many topical ophthalmic drops with the exception of corneal disease as defined in this trial. Adverse events coded corneal disease were actually events of corneal enlargement. This may have been due to the normal growth of the cornea in this age population or secondary to inadequate IOP control.

The types of systemic and ocular adverse events seen are consistent between the treatment groups and are consistent with those seen in the adult trials.

7.1.5.5 Identifying common and drug-related adverse events

Drug-related adverse events for Azopt and Betaxon cannot be reliably determined in this trial due to the small database and the lack of a placebo arm. In general, the types of ocular adverse events reported in this trial are consistent with what is normally seen with most topical drops.

7.1.5.6 Additional analyses and explorations

Additional safety analyses were done for age groups, gender, race and ethnicity. There were no clinically relevant differences in the demographic characteristics between patients with and without adverse events.

7.1.6 Less Common Adverse Events

N/A – the size of the database does not allow for evaluations of adverse events that occur at a rate of < 1%.

7.1.7 Laboratory Findings

N/A - No clinical laboratory evaluations were performed under C-00-17.

7.1.7.1 Overview of laboratory testing in the development program

N/A - No clinical laboratory evaluations were performed under C-00-17.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

N/A - No clinical laboratory evaluations were performed under C-00-17.

7.1.7.3 Standard analyses and explorations of laboratory data

N/A - No clinical laboratory evaluations were performed under C-00-17.

7.1.7.4 Additional analyses and explorations

N/A - No clinical laboratory evaluations were performed under C-00-17.

7.1.7.5 Special assessments

N/A - No clinical laboratory evaluations were performed under C-00-17.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The following vital signs/physical findings were evaluated during this clinical study: visual acuity, ocular signs, dilated fundus parameters, cup/disc ratio, corneal diameter, patient alertness and cardiovascular parameters.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

This amendment contains the results one controlled clinical trial. This was the only trial used for evaluation of vital signs and physical findings.

7.1.8.3 Standard analyses and explorations of vital signs data

Visual Acuity

For pre-verbal patients, visual acuity was determined using a fixation and follow test at baseline and each subsequent visit. Clinically relevant changes were defined as a change from normal to abnormal. For verbal patients, best-corrected visual acuity was measured in Snellen values a baseline and each subsequent visit. The Snellen scores were converted to logMAR. Clinically relevant changes were defined as a decrease of 3 or more logMAR lines.

There were no pre-verbal patients in this trial that experienced a clinically relevant change in visual acuity. There was one patient exposed to Betaxon who experience a clinically relevant change in vision. This patient was lost to follow-up. Overall, there were no statistically significant (p=0.58) treatment group differences comparing the range of visual acuity changes for any visit.

Ocular Signs

An assessment of ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens, vitreous) was performed at baseline and each subsequent visit. Clinically relevant changes were defined as a 1 unit or more increase from baseline.

Clinically Relevant Increase in Ocular Signs From Baseline to Any Visit

	Cornea	**Iris/Anterior Chamber**	**Lens**	**Vitreous**	**Eyelids/Conjunctiva**
Treatment					
Azopt (N=32)	1 (3.1%)	0	1 (3.1%)	0	2 (6.3%)
Betaxon (N=47)	0	0	0	0	3 (6.4%)

Dilated Fundus Examination

An assessment of fundus parameters (optic nerve, retina/macula/choroid, disc pallor) was performed at baseline and at exit. Clinically relevant changes in dilated fundus parameters were defined as an increase of 1 or more units from baseline at any subsequent visit.

There were no clinically relevant changes in fundus parameters from baseline to the exit visit reported for any patient in either treatment group.

Cup/Disc Ratio

An assessment of cup/disc ratio was performed at baseline and at exit. Clinically relevant changes were based on the clinical judgment of the investigator and were reported as adverse event.

There were no clinically relevant changes in cup/disc ratio reported for any patient in either treatment group.

Corneal Diameter

An assessment of corneal diameter was performed at baseline and at exit. Clinically relevant changes were based on the clinical judgment of the investigator and were reported as adverse events.

Two patients in the Azopt group were reported as having a clinically significant change in corneal diameter. Both were recorded as corneal disorder in the adverse events section.

