CLINICAL REVIEW

Application Type	NDA 19-845 NDA 20-963
Submission Numbers	S-020; S-010
Submission Code	SE5
Letter Date	12/15/06
Stamp Date	12/16/06
PDUFA Goal Date	6/18/07
Reviewer Name	Sonal D. Wadhwa, MD
Review Completion Date	5/4/07
Established Names	betaxolol hydrochloride ophthalmic suspension; timolol maleate ophthalmic gel forming solution
Trade Names	Betoptic S 0.25%; Timolol GFS 0.25% and 0.5%
Therapeutic Classes	beta-blockers
Applicant	Alcon Research, Ltd.
Priority Designation	P
Formulations	Ophthalmic suspension/solution
Dosing Regimen	Betoptic S one drop twice a day Timolol GFS one drop once 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 19-845 S-020 and NDA 20-963 S-010 are recommended for approval. The clinical study contained in these supplements supports the use of betaxolol hydrochloride ophthalmic suspension 0.25% and timolol maleate ophthalmic gel forming solution 0.25% and 0.5% in the pediatric population. The benefits of using these drug products outweigh the risks in the treatment of elevated intraocular pressure in pediatric patients.

1.2 Recommendation on Post-marketing Actions

Not applicable-There are no recommendations for post-marketing actions.

1.2.1 Risk Management Activity

Not applicable-There are no recommendations for risk management activity.

1.2.2 Required Phase 4 Commitments

Not applicable-There are no recommendations for Phase 4 commitments.

1.2.3 Other Phase 4 Requests

Not applicable-There are no other recommendations for Phase 4 commitments.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Clinical study C-01-01 was conducted to obtain needed pediatric information on Betoptic S (betaxolol hydrochloride ophthalmic suspension 0.25%) and Timolol GFS (timolol maleate ophthalmic gel forming solution 0.25% and 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 (original) and amendments on May 4, 2001, July 2, 2002, March 5, 2004, and May 7, 2004 for Betoptic S and issued October 15, 1999 (original) and amendments on May 14, 2001, July 3, 2002, March 12, 2004, and May 7, 2004 for Timolol GFS.

Study C-01-01 was designed to describe the safety and clinical response of Betoptic S 0.25% and Timolol GFS 0.25% and 0.5% in patients 0-6 years of age with a clinical diagnosis of glaucoma or ocular hypertension. The clinical safety and efficacy of Betoptic S and Timolol has been established in adult and elderly patients with glaucoma or ocular hypertension in NDA 19-845 [Betoptic S (betaxolol hydrochloride ophthalmic suspension 0.25%)] and NDA 20-963 [Timolol GFS (timolol maleate ophthalmic gel forming solution 0.25% and 0.5%)]. The submission is based on data from a total of 107 patients: 35 exposed to Betoptic S 0.25%, 36 exposed to Timolol GFS 0.25%, and 36 exposed to Timolol GFS 0.5%.

1.3.2 Efficacy

The purpose of the trial contained in this pediatric supplement was to demonstrate the safety of Betoptic S and Timolol GFS when used in pediatric patients under 6 years old. The support for efficacy for both of these products was extrapolated from the adult trials. (b) (4)

[redacted]

1.3.3 Safety

- The study in these NDA supplements is adequate to establish the safety of the use of betaxolol hydrochloride ophthalmic suspension 0.25% and timolol maleate ophthalmic gel forming solution 0.25% and 0.5% in the pediatric population.

- The type of adverse events seen in pediatric patients treated with betaxolol and timolol 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 studied.

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 applicant 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 Betoptic S and Timolol GFS were consistent between these age groups.

2 INTRODUCTION AND BACKGROUND

See original NDA reviews for betaxolol hydrochloride and timolol maleate.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

See original NDA reviews for betaxolol hydrochloride and timolol maleate.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Study C-01-01 was the only source of clinical data for this submission.

4.2 Tables of Clinical Studies

Listing of Pediatric Clinical Studies for
BETOPTIC S® (betaxolol HCl ophthalmic suspension), 0.25% and TIMOLOL GFS (timolol maleate ophthalmic solution), 0.25% and 0.5%

Study No.	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	Duration of Treatment	Study Status; Type of Report; Report #
Study reports of controlled clinical studies pertinent to the claimed indication:							
C-01-01	A Twelve-Week, Multicenter, Double-Masked, Parallel Group, Primary Therapy Study of the Safety and Efficacy of BETOPTIC S® 0.25% Compared to Timolol Gel Forming Solution 0.25% and 0.5 % in Pediatric Patients with Glaucoma or Ocular Hypertension	prospective, randomized, double-masked, parallel group, active-controlled	BETOPTIC S®: 1 drop each qualifying eye, BID; topical ocular TIMOLOL GFS 0.25%: 1 drop each qualifying eye, QD AM + TIMOLOL GFS vehicle 1 drop each qualifying eye, QD PM; topical ocular TIMOLOL GFS 0.5%: 1 drop each qualifying eye, QD AM + TIMOLOL GFS vehicle 1 drop each qualifying eye, QD PM; topical ocular	total 107 (35 BETOPTIC S; 36 TIMOLOL GFS 0.25%; 36 TIMOLOL GFS 0.5%)	glaucoma or ocular hypertension	12 weeks	Complete; Full/Final; TDOC-0004467

(Study start October 3, 2001 - Study end November 8, 2006)

4.3 Review Strategy

Only study C-01-01 was reviewed for this submission.

4.4 Data Quality and Integrity

DSI was consulted for this study. One site (Dr. Plager) was inspected. He was a high enroller and therefore was selected for routine surveillance. DSI concluded there were no issues with the site. There are no known issues affecting data quality or integrity.

4.5 Compliance with Good Clinical Practices

All studies were conducted in accordance with accepted clinical and ethical standards.

4.6 Financial Disclosures

Financial disclosure forms were reviewed. There were no investigators with proprietary interest or with any significant equity interest in the drug product.

5 CLINICAL PHARMACOLOGY

See original NDA reviews for betaxalol and timolol.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The applicant has not proposed to change the indication for betaxolol or timolol. The indication section of the package insert will remain unchanged. Both are currently indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The results of the study conducted in these supplements have been used to add additional information to the Pediatric Use section of each product label.

6.1.1 Methods

The results of one trial, C-01-01, have been submitted for review in this NDA supplement to support the use of betaxolol and timolol in the pediatric population. The trial was conducted in response with the 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-01-01 was designed to describe the safety and efficacy of Betoptic S, Timolol GFS 0.25%, and Timolol GFS 0.5% in patients 0 to 6 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 Betoptic S and Timolol GFS in pediatric patients.

6.1.3 Study Design

Study C-01-01 was designed to describe the safety and efficacy of Betoptic S, Timolol GFS 0.25%, and Timolol GFS 0.5% in patients 0 to 6 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, and 4 years to < 6 years. A minimum of five patients were to be enrolled per treatment group in the 1 week to < 1 year and 1 year to< 2 years age strata. A minimum of 10 patients were to be 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 (all three products were supplied in identical-appearing bottles and were on the same dosing regimen), active-controlled (each group served as a control for the other therapies), parallel comparison trial with 3 treatment groups: Betoptic S, Timolol GFS 0.25%, and Timolol GFS 0.5%. The study 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	Baseline Phase (Screening & Baseline Visit)	Treatment Phase (Week 2, Week 6, and Week 12) On therapy visits were at 9AM (+/-1 hour)
Betoptic S 0.25%	Continue pre-study ocular hypotensive therapy, or no dosing (if no prior therapy)	Betoptic S 0.25% (8AM and 8PM)
Timolol GFS 0.25% and Timolol GFS 0.5%	Continue pre-study ocular hypotensive therapy, or no dosing (if no prior therapy)	Timolol GFS 0.25% or 0.5% QD (8AM) Vehicle QD (8PM)

Patients were randomized in a 1:1:1 ratio to receive Betoptic S 0.25% bid, Timolol GFS 0.25% qd, or Timolol GFS 0.5% qd. Patients randomized to either Timolol GFS arms were also dosed with vehicle (QD 8 PM). Parents and/or legal guardians of eligible patients in both treatment groups were instructed to dose one drop in each study eye from the bottle labeled “morning” at 8 AM (± 30 minutes) and dose one drop in each study eye from the bottle labeled “evening” at 8 PM (± 30 minutes).

