CLINICAL REVIEW

Medical Officer's Review of NDA 20-408
Pediatric Supplement

Proprietary Name:	**Trusopt Ophthalmic Solution 2%**
Established Name:	**dorzolamide HCL ophthalmic solution**
Sponsor:	**Merck & Co. Inc** **BLA-20, P.O. Box 2** **West Point, PA 19486**
NDA Supplement:	**SE5**

(b) (4)

[redacted]

Date of Submission:	October 16, 2003
Date of Review:	February 25, 2004

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Clinical Review for NDA 20-408 Pediatric Supplement

Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 20-408 /SE5-033 is recommended for approval after labeling revisions are made consistent with the recommendations listed in this review. The clinical study contained in this supplement supports the use of dorzolamide 2% in the pediatric population. The benefits of using this drug product outweigh the risks in the treatment of elevated intraocular pressure in pediatric patients.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

(b) (4)

There are no recommendations for phase 4 studies.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Dorzolamide HCL was approved in 1994 as the first topical carbonic anhydrase inhibitor for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or glaucoma. To date the safety and effectiveness of this product has not been established in the pediatric population.

Currently, the only approved drug for the treatment of elevated IOP in the pediatric population is brimonidine tartrate ophthalmic solution. This drug product is labeled for pediatric patients over the age of 2 years old.

A pediatric written request for dorzolamide 2% was issued by the Agency in 1999 with subsequent amendments in 2000 and 2002. The sponsor has conducted a 12-week multicenter, randomized, masked, active-control trial comparing

dorzolamide 2% to timolol GFS in response to this written request. The primary objective of the written request and submitted trial was to obtain data on the safety and clinical response of dorzolamide 2% in the pediatric population.

B. Efficacy

The clinical response data contained in this supplement demonstrates that dorzolamide 2% effectively lowers IOP in the pediatric population. IOP is lowered approximately 7-9mmHg in this population with a baseline IOP of approximately 30 mmHg.

C. Safety

Dorzolamide 2% is safe for use in the pediatric population below the age of 6 years old. Overall, less than 2.5% of patients in the dorzolamide 2% treatment group discontinued from the study due to an adverse event. The safety profile of dorzolamide is similar to that seen in adults. The types of adverse events seen are those commonly expected with topical ophthalmic medications.

D. Dosing

Dosing for this pediatric trial was based on the currently labeled dosing frequency for adult patients. No further dose ranging was warranted. The currently labeled dosing level and frequency is safe in the pediatric population.

E. Special Populations

The sponsor has adequately addressed the safety and clinical response of this drug product in two age cohorts The two age cohorts analyzed were: "patients < 2 years old" and "patients ≥ 2 years but <6 years old". The effects of gender, race, age and iris color were analyzed during the review of the original NDA. Gender effects were not analyzed in this pediatric supplement because the study population is not large enough to perform this analysis and no effects were found in the original NDA submission. There is no additional data needed in other populations for this drug product. Safety and efficacy have been adequately characterized in the target populations.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Proprietary Name :	Trusopt Ophthalmic Solution
Established Name:	dorzolamide HCl ophthalmic solution
Sponsor:	Merck & Co., Inc. BLA-20, P.O. Box 4 West Point PA 19486
NDA Supplement:	SE5
Pharmacologic Category:	carbonic anhydrase inhibitor
Dosage Form and Route of Administration:	Ophthalmic solution for topical ocular administration

(b) (4)

B. State of Armamentarium for Indication(s)

Dorzolamide HCL was approved in 1994 as the first topical carbonic anhydrase inhibitor for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or glaucoma. To date the safety and effectiveness of this product has not been established in the pediatric population.

Currently, the only approved drug for the treatment of elevated IOP in the pediatric population is brimonidine tartrate ophthalmic solution. This drug product is labeled for pediatric patients over the age of 2 years old.

C. Important Milestones in Product Development

Milestones leading up to this pediatric efficacy supplement submission:

12/9/94 – Original NDA approved
6/24/99 – Original pediatric written request issued by the Agency
5/19/00 – Amended written request issued to revise the age group enrollment criteria.

2/12/02 – Amended written request issued to revise the timeframe for submission of pediatric studies.

D. Other Relevant Information

As of July 7, 2003, dorzolamide HCL has received marketing approval for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma in approximately 69 countries. This product has not been withdrawn from the market in any country as of this date.

E. Important Issues with Pharmacologically Related Agents

There are no safety concerns associated with other topical ophthalmic agents in this pharmacologic class.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There were no new consultant reviews required for this efficacy supplement. Full reviews for all disciplines were completed during the review of the original NDA.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

A full pharmacokinetics review was completed for this product in the original NDA review. No new pharmacokinetic data is contained in this pediatric supplement.

B. Pharmacodynamics

No new pharmacodynamic data is contained in this pediatric supplement.

IV. Description of Clinical Data and Sources

A. Overall Data

This pediatric supplement includes one study (P1001C1) that was conducted at 22 U.S. sites and 13 international sites. This material is contained in NDA 20-408/SE5-033 Volume 1. The materials were submitted in hard copy and electronic formats.

B. Tables Listing the Clinical Trials

Protocol Number	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	Demographics	Total Subjects
P100C1	Multicenter, double-masked, randomized, active-controlled	12 weeks	Pediatric patients with glaucoma or ocular hypertension	Trusopt 2% Timolol GFS 0.25% Timolol GFS 0.5%	TID QD QD	Age (1 month – 6 years) 106 males 78 females	184

C. Postmarketing Experience

The existing postmarketing data available in the adult population has been reviewed by the division. The events reported are consistent with the events reported in the clinical study included in this efficacy supplement.

The sponsor searched their own Worldwide Adverse Experience System (WAES) database for reports of adverse experiences with dorzolamide hydrochloride in patients aged <6 years of age. A total of 8 reports were identified. There were 3 reports of local nonserious adverse experiences; skin irritation, ocular burning and corneal clouding. The corneal clouding resolved with the discontinuation of dorzolamide and did not reappear when dorzolamide was restarted.

Two (2) reports described serious adverse experiences that persisted after dorzolamide was discontinued (metabolic acidosis and respiratory acidosis).

Two (2) cases of presumed dorzolamide overdose were received. One patient developed somnolence that resolved within hours. In another patient, rash, red eye, and dehydration occurred after 8 days of treatment.

D. Literature Review

The sponsor has reviewed the medical literature for adverse events in patients

under the age of six. One report of lethargy, hypotension, and hypothermia in a 4 week old patient was published in the medical literature. The patient was taking dorzolamide, betaxolol and brimonidine drops. This report attributed the adverse events to the use of brimonidine tartrate.

V. Clinical Review Methods

A. How the Review was Conducted

The primary objective of this review was to determine the safety profile of dorzolamide HCL in the pediatric population. Clinical response data was also analyzed; however, the division believes that efficacy for this drug product can be reliably extrapolated from the adult population. Safety was assessed by evaluating the adverse event profile, discontinuation data and the drug specific safety concerns addressed in the pediatric written request. This included vital signs, pulse, blood pressure, alertness, intraocular pressure, visual acuity, dilated ophthalmoscopy and corneal diameter.

B. Overview of Materials Consulted in Review

This review was based on the review of a single trial (P100C1) submitted by the sponsor in both paper and electronic format.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits were not conducted for this efficacy supplement. The data was reviewed internally for consistency with other safety and efficacy data available for this drug product.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

There is no evidence to indicate that this trial was not conducted in accordance with accepted ethical standards. The sponsor attests that the study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

E. Evaluation of Financial Disclosure

The sponsor has certified that they have not entered into any financial arrangement with the clinical investigators of this trial whereby the value of compensation to the investigator could be affected by the outcome of the study.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The clinical response data contained in this supplement demonstrates that dorzolamide 2% effectively lowers IOP in the pediatric population. IOP is lowered approximately 7-9mmHg in this population.

B. General Approach to Review of the Efficacy of the Drug

The purpose of this submission was to determine the safety profile of dorzolamide HCL in the pediatric population. It is the division's view that efficacy for this product can be reliably extrapolated from the existing adult database; therefore, this trial was not designed to establish efficacy. Clinical response data was collected and is presented below along with the study design.

C. Detailed Review of Trials by Indication

Title: Three-Month, Double-Masked, Active Treatment Controlled, Multicenter Study of 2% Dorzolamide T.I.D. and of Timolol Maleate in Gel-Forming Solution Q.D. in Pediatric Patients Age <6 Years With Elevated Intraocular Pressure or Glaucoma

Objective:

Primary

To document an acceptable safety profile for initial therapy with dorzolamide 2% t.i.d. taken for up to 3 months in patients <6 years of age with elevated IOP or glaucoma.

The primary safety endpoint for each treatment group will be the proportion of patients who discontinue therapy due to a drug-related adverse experience prior to completing 3 months of therapy.

Secondary

To characterize the IOP-lowering effect of dorzolamide 2% t.i.d., and the need for additional therapy in patients <6 years of age with elevated IOP or glaucoma. To characterize the effect of dorzolamide 2% t.i.d. on total CO2 in patients <6 years of age with elevated IOP or glaucoma.

Study Design: This was a 3-month, double-masked, active-treatment-controlled, multicenter study to investigate the safety and ocular hypotensive effect of dorzolamide 2% t.i.d. in pediatric glaucoma patients younger than 6 years. Timolol maleate gel-forming solution (timolol GFS) once daily (q.d.) was the active treatment control. Patients were randomized 2:1, dorzolamide to timolol GFS therapy. If IOP was inadequately controlled on monotherapy, a change was made to open-label concomitant therapy of dorzolamide 2% t.i.d. and timolol GFS 0.25% q.d. (for patients <2 years of age) or combination therapy of dorzolamide 2%/ timolol 0.5% twice daily (b.i.d.) (for patients ≥2 years but <6 years of age).