Mean Corneal Diameter (mm) Change from Baseline to Exit Visit

Treatment	Baseline Visit	Change at Exit Visit
Azopt	11.85	0.13
Betaxon	11.46	0.06

Reviewer's Comments:
The reporting of clinically significant changes in corneal diameter was based on the clinical judgment of the investigator. There were no criteria set for determining relevant changes. The two adverse events reported were for diameters that increased by 1 mm in one of the treated eyes. The data was reviewed for all patients who had an increase of 1mm or more in corneal diameter. There were an additional three patients who had not had this event coded as an adverse event. The majority of patients that had a 1 mm increase in diameter were in the Azopt arm of the trial.

Clinically Significant Change in Corneal Diameter

Treatment	ID	Age (years)	Reported as AE	Corneal Diameter		
				Screen		Exit
Azopt	3880-221	2	Yes	OD OS	13 12	13.5 13
Azopt	3292-602	4 months	Yes	OD OS	11.75 13	12.75 13.75

Azopt	2906-6531	5	No	OD OS	11 11	12 12
Azopt	3023-9501	1 month	No	OD OS	10 10.5	11 11.5
Azopt	3880-221	2	No	OD OS	13 12	13.5 13
Azopt	3879-721	2	No	OD OS	13 13	14 13.5
Betaxon	2911-6001	6 months	No	OD OS	10 10	11 11
Betaxon	3127-2131	5	No	OD OS	9 9	10 9.5
Betaxon	3666-5121	3	No	OD OS	10 13	11.5 13

Reviewer's Comments:
There were more patients in the Azopt treatment group that had a clinically relevant increase in corneal diameter compared to the Betaxon group (19% vs. 6%). This may have been a result of Azopt not being dosed at therapeutic levels throughout the trial. These patients were not given the midday dose which may have resulted poor IOP control during this time.

Patient Alertness

Patient alertness was assessed at baseline and at each subsequent visit. The Observer's Assessment of Alertness/Sedation Scale was used to evaluate patient alertness based on 4 categories: responsiveness, speech, facial expression and eyes. Relevant changes were recorded as adverse events.

Four patients were assessed as having a clinically relevant change in alertness which included 2 patients in the Azopt group and 2 patients in the Betaxon group. Each change was attributed to normal sleepiness by the investigator and was not recorded as an adverse event. No statistically significant differences (p=0.64) were observed between the 2 treatment groups.

Cardiovascular Parameters

Cardiovascular parameters (pulse and blood pressure) were assessed at baseline and each subsequent visit. Clinically relevant changes were reported as an adverse event based upon the clinical judgment of the study investigator.

There were two (2) events involving changes in pulse rate that were coded as adverse events during the trial. There were no events related to changes in blood pressure. In addition to the changes in pulse rate reported, the database was also evaluated for changes in pulse rate ≥ 10 bpm. Changes of this magnitude are considered clinically meaningful by the Agency. There

were no clinically significant changes in pulse rate from baseline to exit between Azopt and Betaxon. Also, there were no significant changes between age groups.

There were no adverse events reported related to changes in blood pressure. The data was further assessed for clinically significant changes in systolic and diastolic blood pressure. Clinically significant changes were based on the criteria of >20 mmHg change in systolic bp or 10 mmHg change in diastolic bp. There were no significant changes between groups or between age groups for changes in systolic blood pressure. There were twice as many patients treated with Betaxon who had a clinically significant change in diastolic blood pressure. Over half (5 out of 9) of patients in the 1 week to < 1 year age groups demonstrated this change.

Adverse Events Related to Bradycardia

Patient Identification	**Age**	**Treatment**	**Event Description**
C0017.3881.0322	3	Azopt	Patient had a pulse rate of 115 bpm at baseline which decreased to 78 bpm at week 6 but normalized at week 12 (128 bpm)
C0017.3881.0333	5	Betaxon	Patient had pulse rate of 92 bpm at baseline which dropped to 80 bpm at an unscheduled visit occurring 13 days after week 2. Patient d/c the study due to inadequate control of IOP.