Investigators Who Enrolled Patients For Study C-01-01

Alcon Investigator Number	Principal Investigator	Location	Number of Subjects (ITT)	Betoptic S 0.25%	Timolol GFS 0.25%	Timolol GFS 0.5%
2434	Jason Bacharach, MD	Petaluma, CA	1	0	1	0
3601	M. Barsoum-Homsy, MD	Tampa, FL	3	1	1	1
3020	Allen Beck, MD	Atlanta, GA	1	0	0	1
3312	L. Blumenfeld, MD	Orlando, FL	1	0	1	0
4570	J. Brent Bond, MD	Winston-Salem, NC	1	0	0	1
4559	Y. Bradfield, MD	Madison, WI	2	0	2	0
2909	Monte Del Monte, MD	Ann Arbor, MI	2	1	0	1
1637	Diana DeSantis, MD	Wheat Ridge, CO	2	0	2	0
1931	Monte Dirks, MD	Rapid City, SC	2	0	1	1
2564	Robert Feldman, MD	Houston, TX	2	1	0	1
4067	Sai Gandham, MD	Slingerlands, NY	1	0	1	0
3377	David Godfrey, MD	Dallas, TX	3	3	0	0
1952	Kevin Greenidge, MD	Brooklyn, NY	1	1	0	0
4719	Natalio Izquierdo, MD	San Juan, PR	1	0	0	1
3068	V. Jotterand, MD	Long Beach, CA	1	1	0	0
3521	Marybeth Kapp, MD	Cape Girardeau, MO	2	0	2	0
3880	R. Krishnadas, MD	Madurai, India	8	3	3	2
3882	Anil Mandal, MD	Hyderabad, India	4	0	2	2
3529	Lydia Matkovich, MD	Torrance, CA	3	2	1	0
1960	Peter Netland, MD	Memphis, TN	3	1	1	1
3292	David Plager, MD	Indianapolis, IN	10	3	3	4
648	Alan Robin, MD	Baltimore, MD	4	2	0	2
3879	P. Sathyan, MD	Coimbatore, India	9	3	2	4
3902	Devindra Sood, MD	New Delhi, India	8	2	3	3
4561	Elias Traboulsi, MD	Cleveland, OH	3	0	1	2
3317	R.L. Tychsen, MD	St. Louis, MO	3	1	1	1
3881	Lingam Vijaya, MD	Chennai, India	17	7	5	5
4808	Prateep Vyas, MD	Jalna, India	1	0	1	0
1909	Jess Whitson, MD	Dallas, TX	4	1	1	2
3296	Marion Wilson, MD	Charleston, SC	2	1	0	1

A total of 50 investigators at 50 sites (44 US and 6 India) were included. Of these investigators, 48 received IRB/IEC approval to participate in the study. Thirty investigators enrolled patients and participated in the clinical trial (24 in US and 6 in India). Two additional investigators never received IRB approval, received no test article shipments, and never enrolled patients. Randomization was stratified by investigational site and age group in an effort to achieve a balance of treatment assignments within age groups. Randomization in India was stratified by investigational site and age group for the initial enrollment period (41 of 48 patients) and the final 7 of 48 patients in India were randomized from a central series of patient numbers.

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				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
Identify Contact Lens Wearers	X				
Issue New Contact Len(es)[c]		X			X
Collect Contact Lenses[c]					X
Exit Patients					X

[a]All IOPs were to be taken within 1 hr of 9 AM. Screen and Exit IOPs were taken from anesthetized patients if necessary. Goldmann or Perkins tonometer, or Tono-Pen (only one of these) were used for all IOPs.
[b]Visual acuity measurements were taken using age-appropriate tests. 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 (preferred) or indirect ophthalmoscope and penlight.

IOP was measured at 9 AM (± 1 hour). This time point was selected as it is the time at which the IOP is expected to be at the highest point on the diurnal curve and it provides an assessment of trough effect from twice daily dosing or once-daily in the morning dosing. In this study, if anesthesia or sedation 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, and/or Week 6), IOP assessment was not required at these visits. If necessary, IOP was obtained under anesthesia or sedation at the Week 12 Visit.

Inclusion Criteria:

- 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.

- Either treated prior to the study with an ocular hypotensive medicine(s) on stable dosing regimen for at least 3 weeks prior to Screening visit (no wash out) or not undergoing prior treatment with ocular hypotensive medication(s).
- 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.
- 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:

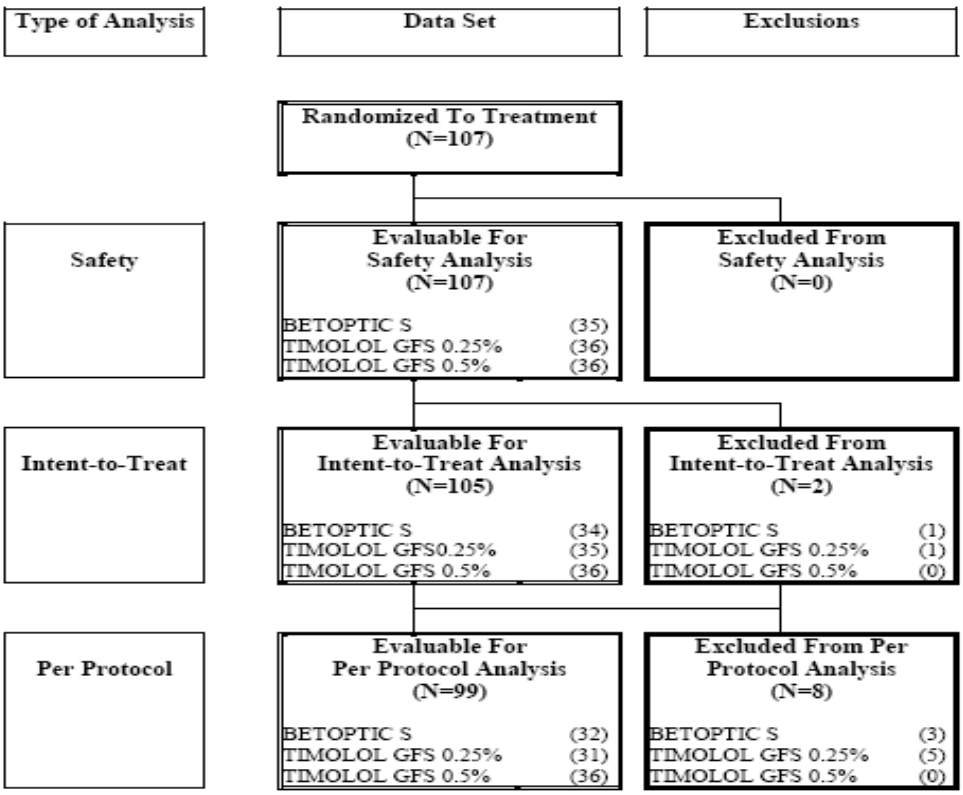
- Children who were >6 yo at the Screening Visit.
- Children who at the time of the Screening Visit were less than one year of age (includes premature neonates) and were at or below the 5th percentile for body weight.
- Patients who had clinically significant or progressive retinal disease such as retinal degeneration, diabetic retinopathy, or retinal detachment in the study eye(s).
- Any abnormality which would have prevented reliable tonometry of either eye.
- History of penetrating keratoplasty in either eye.
- 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.
- Patients with IOP > 36 mmHg in either eye at Screening or Baseline.
- Patients who had any amount of congenital optic atrophy in the study eye(s).
- 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).
- Patients that had fewer than 3 weeks stable dosing (prior to the Screening Visit) of the pre-study IOP-lowering medication(s).
- History of severe or serious hypersensitivity to topical or systemic beta blockers, or any component either of the study medications.
- History of congenital cardiovascular anomalies or abnormalities which would preclude the safe administration of a topical beta blocker. 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.
- 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.
- Therapy with another investigational agent within 30 days of the start of the treatment phase.
- Use of any additional topical or systemic adjunctive ocular hypotensive medication(s) during the study.
- History of severe illness or any other conditions, both ocular and non-ocular, which would have made the patient, in the opinion of the Investigator, unsuitable for the study.
- Additionally, the Alcon Medical Monitor could have declared any patient ineligible for a valid medical reason.