Study Medications:

Dosage	**Formulation Nos.**
Dorzolamide 2% topical	E-9943, E-9990
Dorzolamide placebo topical	E-9887, E-9991
Timolol GFS 0.25% topical	E-9963, E-9994, E-10432
Timolol GFS 0.5% topical	E-9353, E-9995, E-10209
Dorzolamide 2%/Timolol 0.5% topical	E-9817, E-9993

Clinical Sites

Site No.	**Investigator**	**Country**	**Age Cohort < 2 years**		**Age Cohort ≥ 2 years but < 6 years**	
			Dorzolamide 2% (N=56)	**Timolol GFS 0.25% (N=27)**	**Dorzolamide 2% (N=66)**	**Timolol GFS 0.5% (N=35)**
100004	Coats, David K.	U.S.	1	0	2	2
100005	Gandham, Sai B.	U.S.	1	0	0	1
100009	Lueder, Gregg T.	U.S.	3	2	2	1
100010	Medow, Norman B.	U.S.	0	1	2	0
100011	Mills, Monte D.	U.S.	1	0	2	2
100012	Plager, David A.	U.S.	3	1	5	2
100013	Samples, John R.	U.S.	0	0	1	0
100014	Scher, Colin Allen	U.S.	0	0	0	1
100015	Summers, C. Gail	U.S.	3	1	2	1
100016	Wilson, M. Edward	U.S.	1	0	3	1
100017	Zwaan, Johan T.	U.S.	3	2	1	1
100018	May, Michael J.	U.S.	1	0	0	0
100019	Godfrey, David G.	U.S.	0	0	2	1
100022	Wright, Kenneth W.	U.S.	4	2	0	0
100023	Kubacki, Joseph J.	U.S.	0	0	1	0
100027	Song, Jonathan C.	U.S.	3	3	4	2
125001	Aquino, Norman M.	Philippines	5	2	4	2
125002	Hurtado, Maria Isabel	Colombia	0	0	2	1
125004	Arango, Santiago	Colombia	8	3	6	4
125005	Galvez, Flor	Peru	2	1	2	1
125006	Debess, Pedro	Venezuela	0	1	1	0
125007	Spagarino, Manuela	Venezuela	2	0	1	1
125009	Rodriguez, Manuel	Mexico	1	0	2	1

Site No.	Investigator	Country	Age Cohort < 2 years		Age Cohort ≥ 2 years but < 6 years	
			Dorzolamide 2% (N=56)	Timolol GFS 0.25% (N=27)	Dorzolamide 2% (N=66)	Timolol GFS 0.5% (N=35)
125010	Hermes, Federico	Guatemala	2	1	4	2
125011	Czajkowski, Janusz	Poland	1	0	1	1
125013	El Sada, Mohamed	Egypt	8	4	8	4
125014	Gabric, Nikica	Croatia	0	1	1	0
125015	Filous, Ales	Czech Republic	2	2	7	1
125016	Rehurek, Jaroslav	Czech Republic	1	0	0	2

Reviewer's Comments:
*The agency prefers patients to be randomized with at least ten patients per arm per center in multicenter trials so that interaction between centers can be evaluated***.**

Study Population – Inclusion and Exclusion Criteria

Inclusion Criteria
Gender
Male or female.
Age
Patients younger than 6 years (approximately one half of all patients were to be <2 years of age and one half of all patients were to be ≥2 years but <6 years of age). Infants were to be at least 36 weeks gestational age, and at least 1 week of age.

Admission Criteria
1. Pediatric glaucoma or glaucoma suspect with IOP ≥22 mm Hg in one or both eyes.
2. Discontinuation of topical or systemic ocular hypotensive medication for at least 24 hours prior to Study Day 1; a more complete washout of ocular hypotensive medication (according to the washout schedule below) was at the discretion of the investigator.
   - 21 days for topical β-blockers, α-agonists, topical prostaglandin analogues, oral or topical CAIs
   - 7 days for epinephrine or dipivefrin
   - 72 hours for pilocarpine, carbachol, or echothiophate iodide
3. Complete physical examination within 3 months of study start.

Exclusion Criteria

Ocular
1. Currently wearing continuous-wear contact lenses.

2. History or evidence of goniotomy or trabeculotomy within 1 month of study start, filtration or implant surgery within 3 months of study start, or cyclodestructive surgery within 3 months of study start. Patients may have had intraocular laser surgery up to 3 months prior to study start.
3. History or evidence of significant ocular trauma within 3 months prior to study start.
4. Evidence of acute or recent ocular inflammation and/or infection within 1 month prior to study start.
5. Chronic conjunctivitis, chronic keratitis, or lacrimal deficiency.

Pharmacologic

1. Concomitant systemic or topical nonocular medication known to affect intraocular pressure.
2. Participation in a study involving an investigational drug within 4 weeks prior to study start.

General/Systemic

1. History of hypersensitivity to any components of dorzolamide or timolol GFS ophthalmic solutions; known severe or serious hypersensitivity to sulfonamides.
2. Any contraindication to the use of timolol GFS ophthalmic solutions.
3. History or evidence of impaired renal function.

Safety Assessment

The primary study objective was to document an acceptable safety profile for initial therapy with dorzolamide 2% taken for up to 3 months in patients 1 week to <2 years and in patients ≥2 years but <6 years of age. The primary measure of safety for each group was the proportion of patients who discontinued therapy due to a drug-related adverse experience prior to completing 3 months of therapy.

Safety Measures Assessed:

Ocular Examinations (visual acuity, biomicroscopy, dilated fundus exam)
Vital Signs (blood pressure, pulse and respiratory rate)
Alertness Assessment
Laboratory test (CO_2)
Physical Examination
Adverse Experience monitoring

Efficacy Assessment

The efficacy objective of this 3-month study was to characterize the IOP lowering effect of dorzolamide 2% t.i.d., and the need for additional therapy. IOP was measured on Study Day 1, and Weeks 1, 4, and 12, and on Weeks 2 or 5 if a change in therapy was implemented.

Study Schedule

Procedure	Prestudy Screening Day –21 to –1	Study Day 1, Weeks 1, 4, 12[#]	Weeks 2 or 5 if change in therapy was made	Poststudy visit
Ocular and medical history	X			
Physical examination	X[+]			X
Alertness assessment	X	X	X	
Visual acuity	X	X	X	
External and anterior ocular examination	X	X	X	
Intraocular pressure	X	X	X	
Corneal diameter measurements*		X		
Lens and ophthalmoscopy	X			X
Patient Report Card		X	X	X
Vital signs	X	X	X	
Total CO_2		X[@]		
Adverse experience monitoring		X	X	X

[#] Week 12 and Poststudy examinations were to be completed for patients who discontinued prior to Week 12
[+] A complete physical examination by a pediatrician, if not already performed within 3 months of study start.
[*] Corneal diameter measurements were performed on Study Day 1 and Week 12.
[@] Total CO2 levels were to be measured at Study Day 1 and Week 12.

Subject Disposition and Demographics

Patient Disposition (Age Cohort < 2 years)

	Dorzolamide 2%	Timolol GFS 0.25%
Entered (Randomized)	56	27
Masked Monotherapy Phase		
Completed	28	16
Discontinued	6	3
Patient switched to open-label concomitant therapy	22	8
Open-label Concomitant therapy Phase		
Completed	15	7
Discontinued	7	1

Patient Disposition (Age Cohort≥2 years but 6 years)

	Dorzolamide 2%	Timolol GFS 0.25%
Entered (Randomized)	66	35
Masked Monotherapy Phase		
Completed	41	21
Discontinued	6	3
Patient switched to open-label concomitant therapy	19	11
Open-label Concomitant therapy Phase		
Completed	12	7
Discontinued	7	4

Reviewer's Comments:
Approximately 30-40% of patients in each treatment group for both age cohorts were switched to concomitant therapy due to lack of IOP control on monotherapy.

Discontinued Patients and Reason

Patient	Age	Treatment	Reason	Days in Study
2003	2	Dorzolamide 2%	IOP not controlled - surgery	62
2009	7 months	Dorzolamide 2%	IOP not controlled - surgery	39
2031	11 months	Dorzolamide 2%	IOP not controlled - surgery	6
2033	6 months	Dorzolamide 2%	IOP not controlled - surgery	14
2034	1 month	Dorzolamide 2%	IOP not controlled - surgery	21
2044	1	Dorzolamide 2%	IOP not controlled - medication	78
2049	1	Dorzolamide 2%	bradycardia	113
2053	4 months	Dorzolamide 2%	IOP not controlled – surgery	28
2058	2 months	Dorzolamide 2%	IOP not controlled – surgery	3
2079	1	Dorzolamide 2%	IOP not controlled – surgery	4
2094	3 months	Dorzolamide 2%	Lost to follow-up	35
2182	4	Dorzolamide 2%	IOP not controlled – surgery	50
2187	2	Dorzolamide 2%	IOP not controlled – surgery	73
2212	4	Dorzolamide 2%	IOP not controlled – surgery	49
2243	3	Dorzolamide 2%	IOP not controlled – surgery	42
2331	6 months	Dorzolamide 2%	Withdrew consent	89
2342	2 months	Dorzolamide 2%	IOP not controlled – surgery	119
2351	6 months	Dorzolamide 2%	Withdrew consent	17
2355	1	Dorzolamide 2%	IOP not controlled – surgery	15
2385	1	Dorzolamide 2%	IOP not controlled – surgery	16
2389	2 months	Dorzolamide 2%	IOP not controlled – medication	16
2508	5	Dorzolamide 2%	IOP not controlled – surgery	29
2527	4	Dorzolamide 2%	Loss of appetite, malaise, eye pain/redness	61
2535	4	Dorzolamide 2%	Withdrew consent	14
2541	4	Dorzolamide 2%	IOP not controlled – medication	51
2554	2	Dorzolamide 2%	Eye burning/itching	97
2557	2	Dorzolamide 2%	IOP not controlled – medication	15
2580	4	Dorzolamide 2%	IOP not controlled – surgery	16

Patient	Age	Treatment	Reason	Days in Study
2585	5	Dorzolamide 2%	IOP not controlled – surgery	32
2002	6 months	Timolol GFS 0.25%	IOP not controlled – medication	9
2032	2 months	Timolol GFS 0.25%	Corneal diameter/IOP decrease	111
2334	1	Timolol GFS 0.25%	bronchospasm	19
2341	1	Timolol GFS 0.25%	IOP not controlled – surgery	85
2381	1	Timolol GFS 0.25%	IOP not controlled – surgery	16
2161	5	Timolol GFS 0.5%	IOP not controlled – surgery	36
2181	4	Timolol GFS 0.5%	Glaucomatous cupping	50
2189	3	Timolol GFS 0.5%	Eye redness	8
2213	2	Timolol GFS 0.5%	IOP not controlled – surgery	19
2244	4	Timolol GFS 0.5%	IOP not controlled – medication	29
2551	5	Timolol GFS 0.5%	IOP not controlled – medication/completed	88
2555	5	Timolol GFS 0.5%	IOP not controlled – surgery	36
2565	4	Timolol GFS 0.5%	Withdrew consent	37

Reviewer's Comment:
The majority of patients, 30 (73%), discontinued the study due to poor IOP control. Seventy-three (73%) of these patients were in the dorzolamide treatment group versus 8% in the timolol group.