Descriptive Statistics for Pulse Rate (bpm) by visit Day

Baseline Visit			Week 2 Visit	Week 6 Visit	Week 12 Visit
Treatment					
AZOPT	**Mean**	106.3	106.9	102.8	98.9
	Std	20.8	20.9	19.5	20.0
	N	32	31	28	25
	Min	60	70	68	68
	Max	158	152	136	140
BETAXON	**Mean**	103.8	102.4	100.1	100.2
	Std	24.2	20.5	20.4	22.6
	N	48	45	39	39
	Min	64	60	68	60
	Max	173	150	160	167

Data carried forward from Screening to Baseline visit for 5 patients where Baseline visit data were missing or not collected.
Screening value for patient 2910.3501 is used as Baseline value, since patient was dosed at Screening visit.

Pulse Rate (BPM) Change from Baseline to Exit Visit

		Increase									Decrease							
	Total	>30 BPM		21-30 BPM		11-20 BPM		1-10 BPM		No Change		1-10 BPM		11-20 BPM		21-30 BPM		>30 BPM	
Treatment	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	**79**	**2**	**2.5**	**1**	**1.3**	**9**	**11.4**	**19**	**24.1**	**7**	**8.9**	**20**	**25.3**	**12**	**15.2**	**6**	**7.6**	**3**	**3.8**
AZOPT	**32**	**0**	**0.0**	**1**	**3.1**	**5**	**15.6**	**8**	**25.0**	**2**	**6.3**	**6**	**18.8**	**6**	**18.8**	**3**	**9.4**	**1**	**3.1**
1 week to <1 year	6	0	0.0	0	0.0	1	16.7	1	16.7	1	16.7	1	16.7	2	33.3	0	0.0	0	0.0
1 year to <2 years	5	0	0.0	0	0.0	2	40.0	1	20.0	0	0.0	1	20.0	1	20.0	0	0.0	0	0.0
2 years to <4 years	10	0	0.0	0	0.0	2	20.0	2	20.0	1	10.0	2	20.0	1	10.0	2	20.0	0	0.0
4 years to <6 years	11	0	0.0	1	9.1	0	0.0	4	36.4	0	0.0	2	18.2	2	18.2	1	9.1	1	9.1
BETAXON	**47[a]**	**2**	**4.3**	**0**	**0.0**	**4**	**8.5**	**11**	**23.4**	**5**	**10.6**	**14**	**29.8**	**6**	**12.8**	**3**	**6.4**	**2**	**4.3**
1 week to <1 year	9	0	0.0	0	0.0	0	0.0	2	22.2	1	11.1	2	22.2	1	11.1	2	22.2	1	11.1
1 year to <2 years	10	0	0.0	0	0.0	1	10.0	3	30.0	0	0.0	4	40.0	1	10.0	1	10.0	0	0.0
2 years to <4 years	16	1	6.3	0	0.0	2	12.5	3	18.8	2	12.5	4	25.0	3	18.8	0	0.0	1	6.3
4 years to <6 years	12	1	8.3	0	0.0	1	8.3	3	25.0	2	16.7	4	33.3	1	8.3	0	0.0	0	0.0

AZOPT = AZOPT (brinzolamide ophthalmic suspension), 1%
BETAXON = BETAXON (levobetaxolol hydrochloride ophthalmic suspension), 0.5%
p=0.8827 from Cochran-Mantel-Haenszel test.
[a] 1 patient had missing baseline or follow-up pulse rate data.
BPM = beats per minute
Data carried forward from Screening to Baseline visit for 5 patients where Baseline visit data were missing or not collected.
Screening value for patient 2910.3501 is used as Baseline value since patient was dosed at Screening visit. Baseline value is used as a post-dose measurement.