Evaluability

For the safety analysis all patients who received study medication were considered evaluable. In the safety data set (N=107), no imputation was performed for missing data. The intent-to-treat analysis (N=105) included all patients who received study medication and had at least one on-therapy visit. The last IOP observation was carried forward for visits with missing IOP values in the ITT data set. The per protocol analysis (N=99) included all patients who received study medication, had at least one on-therapy visit, and satisfied inclusion/exclusion criteria. No imputation for missing values was performed in the PP data set.

Of the 107 randomized patients, 1 patient on Timolol GFS 0.25% was discontinued from the study prior to collection of any on-therapy study visit data and 1 patient on Betoptic S was discontinued from the study after the Week 6 Visit without any on-therapy IOP assessments; therefore, 105 patients were evaluable for the ITT analysis. In the PP 8 patients were excluded: the abovementioned 2 patients with no on-therapy efficacy data and six patients due to protocol violations [either exclusion criteria violations (n=5) or inadequate time interval from dosing of study medication to IOP assessment at all three on-therapy study visits (n=1)].

Disposition of Randomized, Efficacy-Evaluated, and Safety-Evaluated Patients



[In the ITT group the majority of missing data was due to the 45 patients (14 in Betoptic S, 16 in Timolol GFS 0.25% and 15 in Timolol GFS 0.5%) for whom anesthesia or sedation was required to obtain IOP].

Analysis

The primary statistical objectives of this study were to:

- Describe the IOP-lowering efficacy of Betoptic S, Timolol 0.25%, and Timolol 0.5% in pediatric patients 0 to 5 years of age relative to their baseline status.
- Describe the IOP-lowering efficacy of Betoptic S, Timolol GFS 0.25%, and Timolol GFS 0.5% in pediatric patients 0 to 5 years of age relative to each other in the same age cohort.

The primary efficacy parameter was an assessment of mean IOP change from baseline at 9 AM (=/-1 hour). If only one of a patient's eyes was dosed, the dosed eye was selected for analysis. If both 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 value for each patient. If one of the values was missing or not evaluable then the non-missing value was used as baseline IOP. 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. Effects of the demographic variables (sex, race, ethnicity, iris color, age category and diagnosis) on the results for the primary efficacy variable were examined.

6.1.4 Efficacy Findings

Mean IOP

(b) (4)

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.

(b) (4)

(b) (4)

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(b) (4)

[redacted]

Patients on Topical IOP-lowering Medication at Screening – ITT population (N=105)

Treatment	Number of Patients on Topical IOP-lowering Meds at Screening
Betoptic S	20 (58.8%)
Timolol GFS 0.25%	22 (62.9%)
Timolol GFS 0.5%	28 (77.8%)

6.1.5 Clinical Microbiology

Not applicable. This product is not an antimicrobial.

6.1.6 Efficacy Conclusions

The efficacy of Betoptic S and Timolol GFS has been extrapolated from the adult studies submitted in each of the respective original NDAs. (b) (4)

[redacted]

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The review of safety for Betoptic and Timolol GFS in pediatric patients is based on the results of a single trial. Study C-01-01 enrolled a total of 107 patients with 35 exposed to Betoptic S 0.25%, 36 exposed to Timolol GFS 0.25%, and 36 exposed to Timolol GFS 0.5%. Standard safety measurements were selected to evaluate those parameters associated with use of topical ocular medications and to evaluate possible systemic side effects in pediatric patients. Safety assessments included the following: evaluation of patient alertness, measurement of corneal

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

7.1.1 Deaths

No deaths occurred during this study.

7.1.2 Other Serious Adverse Events

Serious Adverse Events

Patient	Age (in years)	Treatment	Adverse Event	Outcome of Event
648.4031	4	Betoptic S	Convulsion	Resolved w/o treatment
4559.4302	0	Timolol GFS 0.25%	Urinary Tract Infection	Resolved with treatment
3020.1031	5	Timolol GFS 0.5%	Convulsion	Resolved with treatment
3881.4732	5	Timolol GFS 0.5%	Vomiting, Fever, and Infection	Resolved with Treatment

Overall, 4 pediatric patients experienced serious non-ocular adverse events during the study. Overall, no common factors were noted in these serious adverse events that would indicate a safety issue for Betoptic S or Timolol GFS (0.25% and 0.5%).

7.1.3 Dropouts and Other Significant Adverse Events

One pediatric patient with exposure to Betoptic S discontinued participation in the study due to a nonserious ocular adverse event, photophobia (Patient 3879.4505). Overall, no factors were noted in the single adverse event resulting in patient discontinuation that would indicate a safety issue for Betoptic S.

7.1.3.1 Overall profile of dropouts

Patient Status (Safety Population)

	Total	Completed Study	Did NOT Complete Study
Betoptic S	35	30 (85.7%)	5 (14.3%)
Timolol GFS 0.25%	36	29 (80.6%)	7 (19.4%)
Timolol GFS 0.5%	36	33 (91.7%)	3 (8.3%)
TOTAL	107	92 (86%)	15 (14%)

Reasons for Patient Discontinuation from Study (Safety Population)

	Betoptic S (N=35)		Timolol GFS 0.25% (N=36)		Timolol GFS 0.5% (N=36)	
	N	%	N	%	N	%
Inadequate Control of IOP	2	5.7	5	13.9	3	8.3

Adverse Event	1	2.9	0	0	0	0
Patient Decision*	1	2.9	1	2.8	0	0
Noncompliance	1	2.9	1	2.8	0	0

*Patient withdrawn at decision of parent/legal guardian.
**Total patient discontinuations 15 patients (14%)

Reviewer's Comments:
The percentage of patients that discontinued due to inadequate control of IOP varies between the groups.

7.1.3.2 Adverse events associated with dropouts

See section 7.1.3

7.1.3.3 Other significant adverse events

Not applicable. There were no other significant adverse events.

7.1.4 Other Search Strategies

Not applicable-There were no additional search strategies 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 untoward 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 pre-existing/pre-study 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 (optic nerve, retina/macula/choroid, 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.

7.1.5.3 Incidence of common adverse events

Frequency and Incidence of Patients with Adverse Events

	Betoptic S N=35	Timolol GFS 0.25% N=36	Timolol GFS 0.5% N=36
Ocular	11 (31.4%)	7 (19.4%)	8 (22.2%)
Non-ocular	10 (28.6%)	11 (30.6%)	15 (41.7%)
Total	16 (45.7%)	18 (50.0%)	21 (58.3%)

*Patients may have ocular adverse events, non-ocular events, or events of both types. Therefore, the total number may not necessarily correspond to the separate events.