Baseline Patient Characteristics by Treatment Group (Age Cohort < 2 years)

	Dorzolamide 2% (N=56)	Timolol GFS 0.25% (N=27)
Gender		
Male	35 (62.5%)	20 (74.1%)
Female	21 (37.5%)	7 (25.9%)
Race		
Asian	5 (8.9%)	2 (7.4%)
Bi-racial	1 (1.8%)	0
Black	4 (7.1%)	2 (7.4%)
Caucasian	16 (28.6%)	7 (25.9%)
Egyptian	8 (14.3%)	4 (14.8%)
Hispanic	22 (39.3%)	11 (40.7%)
Hispanic/White	0	1 (3.7%)
Age (months)		
Mean	9.7	11.5
Range	1 to 23	0.25 to 22
Iris Color		
Blue	10 (17.9%)	8 (29.6%)
Brown	20 (35.7%)	9 (33.3%)
Dark brown	22 (39.3%)	8 (29.6%)
Hazel	1 (1.8%)	0
Other*	3 (5.4%)	2 (7.4%)
Baseline IOP (mmHg) – Worse Eye		
Mean	32.6	29.9
range	17.3 to 64	14 to 48.7

*other = aniridia or unable to evaluate

Reviewer's Comment:

The treatment groups were well balanced at baseline for both age cohorts.

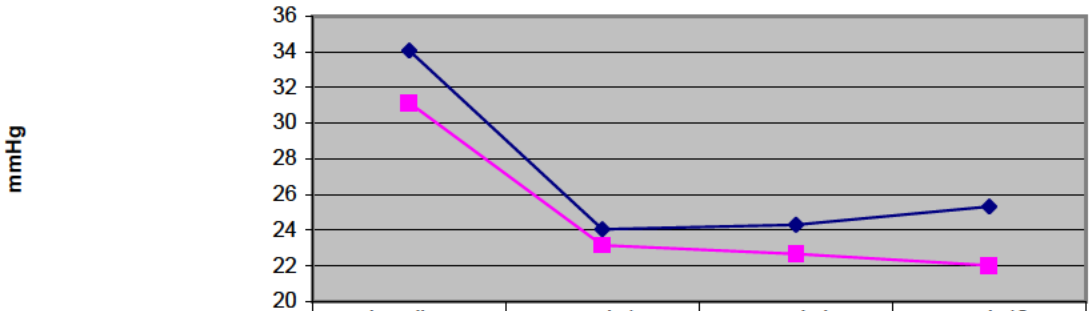
Baseline Patient Characteristics by Treatment Group (Age Cohort ≥2 years but < 6 years)

	Dorzolamide 2% (N=56)	Timolol GFS 0.25% (N=27)
Gender		
Male	33 (50%)	18 (51.4%)
Female	33 (50%)	17 (48.6%)
Race		
Asian	5 (7.6%)	2 (5.7%)
Black	4 (6.1%)	1 (2.9%)
Caucasian	23 (34.8%)	14 (40.0%)
Egyptian	8 (12.1%)	4 (11.4%)
Hispanic	26 (39.4%)	12 (34.3%)
Indian	0	2 (5.7%)
Age (years)		
Mean	3.4	3.5
Range	2 to 6	2 to 6
Iris Color		
Blue	9 (13.6%)	7 (20%)
Brown	19 (28.8%)	7 (20%)
Dark brown	26 (39.4%)	15 (42.9%)
Green	1 (1.5%)	0
Hazel	6 (9.1%)	3 (8.6%)
Other*	5 (7.6%)	3 (8.6%)
Baseline IOP (mmHg) – Worse Eye		
Mean	28.7	30.3
range	18 - 55	22 – 45.5

*other = aniridia or unable to evaluate

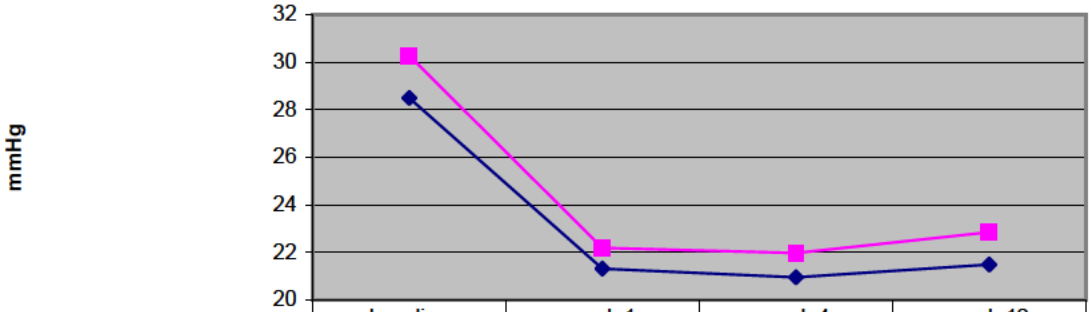
Clinical Response Analyses

Mean IOP (Age Cohort < 2 Years - Monotherapy)



	baseline	week 1	week 4	week 12
dorzolamide HCL 2%	34.07	24.05	24.3	25.33
timolol GFS 0.25%	31.15	23.15	22.67	22.03

Mean IOP (Age Cohort >= 2 Years but < 6 years - Monotherapy)

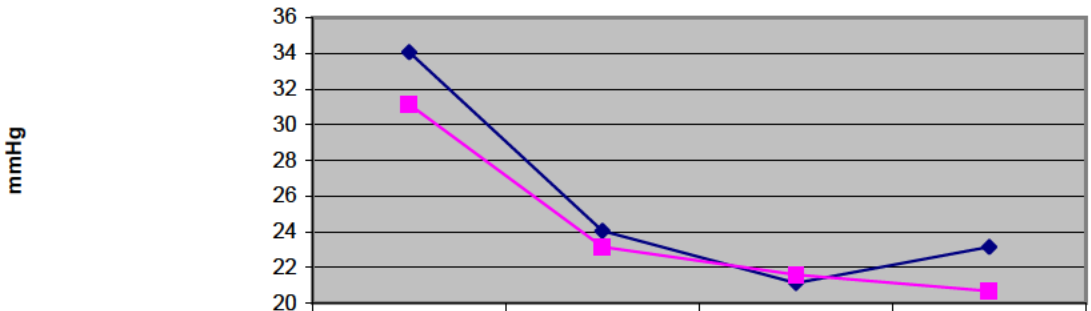


	baseline	week 1	week 4	week 12
dorzolamide HCL 2%	28.49	21.32	20.96	21.49
timolol GFS 0.5%	30.26	22.19	21.97	22.85

Reviewers Comments:

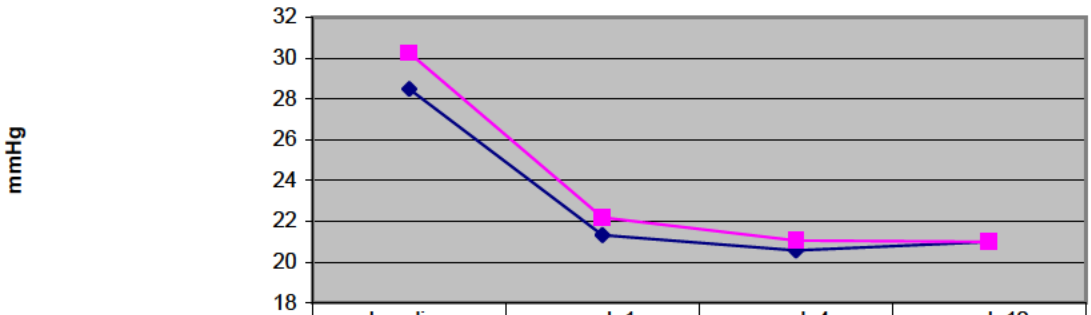
Dorzolamide 2% and timolol GFS have similar IOP lowering ability in the pediatric population. Both drugs lower IOP of approximately 7-9mmHg. The response was similar in both the age groups (i.e. < 2 and ≥ 2 but < 6 years of age).

Mean IOP (Age Cohort < 2 Years - Overall)



	baseline	week 1	week 4	week 12
dorzolamide HCL 2%	34.07	24.05	21.12	23.15
timolol GFS 0.25%	31.15	23.15	21.6	20.68

Mean IOP (Age Cohort >= 2 Years but < 6 Years - Overall)



	baseline	week 1	week 4	week 12
dorzolamide HCL 2%	28.49	21.32	20.57	20.99
timolol GFS 0.5%	30.26	22.19	21.06	21

D. Efficacy Conclusions

It was the division's view that efficacy for this product could be reliably extrapolated from the existing adult database. The clinical response data contained in this study confirms that dorzolamide 2% effectively lowers IOP in pediatric patients under the age of 6.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Dorzolamide 2% is safe for use in the pediatric population below the age of 6 years old. Overall, less than 2.5% of patients in the dorzolamide 2% treatment group discontinued from the study due to an adverse event. The safety profile of dorzolamide is similar to that seen in adults. The types of adverse events seen are those commonly expected with topical ophthalmic medications.

B. Description of Patient Exposure

Age Cohort <2 Years

Monotherapy Phase
Twenty-nine (29) patients took dorzolamide 2% BID for at least 61 days. Sixteen (16) patients took timolol GFS 0.25% QD for at least 61 days.

Concomitant Therapy Phase
Twenty-one (21) patients took dorzolamide 2% TID and timolol GFS 0.25% QD for at least 41 days of the study.