Descriptive Statistics For Systolic Blood Pressure (mmHg) by Visit Day

		Baseline	Week 2	Week 6	Week 12
Treatment					
Azopt	**Mean**	97.3	94.8	96.9	95.1
	Std	13.6	13.0	14.4	14.7
	N	32	31	29	25
	Min	60	70	70	70
	Max	119	116	126	135
Betaxon	**Mean**	94.7	96.9	95.2	95.3
	Std	12.9	13.4	14.4	14.7
	N	48	43	38	40
	Min	64	70	68	70
	Max	122	127	123	131

AZOPT = AZOPT (brinzolamide ophthalmic suspension), 1%
BETAXON = BETAXON (levobetaxolol hydrochloride ophthalmic suspension), 0.5%
mmHg = millimeters of mercury
Data carried forward from Screening to Baseline visit for 6 patients where Baseline visit data were missing or not collected.
Screening value for patient 2910.3501 is used as Baseline value since patient was dosed at Screening

Systolic Blood Pressure (mmHg) Change from Baseline to Exit Visit

		Increase							Decrease							
		>30 mmHg		21-30 mmHg		11-20 mmHg		1-10 mmHg		No Change		1-10 mmHg		11-20 mmHg		21-30 mmHg		>30 mmHg	
Treatment	Total N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	**79**	**2**	**2.5**	**2**	**2.5**	**7**	**8.9**	**14**	**17.7**	**13**	**16.5**	**28**	**35.4**	**9**	**11.4**	**4**	**5.1**	**0**	**0.0**
AZOPT	**32**	**0**	**0.0**	**1**	**3.1**	**2**	**6.3**	**7**	**21.9**	**7**	**21.9**	**10**	**31.3**	**3**	**9.4**	**2**	**6.3**	**0**	**0.0**
1 week to <1 year	6	0	0.0	0	0.0	1	16.7	2	33.3	0	0.0	2	33.3	0	0.0	1	16.7	0	0.0
1 year to <2 years	5	0	0.0	0	0.0	0	0.0	1	20.0	3	60.0	0	0.0	1	20.0	0	0.0	0	0.0
2 years to <4 years	10	0	0.0	1	10.0	0	0.0	2	20.0	3	30.0	3	30.0	0	0.0	1	10.0	0	0.0
4 years to <6 years	11	0	0.0	0	0.0	1	9.1	2	18.2	1	9.1	5	45.5	2	18.2	0	0.0	0	0.0
BETAXON	**47[a]**	**2**	**4.3**	**1**	**2.1**	**5**	**10.6**	**7**	**14.9**	**6**	**12.8**	**18**	**38.3**	**6**	**12.8**	**2**	**4.3**	**0**	**0.0**
1 week to <1 year	9	2	22.2	0	0.0	2	22.2	0	0.0	1	11.1	2	22.2	0	0.0	2	22.2	0	0.0
1 year to <2 years	10	0	0.0	1	10.0	1	10.0	1	10.0	1	10.0	5	50.0	1	10.0	0	0.0	0	0.0
2 years to <4 years	16	0	0.0	0	0.0	2	12.5	4	25.0	2	12.5	5	31.3	3	18.8	0	0.0	0	0.0
4 years to <6 years	12	0	0.0	0	0.0	0	0.0	2	16.7	2	16.7	6	50.0	2	16.7	0	0.0	0	0.0

AZOPT = AZOPT (brinzolamide ophthalmic suspension), 1%
BETAXON = BETAXON (levobetaxolol hydrochloride ophthalmic suspension), 0.5%
p=0.8855 from Cochran-Mantel-Haenszel test.
[a] 1 patient had missing baseline or follow-up systolic blood pressure data.
mmHg = millimeters of mercury
Data carried forward from Screening to Baseline visit for 6 patients where Baseline visit data were missing or not collected.
Screening value for patient 2910.3501 is used as Baseline value since patient was dosed at Screening visit. Baseline value is used as a post-dose measurement.

Descriptive Statistics For Diastolic Blood Pressure (mmHg) by Visit Day

Treatment		Baseline	Week 2	Week 6	Week 12
AZOPT	**Mean**	60.8	59.3	61.1	61.8
	Std	10.8	10.9	10.9	7.6
	N	32	31	28	25
	Min	40	34	39	48
	Max	93	76	84	78
BETAXON	**Mean**	59.8	59.6	58.7	59.6
	Std	11.6	9.7	10.9	11.5
	N	48	43	38	40
	Min	30	40	38	30
	Max	87	83	88	89

Data carried forward from Screening to Baseline visit for 6 patients where Baseline visit data were missing or not collected
Screening value for patient 2910.3501 is used as Baseline value, since patient was dosed at Screening visit.