7.1.5.4 Common adverse event tables

Overall Frequency and Incidence of Adverse Events Occurring at Rates Greater Than or Equal to 1.0% (Safety Population N=107)

Adverse Event	Betoptic S (N=35)	Timolol GFS 0.25% (N=36)	Timolol GFS 0.5% (N=36)
Ocular			
Discomfort Eye	2		
Hyperemia Eye	2	1	4
Increased IOP	2		
Corneal Haze	1		
Accidental Injury	1	1	1
Irritation Eye	1		
Pain Eye	1		2
Photophobia	1	1	
Visual Acuity Decreased	1	2	1
Conjunctivitis		2	
Corneal Disease			1
Discharge Eye		1	
Foreign Body Sensation			1
Lid Crusting			2
Optic Nerve Disease		1	1
Pruritis			1
Sticky Sensation			1
Non-Ocular			
Body As a Whole			
Cold Syndrome	3	1	2
Infection	3	2	3
Allergy	1		1
Fever	1	1	2
Flu Syndrome			1
Headache			2
Surgical/Medical Procedure			1
Cardiovascular System			
Bradycardia	1	2	1

Hypotension	1	2	
Digestive System			
Anorexia			1
Toothache			1
Vomiting			2
Hem/Lymphatic			
Anemia		1	
Nervous System			
Convulsions	1		1
Respiratory System			
Cough	1		
Rhinitis		1	
Skin			
Dermatitis	1		
Alopecia		1	
Herpes Zoster			1
Skin Infection		1	
Urticaria		1	
Urogenital System			
Urinary Tract Infection		1	

Reviewer's Comments:

The most common ocular events (infection, hyperemia of eye, cold syndrome, decreased visual acuity, fever, and bradycardia) identified in all 3 treatment groups are consistent with many topical ophthalmic drops. The types of systemic and ocular adverse events 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 Betoptic S and Timolol GFS 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

Not applicable-The size of the database does not allow for evaluation of adverse events that occur at a rate of <1%.

7.1.7 Laboratory Findings

Not applicable. No clinical laboratory evaluations were performed under C-01-01.

7.1.7.1 Overview of laboratory testing in the development program

Not applicable.

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

Not applicable.

7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable.

7.1.7.4 Additional analyses and explorations

Not applicable.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The following vital signs were evaluated during this clinical study: alertness, pulse, systolic and diastolic blood pressure.

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

This amendment contains the results of 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

Patient Alertness
Patient alertness was assessed at Baseline Visit, each subsequent visit, and at exit. Clinically relevant changes in alertness in the opinion of the study investigator were to be reported as adverse events. The Observer's Assessment of Alertness/Sedation Scale was used to evaluate patient alertness based on 4 categories: responsiveness, speech, facial expression, and eyes. A

composite score (with a range of 1 to 5) was recorded that is the lowest level selected by the observer in any of the 4 assessment categories. Eight patients experienced a decrease in alertness. Each change in alertness was attributed to normal sleepiness or to the use of anesthesia or sedation and was not considered an adverse event by the investigator.

Changes in Patient Alertness

Treatment	Total	Change From Baseline to Exit	Change From Baseline to Any Visit
Total	104 *	7	8
Betoptic S	35	2	2
Timolol GFS 0.25%	34	5	6
Timolol GFS 0.5%	35	0	0

*** 2 patients in T 0.25% group and 1 patient in T 0.5% group had missing baseline or follow-up alertness data**

Statistically significant differences were observed between Timolol GFS 0.25% and Timolol GFS 0.5% for changes from baseline to exit visit ($p = 0.0248$) and baseline to any visit ($p = 0.0112$). No other pair-wise treatment group comparisons revealed a statistically significant difference in patient alertness from baseline to exit visit ($p \geq 0.2595$) or baseline to any visit ($p \geq 0.1506$). An assessment of changes from baseline for the measurement of alertness revealed no safety issues for Betoptic S or Timolol GFS (0.25% and 0.5%) in the overall population or any of the 4 subpopulations.

Cardiovascular Parameters

Cardiovascular parameters (pulse and blood pressure) were assessed at Baseline Visit, each subsequent visit, and at exit. A single measurement was obtained after the patient had been resting for at least 4 minutes. Clinically relevant changes from baseline were based upon the clinical judgment of the study investigator and were reported as an adverse event. There were 7 adverse events associated with cardiovascular parameter and were not unexpected in patients exposed to a beta-blocker.

Adverse Events Associated with Changes in Cardiovascular Parameters

Patient ID	Treatment	Age	Description of Adverse Event	Outcome
Pulse				
3880.4601	Betoptic S	0	Decrease in heart rate	Continuing w/o treatment
3880.4612	Timolol GFS 0.25%	1	Decrease in heart rate	Resolved w/o treatment
3880.4632	Timolol GFS 0.5%	4	Decrease in heart rate	Continuing w/o treatment
3880.4633	Timolol GFS 0.25%	5	Decrease in heart rate	Continuing w/o treatment
Blood Pressure				
3880.4613	Betoptic S	1	Decrease in systolic and diastolic blood pressure	Resolved w/o treatment
3880.4633	Timolol GFS 0.25%	5	Decrease in blood pressure	Continuing w/o treatment
3881.4724	Timolol GFS 0.25%	3	Hypotension	Continuing w/o treatment

Pulse Rate

The majority of patients across all treatment groups experienced a 20 BPM or less change from their baseline measurement. A review of individual patient data indicated that most changes greater than 20 BPM were temporary fluctuations and did not reflect clinically relevant trends. Pair-wise comparisons of the treatment groups for the range of pulse changes revealed no statistically significant differences at the exit visit ($p \geq 0.0508$) or any visit ($p \geq 0.0946$). The mean pulse rate decreased slightly from Baseline to Week 12 for the Betoptic S group while the mean pulse rate was relatively constant across each visit for both Timolol GFS 0.25% and Timolol GFS 0.5%. This decrease in pulse rate may be due to the administration of a beta-blocker, but an examination of the individual patient data indicated that very few patients in the Betoptic S group exhibited a consistent trend towards lower pulse rates at each visit following baseline. The slight decrease in the pulse rate for Betoptic S was not consistently noted in all analyses for this treatment group, and thus, may possibly be attributed to the variability expected when obtaining single measurements in young pediatric patients. Thus, no safety issues were identified based upon the review of the pulse rate at each visit. Shift table analysis indicated no statistically significant shift in the pulse rate for the overall safety population when comparing the baseline pulse rate to the exit visit ($p \geq 0.3114$) or to any visit ($p \geq 0.1406$) for any of the treatment groups. A comparison of the 4 age groups (1 week to <1 year, 1 year to <2 years, 2 years to <4 years, 4 years to <6 years) revealed no clinically relevant differences in pulse rate.