Age Cohort ≥2 Years but <6 Years

Monotherapy Phase
Forty-two (42) patients took dorzolamide 2% TID for at least 61 days. Twenty one (21) patients took timolol GFS 0.5% QD for at least 61 days.

Combination Therapy Phase
Eighteen (18) patients took the dorzolamide 2%/timolol 0.5% combination BID for at least 51 days.

C. Methods and Specific Findings of Safety Review

The primary objective of study P100C1 was to document an acceptable safety profile for initial therapy with dorzolamide 2% taken for up to 3 months in patients 1 week to <2 years and in patients ≥ 2 years but < 6 years of age. The primary measure of safety for each group was the proportion of patients who discontinued therapy due to a drug-related adverse experience prior to completing 3 months of therapy.

Primary Safety Variable

In the age cohort <2 years, 1 patient (1.79%) of 56 initially randomized to the dorzolamide 2% treatment group discontinued study therapy due to a drug-related adverse event. None of the 27 patients initially randomized to the timolol GFS 0.25% treatment group discontinued study therapy due to a drug-related adverse experience.

The drug related adverse event was experienced by a patient (AN 2049) in the dorzolamide 2% group who switched to open-label concomitant therapy (dorzolamide/timolol) on study day 8 because of inadequate IOP control. A drug-related serious adverse experience of bradycardia was observed on study day 24. Timolol administration was discontinued for the patient on the same day that the bradycardia was noted, but the patient was continued on dorzolamide 2% monotherapy. The bradycardia resolved after 8 days, and the subject continued on dorzolamide 2% monotherapy.

Discontinuations Due to Adverse Experiences (Age Cohort < 2 years)

	Dorzolamide 2% (N=56)	**Timolol GFS 0.25% (N=27)**
Masked Monotherapy Phase		
Discontinued due to any drug-related adverse experience[+]	0	0
Discontinued due to any adverse event	0	2 (7.4%)
Open-Label Concomitant Therapy Phase	N=22	N=9
Discontinued due to any drug-related adverse experience[+]	1 (4.6%)	0
Discontinued due to any adverse event	1 (4.6%)	0

[+] determined by the investigator to possibly, probably, or definitely drug related.

In the age cohort ≥2 years but <6 years, 2 patients (3.03%) of 66 initially randomized to the dorzolamide 2% treatment group discontinued study therapy due to a drug-related adverse experience. Both of these patients discontinued due to at least one of the following adverse experiences: eye pain, ocular injection, burning/stinging eye, or eye itching associated with dorzolamide 2% monotherapy treatment. One (2.86%) of the 35 patients initially randomized to the timolol GFS 0.25% treatment group discontinued study therapy due to the drug-related adverse experience of ocular injection.

Discontinuations Due to Adverse Experiences (Age Cohort ≥ 2 years but < 6 years)

	Dorzolamide 2% (N=66)	**Timolol GFS 0.25% (N=35)**
	N (%)	N (%)
Masked Monotherapy Phase		
Discontinued due to any drug-related adverse experience[+]	2 (3%)	1 (3%)
Discontinued due to any adverse event	2 (3%)	2 (5.7%)
Open-Label Concomitant Therapy Phase	N=19	N=11
Discontinued due to any drug-related adverse experience[+]	0	0
Discontinued due to any adverse event	0	0

[+] determined by the investigator to possibly, probably, or definitely drug related.

Reviewer's comments:
Overall, less than 2.5% of patients in the dorzolamide 2% treatment group discontinued from the study due to an adverse event compared to the discontinuation rate in the timolol GFS group of 6.5%.

Adverse Events Leading to Discontinuation

Patient	**Treatment**	**Age**	**Reason**	**Day of Onset**	**Days in Study**	**Phase**
02049	Dorzolamide 2%	1 year	Bradycardia	24	113	Concomitant
02527	Dorzolamide 2%	4 years	Loss of appetite, malaise, eye pain, eye redness	32	61	Monotherapy
02554	Dorzolamide 2%	2 years	Eye burning, eye itching	1	97	Monotherapy
02032	Timolol GFS 0.25%	2 months	Decrease corneal diameter, decreased IOP	31	111	Monotherapy
02334	Timolol GFS 0.25%	1 year	Bronchospasm	17	19	Monotherapy
02181	Timolol GFS 0.5%	4 years	Glaucomatous cupping	49	50	Monotherapy
02189	Timolol GFS 0.5%	3 years	Eye redness	4	8	Monotherapy

Clinical Adverse Event Experiences

Adverse Events in Age Cohort <2 Years

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence > 0 % in One or More Treatment Groups) by Body System (Age Cohort <2 Years)

	Masked Monotherapy Phase				Open-label Concomitant Therapy Phase Dorzolamide 2% + Timolol GFS 0.25% (N=31)			
	Dorzolamide 2% (N=56)		Timolol GFS 0.25% (N=27)		Dorzolamide 2% (m=22)		Timolol GFS 0.25% (m=9)	
	n	(%)	n	(%)	n	(%)‡	n	(%)‡
Patients with one or more adverse experiences	42	(75.0)	17	(63.0)	16	(72.7)	7	(77.8)
Patients with no adverse experience	14	(25.0)	10	(37.0)	6	(27.3)	2	(22.2)
Body as a Whole/Site Unspecified	**18**	**(32.1)**	**5**	**(18.5)**	**1**	**(4.5)**	**3**	**(33.3)**
Infection, viral	1	(1.8)	0	0	0	0	0	0
Infection, RSV	1	(1.8)	0	0	0	0	0	0
Fever	14	(25.0)	5	(18.5)	1	(4.5)	3	(33.3)
Hyperemia	1	(1.8)	0	0	0	0	0	0
Pain, abdominal	1	(1.8)	0	0	0	0	0	0
Failure to thrive	1	(1.8)	0	0	0	0	0	0
Pain, postoperative	1	(1.8)	0	0	0	0	0	0
Cardiovascular System	**0**	**(0)**	**0**	**(0)**	**1**	**(4.5)**	**0**	**(0)**
Bradycardia	0	(0)	0	(0)	1	(4.5)	0	(0)
Digestive System	**13**	**(23.2)**	**2**	**(7.4)**	**5**	**(22.7)**	**2**	**(22.2)**
Anorexia	3	(5.4)	0	(0)	0	(0)	0	(0)
Constipation	2	(3.6)	0	(0)	0	(0)	1	(11.1)
Diarrhea	10	(17.9)	1	(3.7)	3	(13.6)	1	(11.1)
Vomiting	3	(5.4)	0	(0)	2	(9.1)	0	(0)
Enterocolitis, pseudomembranous	0	(0)	0	(0)	1	(4.5)	0	(0)
Gastroenteritis	1	(1.8)	1	(3.7)	1	(4.5)	0	(0)
Stomatitis	0	(0)	0	(0)	1	(4.5)	0	(0)
Ulcer, mouth	1	(1.8)	0	0	0	0	0	0
Pain, dental	1	(1.8)	0	0	0	0	0	0
Hemic and Lymphatic System	**1**	**(1.8)**	**0**	**(0)**	**0**	**(0)**	**1**	**(11.1)**
Anemia	1	(1.8)	0	0	0	0	0	0
Anemia, hypochromic	0	(0)	0	(0)	0	(0)	1	(11.1)
Metabolic/Nutritional/Immune	**1**	**(1.8)**	**1**	**(3.7)**	**2**	**(9.1)**	**0**	**(0)**
Hypovolemia	1	(1.8)	0	0	0	0	0	0
Nutritional abnormality	0	(0)	0	(0)	1	(4.5)	0	(0)
Weight loss	0	(0)	1	(3.7)	1	(4.5)	0	(0)
Musculoskeletal System	**0**	**(0)**	**1**	**(3.7)**	**1**	**(4.5)**	**0**	**(0)**
Pain, foot	0	(0)	1	(3.7)	0	(0)	0	(0)
Sprain, wrist	0	(0)	0	(0)	1	(4.5)	0	(0)
Nervous System and Psychiatric	**6**	**(10.7)**	**2**	**(7.4)**	**2**	**(9.1)**	**1**	**(11.1)**
Hemiplegia	1	(1.8)	0	0	0	0	0	0
Developmental Delay	1	(1.8)	0	0	0	0	0	0
Seizure disorder	1	(1.8)	0	0	0	0	0	0
Depression	1	(1.8)	0	0	0	0	0	0
Anxiety	1	(1.8)	0	0	0	0	0	0
Behavior disturbance	1	(1.8)	0	0	0	0	0	0
Pseudotumor cerebri	0	(0)	0	(0)	0	(0)	1	(11.1)
Intracranial pressure increased	0	(0)	0	(0)	0	(0)	1	(11.1)