Diastolic Blood Pressure (mmHg) Change from Baseline to Exit Visit

		Increase							Decrease							
		>30 mmHg		21-30 mmHg		11-20 mmHg		1-10 mmHg		No Change		1-10 mmHg		11-20 mmHg		21-30 mmHg		>30 mmHg	
Treatment	Total N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	**79**	**1**	**1.3**	**1**	**1.3**	**7**	**8.9**	**20**	**25.3**	**12**	**15.2**	**26**	**32.9**	**11**	**13.9**	**0**	**0.0**	**1**	**1.3**
AZOPT	**32**	**0**	**0.0**	**1**	**3.1**	**2**	**6.3**	**10**	**31.3**	**3**	**9.4**	**13**	**40.6**	**2**	**6.3**	**0**	**0.0**	**1**	**3.1**
1 week to <1 year	6	0	0.0	0	0.0	0	0.0	2	33.3	2	33.3	1	16.7	1	16.7	0	0.0	0	0.0
1 year to <2 years	5	0	0.0	0	0.0	1	20.0	2	40.0	0	0.0	2	40.0	0	0.0	0	0.0	0	0.0
2 years to <4 years	10	0	0.0	1	10.0	0	0.0	4	40.0	0	0.0	4	40.0	0	0.0	0	0.0	1	10.0
4 years to <6 years	11	0	0.0	0	0.0	1	9.1	2	18.2	1	9.1	6	54.5	1	9.1	0	0.0	0	0.0
BETAXON	**47[a]**	**1**	**2.1**	**0**	**0.0**	**5**	**10.6**	**10**	**21.3**	**9**	**19.1**	**13**	**27.7**	**9**	**19.1**	**0**	**0.0**	**0**	**0.0**
1 week to <1 year	9	1	11.1	0	0.0	2	22.2	1	11.1	0	0.0	3	33.3	2	22.2	0	0.0	0	0.0
1 year to <2 years	10	0	0.0	0	0.0	2	20.0	2	20.0	2	20.0	3	30.0	1	10.0	0	0.0	0	0.0
2 years to <4 years	16	0	0.0	0	0.0	1	6.3	3	18.8	4	25.0	4	25.0	4	25.0	0	0.0	0	0.0
4 years to <6 years	12	0	0.0	0	0.0	0	0.0	4	33.3	3	25.0	3	25.0	2	16.7	0	0.0	0	0.0

AZOPT = AZOPT (brinzolamide ophthalmic suspension), 1%
BETAXON = BETAXON (levobetaxolol hydrochloride ophthalmic suspension), 0.5%
p=0.7497 from Cochran-Mantel-Haenszel test.
[a] 1 patient had missing baseline or follow-up diastolic blood pressure data.
mmHg = millimeters of mercury
Data carried forward from Screening to Baseline visit for 6 patients where Baseline visit data were missing or not collected.
Screening value for patient 2910.3501 is used as Baseline value since patient was dosed at Screening visit. Baseline value is used as a post-dose measurement.

7.1.8.4 Additional analyses and explorations

N/A – additional explorations were not conducted.

7.1.9 Electrocardiograms (ECGs)

N/A – ECGs were not conducted during this study.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

N/A – ECGs were not conducted during this study.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

N/A – ECGs were not conducted during this study.

7.1.9.3 Standard analyses and explorations of ECG data

N/A – ECGs were not conducted during this study.

7.1.9.4 Additional analyses and explorations

N/A – ECGs were not conducted during this study.

7.1.10 Immunogenicity

N/A – immunogenicity testing has not been conducted in humans.

7.1.11 Human Carcinogenicity

N/A – the classes of drugs used in this trial are not known to be genotoxic when dosed topically.

7.1.12 Special Safety Studies

N/A – there were no additional special safety studies conducted for these drug products.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

N/A – there is no new information with respect to the withdrawal effects, abuse potential or overdose of Betaxon or Azopt in study C-00-17.