Pulse Rate Shift from Baseline To Any Visit

Treatment	N	Low Baseline			Normal Baseline			High Baseline		
		Low	Normal	High	Low	Normal	High	Low	Normal	High
Betoptic S	33	0	1	0	2	26	1	0	3	0
T 0.25%	33	0	0	0	0	25	4	0	4	0
T 0.5%	36	0	0	0	2	21	4	0	9	0

***2 patients in Betoptic S and 3 patients in Timolol 0.25% had missing baseline or follow-up pulse rate data.**

Pulse Rate Shift from Baseline to Exit Visit

Treatment	N	Low Baseline			Normal Baseline			High Baseline		
		Low	Normal	High	Low	Normal	High	Low	Normal	High
Betoptic S	33	0	1	0	2	26	1	0	3	0
T 0.25%	33	0	0	0	0	24	5	0	4	0
T 0.5%	36	0	0	0	1	22	4	0	8	1

***2 patients in Betoptic S and 3 patients in Timolol 0.25% had missing baseline or follow-up pulse rate data.**
Normal pulse rate for infants (0-27 days)=80 to 180 BPM
Normal pulse rate for infants/toddlers (28 days-<2 yo)=80 to 150 BPM
Normal pulse rate for children (2 yo-11yo)=65 to 110 BPM

Descriptive Statistics for Pulse Rate (BPM) by Visit Day

		Screening Visit	**Baseline Visit**	**Week 2 Visit**	**Week 6 Visit**	**Week 12 Visit**
Betoptic S	Mean	101.8	101.5	101.6	99.3	97.8
	Std.	22.5	20.1	22.8	21.2	22.1
	N	33	33	32	29	30
	Median	100	100	98	96	96

T 0.25%	Mean	100.8	101.8	104.8	100.6	105.5
	Std.	18.1	24	20.7	16	18.8
	N	33	35	33	29	29
	Median	100	98	102	102	102
T 0.5%	Mean	104.3	105.2	99.2	101.4	106.9
	Std.	21.5	17.3	18.2	15.9	22
	N	35	36	34	34	33
	Median	100	103	95.5	101	102

Reviewer's Comments:

An assessment of changes from baseline for the parameter of pulse rate revealed no safety issues for Betoptic S or Timolol GFS (0.25% and 0.5%) in the overall population or in any of the 4 subpopulations of patients.

Descriptive Statistics for Systolic Blood Pressure

The majority of patients across all treatment groups experienced a 30 mmHg or less change from their baseline measurement. A review of individual patient data indicated that changes greater than 30 mmHg were transient fluctuations and did not reflect clinically relevant trends. Pair-wise comparisons of the treatment groups for the range of systolic blood pressure changes revealed no statistically significant differences at the exit visit ($p \geq 0.1019$). A pair-wise comparison of Betoptic S and Timolol GFS 0.25% for the range of change of systolic blood pressure from baseline to any visit did reveal a statistically significant change ($p = 0.0369$). This statistically significant change was noted because more Betoptic S patients experienced a decrease in systolic blood pressure than an increase while more Timolol GFS 0.25% patients experienced an increase in systolic blood pressure than a decrease. The mean systolic blood pressure decreased slightly from Baseline to Week 12 for the Betoptic S group while the mean systolic blood pressure was relatively constant across each visit for both Timolol GFS 0.25% and Timolol GFS 0.5%. A comparison of the mean, median, minimum, and maximum values at the Baseline Visit for Betoptic S to those at Screening Visit indicates that the baseline for Betoptic S may be artificially high, particularly for the 1 week to <1 year age group where the mean values differ by 10 BPM. Thus, no safety issues were identified based upon the review of the systolic blood pressure at each visit. A comparison of the 4 age groups (1 week to <1 year, 1 year to <2 years, 2 years to <4 years, 4 years to <6 years) revealed no clinically relevant differences in systolic blood pressure.

Descriptive Statistics for Systolic Blood Pressure

		Screening Visit	Baseline Visit	Week 2	Week 6	Week 12
Betoptic S	Mean	96.4	98.5	95.9	94.6	93.1
	Std.	14.2	14.7	13.7	15.4	12.4
	N	33	34	32	27	29
	Median	94	100	90	90	90
	Min.	73	78	78	76	72
	Max.	140	150	140	143	120
T 0.25%	Mean	91.1	92.3	94.8	94.8	90.1
	Std.	14.8	12.3	13.3	14.7	11.5
	N	32	34	32	29	28
	Median	90	90	94.5	92	90
	Min.	64	70	65	72	57
	Max.	130	127	118	145	108
T 0.5%	Mean	95.3	96.7	95.9	93.5	94.5
	Std.	14.3	14.1	12.6	11.8	13.8
	N	35	36	35	34	32
	Median	90	92	97	90	95
	Min.	68	70	68	70	70
	Max.	133	133	120	115	134

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

		Increase								Decrease							
	Total	>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	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	**102**	**1**	**1.0**	**2**	**2.0**	**6**	**5.9**	**26**	**25.5**	**24**	**23.5**	**24**	**23.5**	**9**	**8.8**	**6**	**5.9**	**4**	**3.9**
BETOPTIC S	**34[a]**	**0**	**0.0**	**1**	**2.9**	**0**	**0.0**	**7**	**20.6**	**9**	**26.5**	**10**	**29.4**	**2**	**5.9**	**3**	**8.8**	**2**	**5.9**
1 week to <1 year old	6	0	0.0	0	0.0	0	0.0	1	16.7	1	16.7	2	33.3	1	16.7	1	16.7	0	0.0
1 year to <2 years old	7	0	0.0	1	14.3	0	0.0	1	14.3	3	42.9	0	0.0	0	0.0	1	14.3	1	14.3
2 years to <4 years old	11	0	0.0	0	0.0	0	0.0	2	18.2	2	18.2	5	45.5	0	0.0	1	9.1	1	9.1
4 years to <6 years old	10	0	0.0	0	0.0	0	0.0	3	30.0	3	30.0	3	30.0	1	10.0	0	0.0	0	0.0
TIMOLOL GFS 0.25%	**32[b]**	**1**	**3.1**	**1**	**3.1**	**1**	**3.1**	**6**	**18.8**	**11**	**34.4**	**7**	**21.9**	**4**	**12.5**	**0**	**0.0**	**1**	**3.1**
1 week to <1 year old	5	0	0.0	0	0.0	1	20.0	0	0.0	2	40.0	0	0.0	1	20.0	0	0.0	1	20.0
1 year to <2 years old	7	1	14.3	0	0.0	0	0.0	2	28.6	1	14.3	3	42.9	0	0.0	0	0.0	0	0.0
2 years to <4 years old	9	0	0.0	1	11.1	0	0.0	2	22.2	5	55.6	0	0.0	1	11.1	0	0.0	0	0.0
4 years to <6 years old	11	0	0.0	0	0.0	0	0.0	2	18.2	3	27.3	4	36.4	2	18.2	0	0.0	0	0.0
TIMOLOL GFS 0.5%	**36**	**0**	**0.0**	**0**	**0.0**	**5**	**13.9**	**13**	**36.1**	**4**	**11.1**	**7**	**19.4**	**3**	**8.3**	**3**	**8.3**	**1**	**2.8**
1 week to <1 year old	5	0	0.0	0	0.0	0	0.0	1	20.0	0	0.0	1	20.0	1	20.0	1	20.0	1	20.0
1 year to <2 years old	7	0	0.0	0	0.0	1	14.3	4	57.1	1	14.3	0	0.0	1	14.3	0	0.0	0	0.0
2 years to <4 years old	11	0	0.0	0	0.0	2	18.2	5	45.5	1	9.1	2	18.2	0	0.0	1	9.1	0	0.0
4 years to <6 years old	13	0	0.0	0	0.0	2	15.4	3	23.1	2	15.4	4	30.8	1	7.7	1	7.7	0	0.0

BETOPTIC S = betaxolol hydrochloride ophthalmic suspension, 0.25%
TIMOLOL GFS 0.25% = timolol maleate ophthalmic gel forming solution, 0.25%
TIMOLOL GFS 0.5% = timolol maleate ophthalmic gel forming solution, 0.5%
p = 0.2975 (BETOPTIC S versus TIMOLOL GFS 0.25%) from Cochran-Mantel-Haenszel test.
p = 0.1019 (BETOPTIC S versus TIMOLOL GFS 0.5%) from Cochran-Mantel-Haenszel test.
p = 0.5177 (TIMOLOL GFS 0.25% versus TIMOLOL GFS 0.5%) from Cochran-Mantel-Haenszel test.
[a] 1 patient had missing baseline or follow-up systolic blood pressure data.
[b] 4 patients had missing baseline or follow-up systolic blood pressure data.
mmHg = millimeters of mercury
Data from Screening visit used for 17 patients where Baseline visit data were missing or not collected.