	Masked Monotherapy Phase				Open-label Concomitant Therapy Phase Dorzolamide 2% + Timolol GFS 0.25% (N=31)			
	Dorzolamide 2% (N=56)		Timolol GFS 0.25% (N=27)		Dorzolamide 2% (m=22)		Timolol GFS 0.25% (m=9)	
	n	(%)	n	(%)	n	(%)‡	n	(%)‡
Somnolence	0	(0)	0	(0)	1	(4.5)	0	(0)
Irritability	1	(1.8)	1	(3.7)	1	(4.5)	0	(0)
Hypersomnia	0	(0)	1	(3.7)	0	(0)	0	(0)
Insomnia	1	(1.8)	0	0	0	0	0	0
Respiratory System	**25**	**(44.6)**	**9**	**(33.3)**	**8**	**(36.4)**	**4**	**(44.4)**
Bronchoconstriction	0	(0)	1	(3.7)	0	(0)	0	(0)
Bronchitis	2	(3.6)	2	(7.4)	0	(0)	1	(11.1)
Bronchitis, chronic	0	(0)	0	(0)	0	(0)	1	(11.1)
Bronchial disorder	1	(1.8)	0	0	0	0	0	0
Congestion, nasal	3	(5.4)	0	(0)	1	(4.5)	0	(0)
Congestion, pulmonary	0	(0)	0	(0)	1	(4.5)	0	(0)
Cough	12	(21.4)	6	(22.2)	2	(9.1)	0	(0)
Infection, respiratory, upper	7	(12.5)	4	(14.8)	2	(9.1)	2	(22.2)
Influenza	4	(7.1)	1	(3.7)	2	(9.1)	1	(11.1)
Pharyngitis	2	(3.6)	0	(0)	0	(0)	1	(11.1)
Pneumonia	3	(5.4)	0	(0)	1	(4.5)	0	(0)
Rhinitis	2	(3.6)	0	(0)	1	(4.5)	1	(11.1)
Rhinorrhea	2	(3.6)	1	(3.7)	0	(0)	0	(0)
Sinusitis	0	(0)	0	(0)	1	(4.5)	0	(0)
Tonsillitis	0	(0)	1	(3.7)	0	(0)	0	(0)
Skin & Skin Appendage	**5**	**(8.9)**	**3**	**(11.1)**	**3**	**(13.6)**	**0**	**(0)**
Alopecia	0	(0)	0	(0)	1	(4.5)	0	(0)
Flushing	0	(0)	1	(3.7)	0	(0)	0	(0)
Infection, would, postoperative	1	(1.8)	0	0	0	0	0	0
Laceration	0	(0)	1	(3.7)	0	(0)	0	(0)
Rash	4	(7.1)	1	(3.7)	2	(9.1)	0	(0)
Special Senses	**20**	**(35.7)**	**10**	**(37.0)**	**12**	**(54.5)**	**3**	**(33.3)**
Blepharitis	1	(1.8)	1	(3.7)	0	(0)	0	(0)
Burning/stinging, eye	1	(1.8)	0	(0)	1	(4.5)	0	(0)
Cataract	0	(0)	0	(0)	1	(4.5)	0	(0)
Conjunctivitis	2	(3.6)	0	(0)	2	(9.1)	0	(0)
Conjunctivitis, bacterial	1	(1.8)	0	(0)	1	(4.5)	0	(0)
Corneal enlargement	2	(3.6)	0	(0)	0	(0)	0	(0)
Corneal diameter decrease	0	(0)	1	(3.7)	0	(0)	0	(0)
Detachment, retinal	0	(0)	1	(3.7)	0	(0)	0	(0)
Discharge, eye	3	(5.4)	3	(11.1)	1	(4.5)	1	(11.1)
Edema, corneal	1	(1.8)	1	(3.7)	0	(0)	0	(0)
Edema, eyelid	2	(3.6)	0	(0)	1	(4.5)	1	(11.1)
Epiphora	0	(0)	0	(0)	0	(0)	1	(11.1)
Haze, corneal	2	(3.6)	0	(0)	1	(4.5)	0	(0)
Infection, eye	0	(0)	0	(0)	1	(4.5)	1	(11.1)
Injection, ocular	4	(7.1)	3	(11.1)	1	(4.5)	2	(22.2)
Intraocular pressure decrease	0	(0)	1	(3.7)	0	(0)	0	(0)
Irritation, eye	0	(0)	2	(7.4)	1	(4.5)	0	(0)
Inflammation, eyelid	1	(1.8)	1	(3.7)	1	(4.5)	0	(0)
Itching, eye	1	(1.8)	0	0	0	0	0	0
Opacity, corneal	0	(0)	0	(0)	0	(0)	1	(11.1)
Otitis	2	(3.6)	0	(0)	1	(4.5)	0	(0)
Otitis media	1	(1.8)	0	(0)	1	(4.5)	1	(11.1)
Pain, eye	1	(1.8)	0	0	0	0	0	0
Rupture, Descemet's membrane	0	(0)	0	(0)	0	(0)	1	(11.1)
Swelling, eye	1	(1.8)	1	(3.7)	0	(0)	0	(0)

	Masked Monotherapy Phase				Open-label Concomitant Therapy Phase Dorzolamide 2% + Timolol GFS 0.25% (N=31)			
	Dorzolamide 2% (N=56)		Timolol GFS 0.25% (N=27)		Dorzolamide 2% (m=22)		Timolol GFS 0.25% (m=9)	
	n	(%)	n	(%)	n	(%)‡	n	(%)‡
Tearing	2	(3.6)	1	(3.7)	0	(0)	1	(11.1)
Urogenital System	**1**	**(1.8)**	**0**	**(0)**	**0**	**(0)**	**1**	**(11.1)**
Infection, urinary tract	1	(1.8)	0	(0)	0	(0)	1	(11.1)

† Indicates total number of patients (across treatments) who switched to open-label combination therapy.
‡ The percent = Number of patients in each category (n)/ number of patients who switched to open-label combination therapy (m), based on the therapy to which the patient was randomized in the monotherapy phase.

Reviewer's Comments:
There is a higher rate of adverse reactions in the dorzolamide 2% treatment group during monotherapy. This is no longer present during the concomitant therapy phase. The rates appear to be equivalent. There is a four-fold higher rate of diarrhea in the dorzolamide 2% treatment group during the monotherapy phase. This difference is no longer present during concomitant treatment.

Monotherapy Phase
The most common clinical adverse experiences in both treatment groups were fever, cough, and upper respiratory infections. A greater proportion of patients who were randomized to dorzolamide 2% had a digestive system adverse experience compared with the timolol GFS 0.25% group (23.2% versus 7.4%). Specifically, more patients randomized to dorzolamide 2% reported diarrhea (17.9% versus 3.7%). A greater proportion of patients who were randomized to timolol GFS 0.25% had eye discharge (11.1% versus 5.4%) and eye irritation (7.4% versus 0%) compared with the dorzolamide 2% group.

Concomitant Therapy Phase
The most common clinical adverse experience was diarrhea in the dorzolamide 2% group and fever in the timolol GFS 0.25% group. A greater proportion of patients who were initially randomized to dorzolamide 2% had vomiting (9.1% versus 0%), cough (9.1% versus 0%), and conjunctivitis (9.1% versus 0%) compared with the timolol GFS 0.25% group. A greater proportion of these patients also had a skin & skin appendage disorder (13.6% versus 0%); specifically, 2 patients initially randomized to dorzolamide 2% reported rash (9.1% versus 0%). Neither of these 2 patients discontinued the study due to the adverse experience of rash. A greater proportion of patients who were randomized to timolol GFS 0.25% had fever (33.3% versus 4.5%), upper respiratory infection (22.2% versus 9.1%), and ocular injection (22.2% versus 4.5%) compared with the dorzolamide 2% group.

Adverse Events in Age Cohort >2 Years but <6 Years

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence > 0 % in One or More Treatment Groups) by Body System (Age Cohort ≥2 Years but <6 Years)

	Masked Monotherapy Phase				Open-Label Combination Therapy Phase Dorzolamide 2% + Timolol 0.5% (N=30)[†]			
	Dorzolamide 2% (N=66)		Timolol GFS 0.5% (N=35)		Dorzolamide 2% (m=19)		Timolol GFS 0.5% (m=11)	
	n	(%)	n	(%)	n	(%)[‡]	n	(%)[‡]
Patients with one or more adverse experiences	50	(75.8)	24	(68.6)	8	(42.1)	9	(81.8)
Patients with no adverse experience	16	(24.2)	11	(31.4)	11	(57.9)	2	(18.2)
Body as a Whole/Site Unspecified	**14**	**(21.2)**	**10**	**(28.6)**	**2**	**(10.5)**	**3**	**(27.3)**
Cold sensation	0	0	1	(2.9)	0	0	0	0
Edema, swelling	1	1.5	0	0	0	0	0	0
Fever	11	(16.7)	9	(25.7)	0	(0)	3	(27.3)
Infection, viral	1	(1.5)	0	(0)	1	(5.3)	0	(0)
Malaise	1	1.5	0	0	0	0	0	0
Pain, abdominal	2	(3.0)	0	(0)	0	(0)	0	(0)
Pain, postoperative	0	(0)	0	(0)	1	(5.3)	0	(0)
Trauma	0	0	1	(2.9)	0	0	0	0
Cardiovascular System	**0**	**0**	**1**	**(2.9)**	**0**	**0**	**0**	**0**
Hypertension	0	0	1	(2.9)	0	0	0	0
Tachycardia	0	0	1	(2.9)	0	0	0	0
Digestive System	**14**	**(21.2)**	**6**	**(17.1)**	**2**	**(10.5)**	**3**	**(27.3)**
Anorexia	2	(3.0)	1	(2.9)	0	(0)	0	(0)
Constipation	0	(0.0)	1	(2.9)	1	(5.3)	0	(0)
Dental caries	0	(0)	0	(0)	0	(0)	1	(9.1)
Diarrhea	7	(10.6)	4	(11.4)	1	(5.3)	2	(18.2)
Nausea	1	(1.5)	1	(2.9)	0	0	0	0
Vomiting	6	(9.1)	1	(2.9)	1	(5.3)	1	(9.1)
Gastroenteritis, infectious	1	1.5	0	0	0	0	0	0
Gastroenteritis	0	0	1	(2.9)	0	0	0	0
Stomatitis	1	1.5	0	0	0	0	0	0
Hemic and Lymphatic	**1**	**(1.5)**	**0**	**0**	**0**	**0**	**0**	**0**
Lymphadenopathy	1	(1.5)	0	0	0	0	0	0
Metabolic/Nutritional/Immune	**0**	**0**	**1**	**(2.9)**	**0**	**0**	**0**	**0**
Dehydration	0	0	1	(2.9)	0	0	0	0
Musculoskeletal System	**1**	**(1.5)**	**0**	**(0.0)**	**1**	**(5.3)**	**0**	**(0)**
Fracture	1	1.5	0	0	0	0	0	0
Pain, neck	0	(0)	0	(0)	1	(5.3)	0	(0)
Nervous System and Psychiatric	**10**	**(15.2)**	**3**	**(8.6)**	**1**	**(5.3)**	**0**	**(0)**
Headache	7	(10.6)	2	(5.7)	1	(5.3)	0	(0)
Somnolence	1	(1.5)	2	(5.7)	0	(0)	0	(0)
Anxiety	0	0	1	(2.9)	0	0	0	0
Agitation	1	1.5	0	0	0	0	0	0
Irritability	1	1.5	0	0	0	0	0	0
Respiratory System	**29**	**(43.9)**	**11**	**(31.4)**	**3**	**(15.8)**	**3**	**(27.3)**
Bronchitis	2	(3.0)	1	(2.9)	0	(0)	0	(0)
Congestion, nasal	0	(0)	0	(0)	1	(5.3)	0	(0)
Cough	10	(15.2)	3	(8.6)	0	(0)	1	(9.1)
Infection, respiratory, upper	12	(18.2)	5	(14.3)	0	(0)	1	(9.1)
Influenza	7	(10.6)	2	(5.7)	0	(0)	1	(9.1)