7.1.14 Human Reproduction and Pregnancy Data

N/A – this drug has not been tested in pregnant women

7.1.15 Assessment of Effect on Growth

N/A – height and weight data were not collected as part of this protocol

7.1.16 Overdose Experience

N/A – there is no new information with respect to the withdrawal effects, abuse potential or overdose of Betaxon or Azopt in study C-00-17.

7.1.17 Postmarketing Experience

The sponsor has conducted a review of all worldwide spontaneous postmarketing reports since product launch (April 1, 198) through January 31, 2006 for Azopt. Six (6) reports for pediatric patients, aged 3 months to 16 years were identified). Betaxon has not been marketed in any country to date.

Pediatric Postmarketing Reports

Country	Age	Sex	MeDRA Code
Brazil	3 months	F	Hypersensitivity
Germany	14 years	F	Headache, dizziness, loss of consciousness, circulatory collapse, abdominal discomfort
Germany	12 months	M	Eye irritation
France	16 years	F	Diarrhea, Drug ineffective
USA	6 years	F	Alopecia
USA	7 years	M	Pallor, Asthenia, Lethargy

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Study reports of controlled clinical studies pertinent to the claimed indication:					
StudyNo.	**Study Title / Objective**	**Study Design and Type of Control**	**Test Product(s); Dosage Regimen; Route of Administration**	**Total Number of Enrolled Subjects**	**Healthy Subjects or Diagnosis of Patients**
C-00-17	A twelve-week, multicenter, double-masked, parallel group, primary therapy study of the safety and efficacy of BETAXON™ 0.5% compared to AZOPT® 1% in pediatric patients with glaucoma or ocular hypertension	prospective, randomized, double-masked, parallel group, active-controlled	BETAXON™: 1 drop each qualifying eye, twice-daily; topical ocular AZOPT®: 1 drop each qualifying eye, twice-daily; topical ocular	total 80 (32 on AZOPT; 48 on BETAXON)	glaucoma or ocular hypertension

7.2.1.2 Demographics

Demographics by Treatment Group (Safety Population)

Total	**AZOPT (N=32)**		**BETAXON (N=48)**	
Age	N	%	N	%
1 week to <1 year	6	18.8	9	18.8
1 year to <2 years	5	15.6	10	20.8
2 years to <4 years	10	31.3	17	35.4
4 years to <6 years	11	34.4	12	25.0
Sex				
Male	15	46.9	32	66.7
Female	17	53.1	16	33.3
Ethnicity				
Hispanic or Latino	3	9.4	5	10.4
Not Hispanic or Latino	29	90.6	43	89.6

Race				
Asian	15	46.9	20	41.7
Black or African American	3	9.4	6	12.5
Caucasian	10	31.3	17	35.4
Multi-racial	1	3.1	1	2.1
Other	3	9.4	4	8.3
Iris Color				
Blue	3	9.4	9	18.8
Brown	27	84.4	34	70.8
Green	0	0	1	2.1
Grey	1	3.1	2	4.2
Hazel	1	3.1	1	2.1
No Iris[a]	0	0	1	2.1
Diagnosis				
Ocular Hypertension	1	3.1	0	0
Primary Congenital Glaucoma	17	53.1	15	31.3
Primary Glaucoma Associated with Systemic or Ocular Abnormalities	6	18.8	13	27.1
Secondary Glaucoma	8	25.0	20	41.7

Ethnicity data was not collected for patients in Indian sites (investigators 3879 3880 3881 3882 3902) and 'Not Hispanic or Latino' was assigned to those patients.
aPatient C0017.1641.9001 was diagnosed with aniridia.

Reviewer's Comment

Randomization for this trial was 1:1 between the treatment groups; however, the distribution between groups is uneven with the Betaxon group having 16 (50%) more patients then were enrolled in the Azopt group. The sponsor believed that this was due to additional sites that were added during the trial to facilitate the slower than anticipated enrollment. This was predicted to possibly increase the likelihood of uneven distribution within the age group strata and between treatment groups in a protocol amendment submitted in May 2003. The sponsor subsequently conducted an interim analysis to evaluate the balance of treatment groups and noted the uneven distribution. The decision was made to let the study run longer to meet the enrollment requirements as opposed to changing to an adaptive randomization to correct the imbalance.