Reviewer's Comments:

In conclusion, despite the variability in the systolic blood pressure data, an assessment of changes from baseline for the parameter of systolic blood pressure revealed no safety issues for Betoptic S or Timolol GFS (0.25% and 0.5%) in the overall population or in any of the 4 subpopulations of patients. The changes listed above are not statistically significant if corrections are made for the multiple comparisons.

Descriptive Statistics for Diastolic Pressure

The majority of patients across all treatment groups experienced a 20 mmHg or less change from their baseline measurement. A review of individual patient data indicated that changes greater than 20 mmHg were transient fluctuations and did not reflect clinically relevant trends. Pair-wise comparisons of the treatment groups for the range of diastolic blood pressure changes revealed no statistically significant differences at the exit visit ($p \geq 0.1344$) or any visit ($p \geq 0.1196$). Some fluctuation in the data measurements occurred at all the visits, which is expected when single measurements are obtained in children; however the mean diastolic blood pressure was relatively constant across each visit in all treatment groups. A comparison of the 4 age groups (1 week to <1 year, 1 year to <2 years, 2 years to <4 years, 4 years to <6 years) revealed no clinically relevant differences in diastolic blood pressure.

Descriptive Statistics for Diastolic Blood Pressure by Visit Day

		Screening Visit	Baseline Visit	Week 2	Week 6	Week 12
Betoptic S	Mean	60.2	61.8	60.1	59.9	60
	Std.	10.9	9.1	10.7	10.9	11.8
	N	33	34	32	27	29
	Median	60	60	60	60	60
	Min.	30	40	40	40	38
	Max.	80	90	90	90	91
T 0.25%	Mean	56.5	59.1	61	61	57.3
	Std.	12.1	10.6	11.7	9.7	10
	N	32	34	32	29	28
	Median	60	60	60	60	58.5
	Min.	29	35	33	40	36
	Max.	81	89	89	93	74
T 0.5%	Mean	58.7	60.3	60.9	59.7	57.4
	Std.	11.3	11.4	11.4	11.2	11.4
	N	35	36	35	34	32
	Median	60	60	60	60	59
	Min.	36	36	38	39	40
	Max.	84	84	90	90	96

Diastolic Blood Pressure (mmHg) Change from Baseline to Any 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	**102**	**1**	**1.0**	**4**	**3.9**	**14**	**13.7**	**32**	**31.4**	**6**	**5.9**	**22**	**21.6**	**12**	**11.8**	**9**	**8.8**	**2**	**2.0**
BETOPTIC S	**34[a]**	**0**	**0.0**	**2**	**5.9**	**2**	**5.9**	**12**	**35.3**	**2**	**5.9**	**8**	**23.5**	**5**	**14.7**	**2**	**5.9**	**1**	**2.9**
1 week to <1 year old	6	0	0.0	2	33.3	0	0.0	1	16.7	1	16.7	0	0.0	1	16.7	1	16.7	0	0.0
1 year to <2 years old	7	0	0.0	0	0.0	1	14.3	0	0.0	0	0.0	3	42.9	1	14.3	1	14.3	1	14.3
2 years to <4 years old	11	0	0.0	0	0.0	1	9.1	4	36.4	1	9.1	4	36.4	1	9.1	0	0.0	0	0.0
4 years to <6 years old	10	0	0.0	0	0.0	0	0.0	7	70.0	0	0.0	1	10.0	2	20.0	0	0.0	0	0.0
TIMOLOL GFS 0.25%	**32[b]**	**0**	**0.0**	**1**	**3.1**	**7**	**21.9**	**12**	**37.5**	**1**	**3.1**	**7**	**21.9**	**2**	**6.3**	**2**	**6.3**	**0**	**0.0**
1 week to <1 year old	5	0	0.0	1	20.0	0	0.0	0	0.0	0	0.0	3	60.0	0	0.0	1	20.0	0	0.0
1 year to <2 years old	7	0	0.0	0	0.0	3	42.9	2	28.6	0	0.0	0	0.0	1	14.3	1	14.3	0	0.0
2 years to <4 years old	9	0	0.0	0	0.0	2	22.2	4	44.4	0	0.0	2	22.2	1	11.1	0	0.0	0	0.0
4 years to <6 years old	11	0	0.0	0	0.0	2	18.2	6	54.5	1	9.1	2	18.2	0	0.0	0	0.0	0	0.0
TIMOLOL GFS 0.5%	**36**	**1**	**2.8**	**1**	**2.8**	**5**	**13.9**	**8**	**22.2**	**3**	**8.3**	**7**	**19.4**	**5**	**13.9**	**5**	**13.9**	**1**	**2.8**
1 week to <1 year old	5	0	0.0	0	0.0	0	0.0	1	20.0	0	0.0	1	20.0	1	20.0	2	40.0	0	0.0
1 year to <2 years old	7	0	0.0	0	0.0	1	14.3	0	0.0	0	0.0	1	14.3	2	28.6	3	42.9	0	0.0
2 years to <4 years old	11	1	9.1	0	0.0	2	18.2	4	36.4	2	18.2	1	9.1	0	0.0	0	0.0	1	9.1
4 years to <6 years old	13	0	0.0	1	7.7	2	15.4	3	23.1	1	7.7	4	30.8	2	15.4	0	0.0	0	0.0

BETOPTIC S = betaxolol hydrochloride ophthalmic suspension, 0.25%
TIMOLOL GFS 0.25% = timolol maleate ophthalmic gel forming solution, 0.25%
TIMOLOL GFS 0.5% = timolol maleate ophthalmic gel forming solution, 0.5%
p = 0.1447 (BETOPTIC S versus TIMOLOL GFS 0.25%) from Cochran-Mantel-Haenszel test.
p = 0.7645 (BETOPTIC S versus TIMOLOL GFS 0.5%) from Cochran-Mantel-Haenszel test.
p = 0.1196 (TIMOLOL GFS 0.25% versus TIMOLOL GFS 0.5%) from Cochran-Mantel-Haenszel test.
[a] 1 patient had missing baseline or follow-up diastolic blood pressure data.
[b] 4 patients had missing baseline or follow-up diastolic blood pressure data.
To any visit is representative of the worst case scenario and is defined as the maximum change (increase or decrease) in diastolic blood pressure from baseline to any scheduled or unscheduled visit.
If the patient experiences both an increase and a decrease of the same magnitude, the magnitude of the increase is used in this table.
mmHg = millimeters of mercury
Data from Screening visit used for 17 patients where Baseline visit data were missing or not collected.

Reviewer's Comments:

An assessment of changes from baseline for the parameter of diastolic blood pressure revealed no safety issues for Betoptic S or Timolol GFS (0.25% and 0.5%) in the overall population or in any of the 4 subpopulations of patients.

7.1.8.4 Additional analyses and explorations

Not applicable. Additional explorations were not conducted.

7.1.9 Electrocardiograms (ECGs)

Not applicable. ECGs were not conducted during this study.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

Not applicable. The drugs used in this trial are not known to be genotoxic when dosed topically.