	Masked Monotherapy Phase				Open-Label Combination Therapy Phase Dorzolamide 2% + Timolol 0.5% (N=30)†			
	Dorzolamide 2% (N=66)		Timolol GFS 0.5% (N=35)		Dorzolamide 2% (m=19)		Timolol GFS 0.5% (m=11)	
	n	(%)	n	(%)	n	(%)‡	n	(%)‡
Pharyngitis	2	(3.0)	0	(0.0)	1	(5.3)	0	(0)
Pneumonia	0	(0)	0	(0)	0	(0)	1	(9.1)
Rhinitis	4	(6.1)	1	(2.9)	0	(0)	0	(0)
Rhinorrhea	5	(7.6)	3	(8.6)	1	(5.3)	0	(0)
Sinus disorder	2	(3.0)	0	(0.0)	0	(0)	0	(0)
Sneezing	1	1.5	0	0	0	0	0	0
Hoarseness	1	1.5	0	0	0	0	0	0
Skin & Skin Appendage	**5**	**(7.6)**	**2**	**(5.7)**	**1**	**(5.3)**	**1**	**(9.1)**
Bite/sting, nonvenomous	0	(0)	0	(0)	1	(5.3)	0	(0)
Contusion	0	0	1	(2.9)	0	0	0	0
Dry skin	0	(0)	0	(0)	1	(5.3)	0	(0)
Varicella	1	1.5	0	0	0	0	0	0
Impetigo	1	1.5	0	0	0	0	0	0
Dermatitis, contact	1	1.5	0	0	0	0	0	0
Pallor	0	(0)	0	(0)	0	(0)	1	(9.1)
Rash	2	(3.0)	1	(2.9)	0	(0)	0	(0)
Sunburn	1	1.5	0	0	0	0	0	0
Sweating	0	(0)	0	(0)	0	(0)	1	(9.1)
Special Senses	**22**	**(33.3)**	**13**	**(37.1)**	**3**	**(15.8)**	**5**	**(45.5)**
Blurred Vision	1	(1.5)	0	(0)	0	(0)	0	(0)
Burning/stinging, eye	9	(13.6)	3	(8.6)	0	(0)	1	(9.1)
Conjunctivitis	2	(3.0)	2	(5.7)	1	(5.3)	1	(9.1)
Conjunctivitis, bacterial	1	1.5	0	0	0	(0)	0	(0)
Conjunctivitis, follicular	0	(0)	1	(2.9)	0	(0)	0	(0)
Conjunctival disorder	1	1.5	0	(0)	0	0	0	(0)
Cupping, optic disc	0	(0.0)	1	(2.9)	0	(0)	1	(9.1)
Cyst, iris	0	(0.0)	1	(2.9)	0	(0)	0	(0)
Discharge, eye	0	(0.0)	4	(11.4)	0	(0)	0	(0)
Edema, eyelid	1	(1.5)	1	(2.9)	1	(5.3)	0	(0)
Foreign body sensation	1	(1.5)	0	(0)	0	(0)	0	(0)
Heterochromia	1	(1.5)	0	(0)	0	(0)	0	(0)
Hordeolum	1	(1.5)	0	(0)	0	(0)	0	(0)
Infection, eye	0	(0)	1	(2.9)	0	(0)	0	(0)
Inflammation, eyelid	2	(3.0)	0	(0.0)	0	(0)	0	(0)
Injection, conjunctival	2	(3.0)	1	(2.9)	0	(0)	1	(9.1)
Injection, ocular	7	(10.6)	6	(17.1)	0	(0)	2	(18.2)
Itching, eye	2	(3.0)	1	(2.9)	0	(0)	0	(0)
Opacity, vitreous	1	(1.5)	0	(0)	0	0	0	(0)
Otitis media	3	(4.5)	0	(0.0)	0	(0)	0	(0)
Pain, eye	4	(6.1)	2	(5.7)	0	(0)	1	(9.1)
Ptosis	0	(0.0)	1	(2.9)	0	(0)	0	(0)
Tearing	0	(0.0)	3	(8.6)	2	(10.5)	0	(0)
Uveitis	0	(0.0)	1	(2.9)	0	(0)	0	(0)
Urogenital System	**1**	**(1.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Infection, urinary tract	1	(1.5)	0	(0.0)	0	(0.0)	0	(0.0)

† Indicates total number of patients (across treatments) who switched to open-label combination therapy.
‡ The percent = Number of patients in each category (n)/ number of patients who switched to open-label combination therapy (m), based on the therapy to which the patient was randomized in the monotherapy phase.

Reviewer's Comments:
There are approximately twice as many adverse events documented during the open-label treatment phase in the patient population initially randomized to timolol GFS 0.5% therapy. The clinical significance of this is uncertain since both patient populations were being treated with Cosopt. The adverse event profile would be expected to be similar.

Monotherapy Phase
The two most common clinical adverse experiences in both treatment groups were fever and upper respiratory infections. A greater proportion of patients who were randomized to dorzolamide 2% had reported vomiting (9.1% versus 2.9%), headache (10.6% versus 5.7%), cough (15.2% versus 8.6%), and influenza (10.6% versus 5.7%) compared with the timolol GFS 0.5% group. A greater proportion of patients who were randomized to timolol GFS 0.5% had eye discharge (11.4% versus 0%) and tearing (8.6% versus 0%) compared with the dorzolamide 2% group.

Combination Therapy Phase
The most common clinical adverse experience was tearing in the dorzolamide 2% group and fever in the timolol GFS 0.5% group. A greater proportion of patients who were initially randomized to timolol GFS 0.5% reported one or more adverse experiences (81.8% versus 42.1%) compared with the dorzolamide 2% group. A greater proportion of patients who were initially randomized to dorzolamide 2% reported tearing (10.5% versus 0%) compared with the timolol GFS 0.5% group. A greater proportion of patients who were initially randomized to timolol GFS 0.5% had fever (27.3% versus 0%), diarrhea (18.2% versus 5.3%), and ocular injection (18.2% versus 0%) compared with the dorzolamide 2% group.

Emergent and Worsening Ocular Symptoms

Number (%) of Patients With Emergent or Worsening Ocular Symptoms (Incidence > 0 % in One or More Treatment Groups) (Age Cohort <2 Years)

	Masked Monotherapy Phase				Open-label Concomitant Therapy Phase Dorzolamide 2% + Timolol GFS 0.25% (N=31)			
	Dorzolamide 2% (N=56)		Timolol GFS 0.25% (N=27)		Dorzolamide 2% (m=22)		Timolol GFS 0.25% (m=9)	
	n	(%)	n	(%)	n	(%)	n	(%)
Burning/stinging, eye	1	(1.8)	0	0	1	(4.5%)	0	0
Discharge, eye	3	(5.4)	3	(11.1%)	1	(4.5%)	1	(11.1%)
Inflammation, eyelid	1	(1.8)	1	(3.7%)	1	(4.5%)	0	0
Injection, ocular	4	(7.1)	3	(11.1%)	1	(4.5%)	2	(22.2%)
Irritation, eye	0	0	2	(7.4%)	1	(4.5%)	0	0
Itching, eye	1	(1.8)	0	0	0	0	0	0
Pain, eye	1	(1.8)	0	0	0	0	0	0
Swelling, eye	1	(1.8)	1	(3.7%)	0	0	0	0
tearing	2	(3.6)	1	(3.7%)	0	0	1	(11.1%)

Number (%) of Patients With Emergent or Worsening Ocular Symptoms (Incidence > 0 % in One or More Treatment Groups) (Age Cohort ≥ 2 Years but < 6 Years)

	Masked Monotherapy Phase				Open-label Concomitant Therapy Phase Dorzolamide 2%/Timolol GFS 0.5% (N=30)			
	Dorzolamide 2% (N=66)		Timolol GFS 0.5% (N=35)		Dorzolamide 2% (m=19)		Timolol GFS 0.5% (m=11)	
	n	(%)	n	(%)	n	(%)	n	(%)
Blurred vision	1	(1.5%)	0	0	0	0	0	
Burning/stinging, eye	9	(13.6%)	3	(8.6%)	0	0	1	0
Discharge, eye	0	0	4	(11.4%)	0	0	0	(9.1%)
Foreign body sensation	1	(1.5%)	0	0	0	0	0	0
Inflammation, eyelid	2	(3.0%)	0	0	0	0	0	0
Injection, conjunctival	2	(3.0%)	1	(2.9%)	0	0	1	(9.1%)
Injection, ocular	7	(10.6%)	6	(17.1%)	0	0	2	(18.2%)
Itching, eye	2	(3.0)	1	(2.9%)	0	0	0	0
Pain, eye	4	(6.1)	2	(5.7%)	0	0	1	(9.1%)
Tearing	0	(0.0)	3	(8.6%)	2	(10.5%)	0	0

Nonfatal Serious Clinical Adverse Experiences

Serious Clinical Adverse Experiences (Age cohort < 2 Years –Masked Monotherapy)

Patient	Age (months)	Day of Onset	Adverse Experience	Disposition
Dorzolamide 2%				
2055	20	77	Hemiplegia	Recovered
2094	3	19	Infection, RSV	Recovered
2048	4	12	Bronchiolitis	Recovered
2326	5	3	Pneumonia	Recovered
2309	3	65	Pneumonia	Recovered
2364	1	30	Seizure disorder	Recovered
Timolol GFS 0.25%				
2334	14	17	Bronchoconstriction	Discontinued

Serious Clinical Adverse Experiences (Age cohort < 2 Years – Open-Label Concomitant Therapy)

Patient	Age (months)	Day of Onset	Adverse Experience	Disposition
Dorzolamide 2%				
2049	18	16	Diarrhea	Recovered
Timolol GFS 0.25%				
2350	5	12	Increase intracranial pressure, pseudotumor cerebri	Recovered
2392	9	47	Fever, pharyngitis, bronchitis	Recovered

Serious Clinical Adverse Experiences (Age cohort ≥ 2 Years but < 6 –Masked Monotherapy)

Patient	Age (years)	Day of Onset	Adverse Experience	Disposition
Dorzolamide 2%				
2003	2	13	Urinary tract infection	Recovered
2374	2	6	Otitis media	Recovered
2592	2	81	Anorexia, stomatitis	Recovered
Timolol GFS 0.5%				
2159	3	35	Gastroenteritis	Recovered

There were no serious clinical adverse experiences reported during the combination therapy phase for the age cohort ≥ 2 Years but < 6.