Age Distribution of Enrolled Patients (Safety Population)

Age					
Country		1 week to < 1 year old	1 year to < 2 years old	2 years to < 4 years old	4 years to < 6 years old
US	Azopt	3	1	4	9
	Betaxon	6	5	9	8
India	Azopt	3	4	6	2
	Betaxon	3	5	8	4

Patients on Topical IOP-lowering Medication at Screening – ITT

Treatment	**On Topical IOP-Lowering Meds at Screening**
Azopt	22 (68.8%)
Betaxon	29 (63%)

7.2.1.3 Extent of exposure (dose/duration)

Duration of Exposure to Study Drug by Age

	0 to 15 days	**16 to 43 days**	**44 to 85 days**	**>85 days**
Treatment				
AZOPT	**3 (9.4%)**	**2 (6.3%)**	**16 (50%)**	**11 (34.4%)**
1 week to <1 year	1 (16.7%)	1 (16.7%)	4 (66.7%)	0
1 year to <2 years	0	1 (20%)	4 (80%)	0
2 years to <4 years	1 (10%)	0	5 (50%)	4 (40%)
4 years to <6 years	1 (9.1%)	0	3 (27.3%)	7 (63.6%)
BETAXON	**5 (10.4%)**	**3 (6.3%)**	**31 (64.6%)**	**9 (18.8%)**
1 week to <1 year	1 (11.1%)	0	5 (55.6%)	3 (33.3%)
1 year to <2 years	1 (10%)	1 (10%)	6 (60%)	2 (20%)
2 years to <4 years	3 (17.6%)	1 (5.9%)	10 (58.8%)	3 (17.6)
4 years to <6 years	0	1 (8.3%)	10 (83.3%)	1 (8.3)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

N/A – there were no secondary sources of information used to review this NDA amendment.

7.2.2.1 Other studies

N/A – there were no secondary sources of information used to review this NDA amendment.

7.2.2.2 Postmarketing experience

The sponsor has conducted a review of all worldwide spontaneous postmarketing reports since product launch (April 1, 198) through January 31, 2006 for Azopt. Six (6) reports for pediatric patients, aged 3 months to 16 years were identified. Betaxon has not been marketed in any country to date.

Country	**Age**	**Sex**	**MeDRA Code**
Brazil	3 months	F	Hypersensitivity
Germany	14 years	F	Headache, dizziness, loss of consciousness, circulatory collapse, abdominal discomfort
Germany	12 months	M	Eye irritation
France	16 years	F	Diarrhea, Drug ineffective
USA	6 years	F	Alopecia
USA	7 years	M	Pallor, Asthenia, Lethargy

7.2.2.3 Literature

N/A – no additional information from the literature was submitted with this NDA amendment.

7.2.3 Adequacy of Overall Clinical Experience

The study contained in this NDA amendment conformed to the requirements of the pediatric written request. However, the safety database collected during this trial is not adequate to assess the safety of Azopt when dosed as labeled. Azopt is labeled to be administered three times a day (TID). This trial was conducted with Azopt being administered twice and day (BID). It was not the intent of this pediatric program nor is there data in this amendment that would support a change in dosing for pediatric patients from the dose currently approved in adults. Therefore, when given as currently labeled which is three times a day (t.i.d), there is inadequate safety data in this amendment for labeling in pediatric patients.

The design of the trial as well as the number and types of patients studied were adequate to assess the safety of Betaxon in pediatric patients.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

N/A – there is no new pharmacology/toxicology information submitted in the amendment

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of topical ophthalmic drops (i.e. biomicroscopy, visual acuity, etc.) were adequately addressed in the design and conduct of this clinical trial.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

N/A – there is no new clinical pharmacology information submitted in the amendment.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

See section 7.2.3.

7.2.8 Assessment of Quality and Completeness of Data

See section 7.2.3.