7.1.12 Special Safety Studies

The following physical findings were evaluated during this clinical study: visual acuity, ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens, vitreous), dilated fundus parameters (retina/macula/choroid, optic nerve, disc pallor), cup/disc ratio, and corneal diameter.

Visual Acuity

Visual acuity was measured at Baseline Visit, each subsequent visit, and at exit. For pre-verbal patients visual acuity was determined using a fixation and follow test and for verbal patients BCVA was measured in Snellen values and then converted to logMAR-equivalent score. Clinically relevant changes in visual acuity for pre-verbal patients were defined as a change from normal to abnormal, and for verbal patients was defined as a decrease of 3 or more logMAR-equivalent lines. No pre-verbal patients experienced a clinically relevant change and a total of 5 verbal patients experienced a clinically relevant worsening in visual acuity.

Adverse Events Associated With a Change in Visual Acuity

Patient ID	Treatment	Age	Description of Adverse Event	Outcome
648.4031	Betoptic S	4	Decreased visual acuity OD	Continuing with treatment
648.4032	Timolol GFS 0.5%	5	Decreased visual acuity OD	Resolved without treatment
1909.0932	Timolol GFS 0.25%	5	Decreased visual acuity OU	Continuing without treatment
3880.4634	Timolol GFS 0.25%	4	Decreased visual acuity OD	Continuing without treatment

Pair-wise comparisons of the treatment groups and age groups revealed no statistically significant differences at the exit visit ($p \geq 0.6398$). Additional analysis showed no safety issues when analyzing visual acuity changes from baseline to exit visit and baseline to any visit for Betoptic S or Timolol GFS (0.25% and 0.5%) in the overall population or in any of the age-specific subpopulations.

Ocular Signs

An assessment of ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens, vitreous) was performed at Baseline Visit, each subsequent visit, and at exit. Clinically relevant changes in ocular signs were defined as a 1 unit or more increase from baseline. One patient had a change in the cornea and three patients had a change in eyelids/conjunctiva. No patients experienced a clinically relevant increase in iris/anterior chamber, lens, or vitreous.

Adverse Events Related To Increase in Ocular Signs Changes

Patient ID	Treatment	Age	Adverse Event	Outcome
Cornea				
3292.1303	Betoptic S	0	Corneal haze OS	Resolved with treatment
Eyelid/Conj				
3296.1421	Betoptic S	2	Redness OU	Resolved without treatment
3902.5011	Timolol GFS	1	Conjunctival	Continuing with treatment

	0.5%		Congestion OU	
2564.5332	Timolol GFS 0.5%	5	Eyelid crusting OU	Resolved without treatment

Pair-wise comparisons of the treatment groups and age groups revealed no statistically significant differences for cornea or eyelids/conjunctiva ($p \geq 0.4930$). Additional analysis showed no safety issues based upon an analysis of changes in ocular signs parameters (eyelids/conjunctiva, cornea, iris/anterior chamber, lens, vitreous) from baseline for Betoptic S or Timolol GFS (0.25% and 0.5%).

Dilated Fundus Parameters

An assessment of fundus parameters (optic nerve, retina/macula/choroid, disc pallor) was performed at Screening visit and at exit. Clinically relevant changes in dilated fundus parameters were defined as an increase of 1 or more units from baseline. One patient in the experienced a clinically relevant change in optic nerve from baseline to the exit visit. No patients experienced a clinically relevant increase in retina/macula/choroid or disc pallor.

Adverse Event Associated With Optic Nerve Change

Patient ID	Treatment	Age	Description of Adverse Event	Outcome
3880.4634*	Timolol GFS 0.25%	4	Progressive glaucomatous optic nerve damage OU	Continuing with treatment

*This patient, who was on Timolol 0.5% before entering the study, had moderate optic nerve damage in both eyes at Screening that progressed to a more severe form by Week 12.

Pair-wise comparisons of the treatment groups and age groups revealed no statistically significant differences for optic nerve ($p \geq 0.4928$). No safety issues were identified based upon an analysis of changes in dilated fundus parameters from baseline for Betoptic S or Timolol GFS (0.25% and 0.5%) in the overall population or in any of the age-specific subpopulations.

Cup/Disc Ratio

An assessment of cup/disc ratio was performed at Screening visit and at exit. Clinically relevant changes in cup/disc ratio in the opinion of the study investigator were reported as adverse events. One patient experienced a clinically relevant change in cup/disc ratio from baseline to the exit visit.

Adverse Event Associated With a Change in Cup/Disc Ratio

Patient ID	Treatment	Age	Description of Adverse Event	Outcome
3292.1304	Timolol GFS 0.5%	0	Increase in cup/disc ratio OD	Continuing without treatment

*This patient, who was on Timolol 0.25% prior to enrolling in this study, had a diagnosis of congenital glaucoma. At Screening, the right eye had a measurement of 0.4 that progressed to a measurement of 0.5 at Week 12, which the investigator felt was a clinically relevant change in cup/disc ratio.

No statistically significant differences ($p \geq 0.1748$) for changes from baseline in cup/disc ratio were noted in any of the treatment groups or age groups. No safety issues were noted based upon a review of cup/disc ratio analyses for Betoptic S or Timolol GFS (0.25% and 0.5%) in the overall safety population or in any of the age-specific subpopulations.

Corneal Diameter

An assessment of corneal diameter was performed at Screening visit and at exit. Clinically relevant changes in corneal diameter in the opinion of the study investigator were to be reported as adverse events. The worse study eye was used for analyses, which is the eye treated with study drug that showed the largest increase in corneal diameter. Two patient-eyes (in 2 separate patients) experienced a corneal diameter increase of 1 mm or greater.

Patient Eyes with a Corneal Diameter Increase of 1mm or Greater

Patient ID	Treatment	Age	Eye	Baseline Visit	Exit Visit	Change at Exit Visit
3292.1304	Timolol GFS 0.5%	0	OD	12.0	13.0	1.0
3879.4501	Timolol GFS 0.25%	0	OS	10.0	11.0	1.0

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

	Baseline Visit	Change at Exit Visit
Betoptic S	12.11	-0.09
Timolol GFS 0.25%	12.38	0.01
Timolol GFS 0.5%	12.24	0.02

A review of the change in corneal diameter for worse study eye and worse eye and a review of the patient listing of corneal diameter changes revealed no clinically relevant differences in corneal diameter when comparing the 4 age groups. In an assessment of changes from baseline for corneal diameter revealed no safety issues for Betoptic S or Timolol GFS (0.25% and 0.5%) in the overall population or in any of the 4 subpopulations of patients.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no new information or expectation that the products will have withdrawal effects or abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

This drug has not been tested in pregnant women.

7.1.15 Assessment of Effect on Growth

Height and weight data were not collected as part of this protocol.

7.1.16 Overdose Experience

There is no new information or expectation of potential overdoses with Betoptic S or Timolol GFS.

7.1.17 Post-marketing Experience

Betoptic S is currently approved in 89 countries. A review of all worldwide spontaneous post-marketing reports since product approval (December 1989) through August 31, 2006 for Betoptic S identified 2 reports for pediatric patients (less than 18 years old).

Pediatric Post-Marketing Reports for Betoptic S

Country	Age	Sex	MedDRA Code	Outcome	Details of Report
US	3 yo	M	Speech disorder, hyperkinesia	Resolved	Patient is developmentally delayed. Upon follow up, patient is now on Timoptic with no difficulties. Mother gave him an OTC cough/cold/flu preparation and noted the same reaction. She believes that her son also received this type of OTC medication while on Betoptic S.
US	5 yo	F	Headache	Continuing	Patient had a corneal transplant several years prior and was using Xalatan concomitantly. Two days after starting Betoptic S, patient experienced a headache and was taken to the emergency department for treatment (unknown). Patient continues to have headaches frequently.