Deaths

There were no deaths in patients randomized into the study. However, there was one patient who died who was screened but not randomized. This was a 43 day old male with a history of face malformation, facial dysmorphism and congenital glaucoma who died secondary to cerebral edema.

Laboratory Values

The chemistry laboratory test total CO2 was performed at study day 1 and week 12 as the protocol-specified laboratory test. The laboratory tests pCO2 and HCO3 were performed in error at some of the International study sites. These study sites were located in the following countries: (b) (4)

A clinically significant laboratory abnormality (CSLA) for total CO2 was defined as a value ≤ 78% of the lower limit of normal (LLN). Two (2) patients experienced a CSLA during study therapy (both in the age cohort <2 years). Patient AN 2049 was initially on

dorzolamide 2% monotherapy, switched to open-label concomitant therapy on study day 8 , and a CSLA for total CO2 was reported on study day 90. For patient AN 2046, who was randomized to timolol GFS 0.25% monotherapy, no baseline laboratory test was recorded. A CSLA for total CO2 was reported on study day 14. The total CO2 result at the week 12 (study day 112) assessment did not qualify as a CSLA.

Mean Change (SD) in Total CO_2 (mmol/L) to the Last Observation in Treatment Phase (Age Cohort <2 years)

Treatment Phase	Treatment	N	Mean (SD)			
			Baseline	Treatment	Change	% Change
Monotherapy	Dorzolamide 2%	18	21.6 (4.5)	22.9 (3.3)	1.3 (4.3)	10.9 (29.6)
	Timolol GFS 0.25%	10	25.1 (4.5)	23.3 (2.5)	-1.8 (3.0)	-6.0 (9.86)
Overall	Dorzolamide 2%	30	22.3 (4.2)	22.7 (4.0)	0.4 (4.3)	4.6 (25.3)
	Timolol GFS 0.25%	15	24.4 (4.5)	22.8 (3.0)	-1.6 (3.6)	-4.8 (14.07)

Mean Change (SD) in Total CO_2 (mmol/L) to the Last Observation in Treatment Phase (Age Cohort ≥ 2 years but < 6 years)

Treatment Phase	Treatment	N	Mean (SD)			
			Baseline	Treatment	Change	% Change
Monotherapy	Dorzolamide 2%	22	24.3 (2.9)	23.7 (3.4)	-0.6 (3)	-2.0 (12.3)
	Timolol GFS 0.5%	12	25.5 (3.9)	25.6 (4.6)	0.1 (4)	1.2 (16.7)
Overall	Dorzolamide 2%	32	24.7 (2.6)	23.6 (3.1)	-1.1 (3)	-3.9 (11.8)
	Timolol GFS 0.5%	18	24.4 (4.2)	24.4 (4.4)	-0.0 (3.6)	0.9 (15.1)

Reviewer's Comments:
There was no clinically meaningful difference in the mean CO2 values between treatment groups for either of the age cohorts at the end of the study. All mean CO2 values are within normal limits for the pediatric population.

Vital Signs

Summary statistics, including the mean and mean percent change from baseline for the last visit of the study phase (monotherapy, open-label), are presented for each vital sign measure by treatment group. The last monotherapy visit served as the point of reference (baseline) for the concomitant/combination therapy phase analysis.

Mean Change (SD) in Vital Signs to the Last Observation in Treatment Phase (Age Cohort <2 Years—Monotherapy)

Measurement (Unit)	Treatment	Mean (SD)				
		N	Baseline	Treatment	Change	% Change
Systolic BP (mm Hg)	Dorzolamide 2%	53	102.5 (21.16)	101.4 (17.83)	-1.1 (21.26)	2.2 (24.72)
	Timolol GFS 0.25%	26	108.8 (20.30)	109.2 (19.55)	0.3 (15.42)	1.3 (12.74)
Diastolic BP (mm Hg)	Dorzolamide 2%	53	62.4 (16.00)	60.8 (15.27)	-1.6 (19.63)	3.0 (37.15)
	Timolol GFS 0.25%	26	67.9 (12.70)	66.7 (13.81)	-1.2 (11.68)	-0.7 (18.46)
Pulse Rate (beats per minute)	Dorzolamide 2%	52	110.3 (21.13)	108.3 (22.19)	-2.0 (27.04)	1.4 (28.93)
	Timolol GFS 0.25%	26	104.7 (18.43)	115.3 (25.98)	10.6 (24.35)	12.1 (26.19)
Respiratory Rate (breaths per minute)	Dorzolamide 2%	52	29.7 (12.27)	28.0 (10.46)	-1.7 (8.63)	-1.6 (22.66)
	Timolol GFS 0.25%	25	30.2 (16.98)	28.7 (14.20)	-1.4 (6.24)	-1.4 (16.69)

N = Sample size.

SD = Standard deviation; BP = Blood pressure.

Mean Change (SD) in Vital Signs to the Last Observation in Treatment Phase (Age Cohort <2 Years—Concomitant Therapy)

Measurement (Unit)	Treatment	Mean (SD)				
		N	Baseline	Treatment	Change	% Change
Systolic BP (mm Hg)	Dorzolamide 2%	21	99.3 (12.59)	100.0 (17.37)	0.8 (20.35)	2.0 (19.22)
	Timolol GFS 0.25%	9	104.1 (14.34)	105.8 (19.48)	1.7 (17.98)	2.4 (18.99)
Diastolic BP (mm Hg)	Dorzolamide 2%	21	61.1 (14.35)	61.0 (9.78)	-0.2 (15.80)	3.4 (21.87)
	Timolol GFS 0.25%	9	65.6 (9.08)	64.7 (16.95)	-0.8 (18.74)	0.3 (28.45)
Pulse Rate (beats per minute)	Dorzolamide 2%	20	108.3 (18.26)	105.6 (15.79)	-2.7 (20.52)	0.6 (24.66)
	Timolol GFS 0.25%	9	109.3 (18.69)	101.2 (21.55)	-8.1 (15.83)	-7.1 (14.45)
Respiratory Rate (breaths per minute)	Dorzolamide 2%	21	30.5 (14.44)	30.2 (16.28)	-0.3 (7.44)	0.8 (25.81)
	Timolol GFS 0.25%	9	26.9 (8.49)	24.0 (3.61)	-2.9 (6.25)	-6.3 (18.01)

N = Sample size.
SD = Standard deviation.
BP = Blood pressure.

Mean Change (SD) in Vital Signs to the Last Observation in Treatment Phase (Age Cohort ≥2 Years but <6 Years—Monotherapy)

Measurement (Unit)	Treatment	Mean (SD)				
		N	Baseline	Treatment	Change	% Change
Systolic BP (mm Hg)	Dorzolamide 2%	64	109.6 (17.76)	110.3 (14.33)	0.7 (17.81)	2.8 (19.79)
	Timolol GFS 0.5%	35	107.4 (14.28)	104.5 (14.50)	-2.9 (13.32)	-1.9 (12.46)
Diastolic BP (mmHg)	Dorzolamide 2%	64	67.3 (11.83)	66.8 (10.83)	-0.4 (13.69)	2.2 (22.91)
	Timolol GFS 0.5%	35	63.8 (11.22)	61.4 (10.01)	-2.4 (11.49)	-1.6 (18.96)
Pulse Rate (beats per minute)	Dorzolamide 2%	65	98.3 (15.55)	99.3 (15.43)	0.9 (18.08)	2.8 (21.07)
	Timolol GFS 0.5%	35	104.5 (14.58)	99.6 (15.44)	-4.9 (17.16)	-3.2 (20.70)
Respiratory Rate (breaths per minute)	Dorzolamide 2%	61	23.7 (5.86)	23.2 (4.33)	-0.5 (5.43)	1.0 (21.78)
	Timolol GFS 0.5%	34	23.9 (5.29)	23.9 (4.96)	-0.0 (5.01)	2.2 (20.74)

N = Sample size.
SD = Standard deviation.
BP = Blood pressure.

Mean Change (SD) in Vital Signs to the Last Observation in Treatment Phase (Age Cohort ≥2 Years but <6 Years—Combination Therapy)

Measurement (Unit)	Treatment	N	Mean (SD)			
			Baseline	Treatment	Change	% Change
Systolic BP (mm Hg)	Dorzolamide 2%	18	107.9 (11.64)	107.4 (19.34)	-0.5 (17.41)	-0.2 (15.14)
	Timolol 0.5%	11	105.9 (18.38)	104.2 (12.05)	-1.7 (20.54)	1.7 (25.53)
Diastolic BP (mm Hg)	Dorzolamide 2%	18	66.4 (11.06)	63.0 (4.93)	-3.4 (10.07)	-3.2 (13.66)
	Timolol 0.5%	11	59.8 (8.87)	66.6 (8.57)	6.8 (10.21)	13.5 (22.43)
Pulse Rate (bpm)	Dorzolamide 2%	19	102.1 (17.42)	91.3 (18.85)	-10.8 (21.19)	-9.1 (18.49)
	Timolol 0.5%	11	99.5 (20.43)	97.7 (14.46)	-1.8 (15.71)	-0.2 (14.42)
Respiratory Rate (bpm)	Dorzolamide 2%	18	22.2 (4.37)	23.7 (5.74)	1.6 (4.78)	8.0 (19.61)
	Timolol 0.5%	10	25.9 (6.30)	23.2 (3.65)	-2.7 (3.47)	-8.7 (10.65)

N = Sample size.
SD = Standard deviation.
BP = Blood pressure.