7.2.9 Additional Submissions, Including Safety Update

N/A – there are no additional safety submissions associated with this amendment.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Drug-related adverse events for Azopt and Betaxon cannot be reliably determined in this trial due to the small database and the lack of a placebo arm. In general, the types of ocular and systemic adverse events reported in this trial are consistent with what is normally seen with most topical drops.

7.4 General Methodology

N/A – all methodological issues have been discussed throughout the review.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

N/A – there is only one study contained in this NDA supplement. There are no other pediatric studies available.

7.4.1.1 Pooled data vs. individual study data

N/A – there is only one study contained in this NDA supplement. There are no other pediatric studies available.

7.4.1.2 Combining data

N/A – there is only one study contained in this NDA supplement. There are no other pediatric studies available.

7.4.2 Explorations for Predictive Factors

Drug-related adverse events for Azopt and Betaxon cannot be reliably determined in this trial due to the small database and the lack of a placebo arm. Predictive factors related to 4 age groups were explored in this trial. In review of the 4 age groups (1 week to < 1 year, 1 year to < 2 years, 2 years to < 4 years, and 4 years to < 6 years), there were similarities in the types of adverse events seen during therapy. There were no clinically relevant differences in the adverse event profile between the data sets.

Dose, drug-disease and drug-drug interaction predictive factors were not explored.

7.4.2.1 Explorations for dose dependency for adverse findings

See section 7.4.2

7.4.2.2 Explorations for time dependency for adverse findings

See section 7.4.2

7.4.2.3 Explorations for drug-demographic interactions

See section 7.4.2

7.4.2.4 Explorations for drug-disease interactions

See section 7.4.2

7.4.2.5 Explorations for drug-drug interactions

See section 7.4.2

7.4.3 Causality Determination

Drug-related adverse events for Azopt and Betaxon cannot be reliably determined in this trial due to the small database and the lack of a placebo arm. In general, the types of ocular adverse events reported in this trial are consistent with what is normally seen with most topical drops.

8 ADDITIONAL CLINICAL ISSUES

N/A – there are no additional clinical issues. All issues have been adequately addressed in the original NDA reviews and other sections of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

- *The study in this NDA amendment is adequate to establish the safety of the use of levobetaxolol hydrochloride ophthalmic suspension in the pediatric population.*
- *The type of adverse events seen in patients treated with levobetaxolol are consistent with those seen in the adult population.*
- *There were no clinically relevant differences in the adverse event profile between the age group strata that were studied (i.e. 1 week to < 1 year, 1 year to < 2 years, 2 years to < 4 years, and 4 years to < 6 years*
- *There was inadequate safety data gathered in this trial to support the use of Azopt in the pediatric population.*

9.2 Recommendation on Regulatory Action

NDA 21-114/SE8 (b) (4) *labeling revisions are made consistent with the recommendations listed in this review. The clinical study contained in this supplement* (b) (4) *of levobetaxolol hydrochloride ophthalmic suspension in the pediatric population.* (b) (4)

NDA (b) (4) *816/SE8* (b) (4) *labeling describing the increased corneal diameters and minimal IOP lowering observed with b.i.d dosing. The clinical data generated in the amendment is not sufficient to determine the safety of brinzolamide ophthalmic suspension in the pediatric population.*

9.3 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions

9.3.1 Risk Management Activity

There are no recommended risk management activities.

9.3.2 Required Phase 4 Commitments

There are no recommendations for Phase 4 commitments.

9.3.3 Other Phase 4 Requests

There are no recommendations for Phase 4 commitments.

9.4 Labeling Review

Changes have been made to the Azopt and Betaxon labels. There is no proposed change to the indication section. The Pediatric Use and Adverse Events sections of the Betaxon label have been updated to reflect the results of the pediatric trial. The Pediatric Use section of the Azopt label has been revised. No changes were made to the Adverse Event section due to the lack of information gained from the trial.

9.5 Comments to Applicant

The sponsor should be informed that due to the inadequate dosing of Azopt in the pediatric trial; there was not enough information gained to make definitive statements in the label about the use of this drug in the pediatric population when dosed t.i.d.

10 APPENDICES

10.1 Line-by-Line Labeling Review

(b) (4)

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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8/24/2006 01:56:14 PM
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