Timolol GFS 0.25% and 0.5% is currently approved in 19 countries. A review of all worldwide spontaneous post-marketing reports since product launch (December 1998) through August 31, 2006 for Timolol GFS (0.25% and 0.5%) identified no spontaneously reported adverse reactions reported for the pediatric population (less than 18 years of age) for Timolol GFS 0.25% or 0.5%.

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

See section 4.2

7.2.1.2 Demographics

Demographics by Treatment Group (N=107)

	Total (N=107)		**Betoptic S 0.25% (N=35)**		**Timolol GFS 0.25% (N=36)**		**Timolol GFS 0.5% (N=36)**	
Age	N	%	N	%	N	%	N	%
1 week to <1 y.o.	17	15.9	6	17.1	6	16.7	5	13.9
1 year to <2 y.o.	21	19.6	7	20	7	19.4	7	19.4
2 years to <4 y.o.	33	30.8	11	31.4	11	30.6	11	30.6
4 years to <6 y.o.	36	33.6	11	31.4	12	33.3	13	36.1
Sex								
Male	63	58.9	18	51.4	27	75	18	50
Female	44	41.1	17	48.6	9	25	18	50
Ethnicity								
Hispanic or Latino	11	10.3	5	14.3	3	8.3	3	8.3
Not Hispanic or Latino	96	89.7	30	85.7	33	91.7	33	91.7
Race								
Asian	48	44.9	16	45.7	16	44.4	16	44.4
Black or African American	15	14	4	11.4	4	11.4	7	19.4
Caucasian	36	33.6	12	34.3	13	36.1	11	30.6
Multi-Racial	2	1.9	0	0	1	2.8	1	2.8
Other	6	5.6	3	8.6	2	5.6	1	2.8
Iris Color								
Blue	14	13.1	5	14.3	6	16.7	3	8.3
Brown	79	73.8	26	74.3	26	72.2	27	75
Green	1	0.9	0	0	1	2.8	0	0
Grey	2	1.9	1	2.9	1	2.8	0	0
Hazel	8	7.5	3	8.6	1	2.8	4	11.1
No iris**	3	2.8	0	0	1	2.8	2	5.6
Diagnosis								
Ocular Hypertension	2	1.9	1	2.9	1	2.8	0	0
Primary Congenital Glaucoma	63	58.9	17	48.6	26	72.2	20	55.6
Primary Glaucoma Associated with Systemic or Ocular Abnormalities	16	15	4	11.4	5	13.9	7	19.4
Secondary Glaucoma	26	24.3	13	37.1	4	11.1	9	25

*Mean age 2.5 years old (Range 12 days-5 years old)
**3 Patients (3292.1313, 3317.2122, and 4808.8001) had "No iris" secondary to diagnosis of Aniridia.
*******Overall, there were more male (58.9%) than female (41.1%) patients. Most patients were Caucasian (33.6%) or Asian (44.9%), and the majority were classified as Not Hispanic (89.7%). Further, the majority of patients had brown irides (73.8%), and most patients were diagnosed with primary congenital glaucoma (58.9%).

Age Distribution of Enrolled Patients (Safety Population N=107)

Country	Treatment	1 week to <1 y.o.	1 year to <2 y.o.	2 years to <4 y.o.	4 years to <6 y.o.	Total
US	Betoptic S	4	3	6	6	19
	Timolol GFS 0.25%	3	5	5	7	20
	Timolol GFS 0.5%	3	3	5	9	20
India	Betoptic S	2	4	5	5	16
	Timolol GFS 0.25%	3	2	6	5	16
	Timolol GFS 0.5%	2	4	6	4	16
Total	Betoptic S	6	7	11	11	35
	Timolol GFS 0.25%	6	7	11	12	36
	Timolol GFS 0.5%	5	7	11	13	36
	Subtotal	17	21	33	36	107

7.2.1.3 Extent of exposure (dose/duration)

Duration of Exposure to Study Drug
Safety Population (N=107)

	1-15 Days	16-43 Days	44-85 Days	>85 Days	Total
Betoptic S	2 (5.7%)	3 (8.6%)	16 (45.7%)	14 (40%)	35
Timolol GFS 0.25%	4 (11.1%)	3 (8.3%)	18 (50%)	11 (30%)	36
Timolol GFS 0.5%	1 (2.8%)	0	28 (77.8%)	7 (19.4%)	36
Total	7 (6.5%)	6 (5.6%)	62 (57.9%)	32 (29.9%)	107

Patients with 12 Weeks Exposure to Study Drug
Safety Population (N=107)

Treatment	Total	12 Weeks	
		N	%
Betoptic S	35	30	85.7
Timolol GFS 0.25%	36	28	77.8
Timolol GFS 0.5%	36	28	77.8

*12 weeks of exposure to study drug defined as 81 days or greater.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable. There were no secondary sources of information used to review these NDA supplements.

7.2.2.1 Other studies

Not applicable. There were no secondary sources of information used to review these NDA supplements.

7.2.2.2 Post-marketing experience

See section 7.1.17

7.2.2.3 Literature

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

7.2.3 Adequacy of Overall Clinical Experience

The study contained in these NDA supplements conformed to the requirements of the pediatric written request. The design of the trial as well as the number and types of patients studied were adequate to assess the safety of betaxolol and timolol.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable. There was 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 were adequately addressed in the design and conduct of this clinical trial.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

There is no new clinical pharmacology information submitted in these supplements.

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

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

The type of ocular and systemic adverse events reported in this trial are consistent with prior trials of these drug products.

7.4 General Methodology

All methodological issues have been discussed throughout the review.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

There is only one study contained in these NDA supplements.

7.4.1.1 Pooled data vs. individual study data

There is only one study contained in these NDA supplements

7.4.1.2 Combining data

There is only one study contained in these NDA supplements.

7.4.2 Explorations for Predictive Factors

Predictive factors related to 4 age groups were explored in this trial. In review of the 4 age groups 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. 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

See section 7.3

8 ADDITIONAL CLINICAL ISSUES

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 these NDA supplements is adequate to establish the safety of the use of betaxolol ophthalmic suspension 0.25% and timolol maleate ophthalmic gel forming solution 0.25% and 0.5% in the pediatric population.*

- *The type of adverse events seen in pediatric patients treated with betaxolol and timolol are consistent with those seen in the adult population.*

- *There were no clinically relevant differences in the adverse event profiles between the age group strata studied.*

9.2 Recommendation on Regulatory Action

NDA 19-845/SE5 and NDA 20-963/SE5 are recommended for approval. The clinical study contained in this supplement supports the use of betaxolol ophthalmic suspension 0.25% and timolol maleate ophthalmic gel forming solution 0.25% and 0.5% in the pediatric population. The benefits of using this drug product outweigh the risks in the treatment of elevated intraocular pressure in pediatric patients.

9.3 Recommendation on Post-marketing Actions

There are no recommendations for post-marketing actions.

9.3.1 Risk Management Activity

There are no recommendations for 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

The labeling has been re-written into the new Physician Labeling Rule format. Changes have been made to the Betoptic S, Timolol GFS 0.25%, and Timolol GFS 0.5% labels. There is no proposed change to the indication section. The Pediatric Use and Adverse Events sections have been updated to reflect the results of the pediatric study.

9.5 Comments to Applicant

None.

10 Appendices

10.1 Review of Individual Study Reports

Not applicable.

10.2 Line-by-Line Labeling Review

Sponsor recommended additions are double underlined and deletions are noted by double strike-through. Reviewer's recommended changes are in red.

15 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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6/5/2007 02:13:50 PM
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