Reviewer's Comments:

There were no clinically significant changes in pulse, blood pressure or respiratory rate in either of the treatment groups for both age cohorts. There was an increase in pulse rate noted in the timolol monotherapy treatment group for age cohort < 2. This is counterintuitive based on the mechanism of action of beta-blockers. This event, however, was not clinically significant.

Alertness Assessment

The response to the alertness assessment at baseline and at Week 12 was summarized by constructing 5x5 contingency tables by treatment group (Grades 1 to 5 at baseline versus Grades 1 to 5 at Week 12). In addition, the number and percent of patients whose responsiveness deteriorated at any point during the study was determined by treatment group. Results were determined for those who completed the study while on monotherapy, and overall.

Patients With Worsening Alertness Assessments for All Patients as Treated – Evaluable* (Age Cohort < 2 Years)

	Dorzolamide 2% (N=55)	**Timolol GFS 0.25% (N=27)**
Monotherapy	0	1 (3.7%)
Overall	1 (1.8)	1 (3.7)

*Patients who were evaluable had a baseline assessment and at least one on-treatment assessment
N=sample size

Patient Alertness: Change From Baseline to Week 12 (End of Study) for All Patients as Treated—Evaluable† (Age Cohort <2 Years—Monotherapy)

Dorzolamide 2% (N=33)					
Grade at Baseline	**Grade at Week 12 (End of Study)**				
	1	**2**	**3**	**4**	**5**
1	30	0	0	0	0
2	1	1	0	0	0
3	1	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
Timolol GFS 0.25% (N=18)					
Grade at Baseline	**Grade at Week 12 (End of Study)**				
	1	**2**	**3**	**4**	**5**
1	15	0	0	0	1
2	0	1	0	0	0
3	0	0	0	0	0
4	0	1	0	0	0
5	0	0	0	0	0

† Patients who were evaluable had a baseline assessment and at least one on-treatment assessment.
Note: The last assessment was analyzed for patients who discontinued the study prior to Week 12.
1 = Responds readily to name spoken in normal tone.
2 = Lethargic response to name spoken in normal tone.
3 = Responds only after name is spoken loudly and/or repeatedly.
4 = Responds only after mild prodding or shaking.
5 = Does not respond to mild prodding or shaking.

Reviewer's Comments:
One patient (AN 2035) was assessed as 1 (responds readily) at baseline and 5 (does not respond) at the 12 week visit. Based on the investigator information, this assessment was made during the time that the patient was sedated for IOP measurements. It is not believed to be a clinical adverse event.

Patients With Worsening Alertness Assessments for All Patients as Treated – Evaluable* (Age Cohort ≥ 2 Years but < 6 Years)

	Dorzolamide 2% (N=65)	Timolol GFS 0.5% (N=35)
Monotherapy	0	0
Overall	0	0

*Patients who were evaluable had a baseline assessment and at least one on-treatment assessment
N=sample size

Patient Alertness: Change From Baseline to Week 12 (End of Study) for All Patients as Treated—Evaluable† (Age Cohort ≥2 Years but <6 Years—Monotherapy)

Dorzolamide 2% (N=47)					
Grade at Baseline	**Grade at Week 12 (End-of-Study)**				
	1	**2**	**3**	**4**	**5**
1	45	0	0	0	0
2	1	1	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
Timolol GFS 0.5% (N=24)					
Grade at Baseline	**Grade at Week 12 (End-of-Study)**				
	1	**2**	**3**	**4**	**5**
1	23	0	0	0	0
2	1	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0

† Patients who were evaluable had a baseline assessment and at least one on-treatment assessment.
Note: The last assessment was analyzed for patients who discontinued the study prior to Week 12.

1 = Responds readily to name spoken in normal tone.
2 = Lethargic response to name spoken in normal tone.
3 = Responds only after name is spoken loudly and/or repeatedly.
4 = Responds only after mild prodding or shaking.
5 = Does not respond to mild prodding or shaking.

Reviewer's Comments:
There were no clinically meaningful changes in patient alertness for this age cohort.

Corneal Diameter

Corneal diameter measurements were obtained at baseline and at Week 12. If the patient discontinued the study prior to Week 12, the corneal diameter was to be measured at the discontinuation visit. The mean and standard deviation at baseline and Week 12, as well as the change and percent change from baseline to Week 12, are presented for the corneal diameter of the study eye. Nominal p-values were calculated on mean change and mean percent change from baseline within treatment groups based on the paired t-test. Results were determined for those who completed the study while on monotherapy, and overall.

Corneal Diameter (mm) Summary Statistics for All Patients as Treated—Evaluable† (Age Cohort <2 Years—Monotherapy)

Treatment	N	Baseline			Week 12			Change			Percent Change (p-Value)
		Mean	SD	Med	Mean	SD	Med	Mean (p-Value)	SD	Med	
Dorzolamide 2%	27	12.89	1.35	13.00	12.96	1.24	12.80	0.1 (0.364)	0.43	0.000	0.8 (0.304)
Timolol GFS 0.25%	15	12.83	1.37	12.50	12.72	1.34	12.50	-0.1 (0.599)	0.84	0.000	-0.7 (0.677)

† Patients who were evaluable had a baseline assessment and at least one on-treatment assessment.
Note: p-Values are for within-group changes from baseline (paired t-test).
SD = Standard deviation.
Med = Median.

Corneal Diameter (mm) Summary Statistics (Age Cohort ≥2 Years but <6 Years—Monotherapy)

Treatment	N	Baseline			Week 12			Change			Percent Change (p-Value)
		Mean	SD	Med	Mean	SD	Med	Mean (p-Value)	SD	Med	
Dorzolamide 2%	42	12.68	2.21	13.00	12.73	2.18	13.00	0.0 (0.493)	0.39	0.000	0.4 (0.417)
Timolol GFS 0.5%	22	12.77	1.53	12.25	12.61	1.48	12.25	-0.2 (0.110)	0.45	0.000	-1.2 (0.106)

Note: p-Values are for within-group changes from baseline (paired t-test).
SD = Standard deviation.
Med = Median.

Reviewer's Comments:
There were no clinically significant changes in corneal diameter in either treatment group for both of the age cohorts. The mean baseline and end of study corneal diameters in this study are outside of normal limits. The values are borderline for megalocornea which is consistent with this disease process.

Visual Acuity

Baseline visual acuity (VA) of the study eye was summarized by age cohort and treatment group. Pre-verbal patients were summarized according to the category listed by the investigator. Patients with results listed in a numerator/denominator format were summarized according to the Snellen equivalent.

One patient in each treatment group (1.8% and 3.7% for dorzolamide 2% and timolol GFS 0.25%, respectively) in the age cohort <2 years experienced a worsening at the Week 12 visit. Three (3) patients (4.5%) in the dorzolamide 2% group and 2 patients (5.7%) in the timolol 0.5% group in the age cohort ≥2 years but <6 years experienced a worsening at the Week 12 visit.

Listing of Patients With a Worsening in Visual Acuity for the Study Eye— Baseline Versus Week 12

Age Cohort	Treatment	Allocation Number (AN)	Baseline Assessment	Week 12 Assessment
<2 Years	Dorzolamide 2%	2058	fixates and follows	poor fixation
	Timolol GFS 0.25%	2329	fixates and follows	no fixation
≥2 Years but <6 Years	Dorzolamide 2%	2157	20/100	20/125
		2169	20/20	20/25
		2204	20/20	20/25
	Timolol GFS 0.5%	2244	20/70	20/200
		2587	5/60	4/60

Three (3) patients who were ≥2 years but <6 years of age, 1 on Dorzolamide 2% (AN 2252) and 2 on Timolol GFS 0.5% (ANs 2253, 2161), were excluded from the analysis due to data entry errors.

Reviewer's Comments:

Two (2) of the seven patients reported as having a worsening in visual acuity had a clinically significant change in vision. Both patients were in the timolol GFS treatment group. Patient 2244 was discontinued from the study at week 29 for poor IOP control. Patient 2329 completed the study.

D. Adequacy of Safety Testing

The submitted study complies with the pediatric written request issued by the Agency and is of adequate duration to assess the safety of this product in the pediatric population. The evaluation methods were appropriate and there is no need for further safety testing.

E. Summary of Critical Safety Findings and Limitations of Data

There were no critical safety findings identified in this study.

VIII. Dosing, Regimen, and Administration Issues

Dosing for this pediatric trial was based on the currently labeled dosing frequency for adult patients. No further dose ranging was warranted. The currently labeled dosing level and frequency is safe in the pediatric population.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The sponsor analyzed data for each of 2 age cohorts: "patients <2 years old" and "patients ≥ 2 years but <6 years old". The Sponsor has adequately addressed the safety and clinical response of this drug product in these two cohorts. Gender effects were not analyzed in this pediatric supplement. The effects of gender, race, age and iris color were analyzed during the review of the original NDA.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The sponsor did not analyze the effects of age, race or ethnicity in this pediatric supplement. The effects of gender, race, age and iris color were analyzed during the review of the original NDA.

C. Evaluation of Pediatric Program

The Agency issued a written request for this drug product to gather data on the safety profile in pediatric patients below the age of 6. The Agency believed that efficacy for this product could be reliably extrapolated from the adult population. The study contained in this pediatric efficacy supplement adequately addresses all of the criteria of the pediatric written request. The data has confirmed that this drug product is safe for pediatric use for the labeled indication.

D. Comments on Data Available or Needed in Other Populations

There is no additional data needed in other populations for this drug product. Safety and efficacy have been adequately characterized in the target populations.

X. Conclusions and Recommendations

A. Conclusions

This clinical study supports the use of dorzolamide HCL in the Pediatric population. The benefits of using this drug product outweigh the risks in the treatment of elevated intraocular pressure in pediatric patients below the age of 6. There are no unresolved scientific or regulatory issues.

B. Recommendations

NDA 20-408 /SE5-033 is recommended for approval after labeling revisions are made consistent with the recommendations listed in this review.

XI. Labeling

Recommended additions are shown by underlining and recommended deletions are shown by strikethrough lines.

(b) (4)

9 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

Jennifer Harris
3/29/04 12:50:56 PM
MEDICAL OFFICER

Wiley Chambers
3/29/04 04:12:27 PM
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