U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-493/S-009
Drug Name:	ZYMAR® (gatifloxacin ophthalmic solution) 0.3%
Indication(s):	Treatment of bacterial conjunctivitis (b) (4)
Applicant:	Allergan, Inc
Date(s):	Submitted: March 30, 2009
	PDUFA due date: September 30, 2009
Review Priority:	Standard
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Keywords: bacterial conjunctivitis, clinical success rate, microbiological cure rate

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

ZYMAR® (gatifloxacin ophthalmic solution) 0.3% was approved under NDA 21,493 on 28 March 2003 for the treatment of bacterial conjunctivitis in subjects 1 year of age and older. This supplemental New Drug Application (sNDA) includes the results from a Phase 4 pediatric study (Study 198782-003) for the safety and efficacy of ZYMAR® in patients from birth to 31 days of age. This submission fulfills the written pediatric study request from the FDA.

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1.2 Brief Overview of Clinical Studies

Study 198782-003, the single study included in this sNDA, was a 7-day, Phase 4, randomized, double-masked, parallel-group, multicenter, superiority study conducted to evaluate the safety and efficacy of topical gatifloxacin 0.3% ophthalmic solution compared with topical moxifloxacin 0.5% ophthalmic solution for the treatment of presumed bacterial conjunctivitis in subjects from birth to 31 days of age.

This study was designed for inclusion of subjects from birth to 31 days of age who were in good general health and were clinically diagnosed with presumed bacterial conjunctivitis or bacterial blepharoconjunctivitis as defined by the presence of mild, moderate, or severe conjunctival erythema and discharge. Enrolled subjects were randomized (1:1 treatment allocation ratio) to receive 6 days of treatment with either gatifloxacin 0.3% ophthalmic solution or moxifloxacin 0.5% ophthalmic solution. Of 171 subjects enrolled into the study, 85 were randomized to the gatifloxacin 0.3% ophthalmic solution group and 86 were randomized to the moxifloxacin 0.5% ophthalmic solution group. The study was conducted at 22 clinical study sites, including 21 US sites and one Canadian site with 11 subjects enrolled.

Subjects in both treatment groups received one drop of the assigned study medication TID in each eye clinically diagnosed with bacterial conjunctivitis starting on Day 1 and continuing through Day 6. All subjects were to complete visits on Days 1 (baseline), 2, 3, 5, and 7.

The primary efficacy endpoint was clinical success rate, defined as the proportion of subjects with clearing of both conjunctival erythema and conjunctival discharge (i.e., both the conjunctival erythema and conjunctival discharge scores reached 0) in the study eye at Day 7. Secondary efficacy measures included microbiological improvement and improvement in ocular signs, i.e., lid crusting, lid erythema, lid edema, conjunctival discharge, conjunctival erythema, conjunctival edema, and corneal appearance.

1.3 Statistical Issues and Findings

Two issues that are related to sample size estimation and efficacy evaluation are discussed in this section. The statistical analysis results for the primary efficacy endpoint and important secondary efficacy endpoints presented in the Clinical Study Report (CSR) were replicated by the reviewer. No specific statistical issues related to analysis were noted.

1.3.1 Sample Size Determination

According to the study protocol, the sample size of the study was determined based on the assumption that the clinical success rate of moxifloxacin 0.5% ophthalmic solution would be 53%, which was observed in a previously conducted study in neonates (Study C-01-34, (b) (4)

(b) (4). With 60 subjects in each treatment group who had a positive culture at baseline and were therefore eligible to be included in the mITT population, there would be 62%, 79%, and 82% power to detect a true difference of 20%, 24%, and 25% in clinical success rates between gatifloxacin 0.3% ophthalmic solution and moxifloxacin 0.5% ophthalmic solution on Day 7.

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1.3.2 Efficacy Evaluation

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2. INTRODUCTION

2.1 Overview

Gatifloxacin is a synthetic, broad-spectrum 8-methoxy fluoroquinolone antibiotic agent that exerts its antibacterial action by inhibiting DNA gyrase (an enzyme involved in the replication, transcription and repair of bacterial DNA) and topoisomerase IV (an enzyme that plays a key role in the partitioning of the chromosomal DNA during bacterial cell division). Gatifloxacin has been shown to be active, both *in vitro* and in conjunctival infections, against most strains of *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Haemophilus influenzae, Corynebacterium propinquum,* and *Streptococcus mitis*.

The original NDA 21-493 was submitted on 29 May 2002. ZYMAR® (gatifloxacin 0.3% ophthalmic solution) received approval on 28 March 2003 for the treatment of bacterial conjunctivitis in subjects 1 year of age and older. The Agency issued a formal Written Request for a pediatric study in neonates (birth to 31 days of age) on 04 October 2001. The Written Request was subsequently amended on 02 July 2002, 07 May 2004 and 13 July 2007.

In accordance with the Written Request and advice received from FDA, Allergan conducted Study 198782-003, a randomized, multicenter, Phase 4 clinical trial for the use of gatifloxacin 0.3% ophthalmic solution in the treatment of bacterial conjunctivitis in neonates from birth to 31 days of age. A meeting with FDA was held on 30 October 2006 to discuss the clinical trial design for the pediatric study. The agreements from the meeting were incorporated into the clinical trial design and statistical analysis plan for the study. The agreements include the following:

- Use of Vigamox® (moxifloxacin 0.5% ophthalmic solution) as the acceptable comparator
- The "success" endpoint for this indication is a statistically significant difference in the resolution of the signs and symptoms of bacterial conjunctivitis (normal conjunctiva, no discharge) when both the conjunctival discharge and conjunctival erythema scores reach a score of zero.
- The current PI for ZYMAR® instructs patients to instill 1 drop in each affected eye every 2 hours on Days 1 and 2 followed by 1 drop 4 times a day for Days 3 and 7. The dosing regimen to be used in the neonatal study was 1 drop of either moxifloxacin 0.5% ophthalmic solution or gatifloxacin 0.3% ophthalmic solution in the affected eye(s) TID starting on Day 1 and continuing to Day 7.

2.2 Data Sources

The sNDA submission, including the Applicant's study report and data sets for the clinical study are available on EDR at "\\CDSESUB1\EVSPROD\NDA021493\0002".

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study 198782-003 was a 7-day, Phase 4, randomized, double-masked, parallel-group, multicenter, superiority study comparing gatifloxacin 0.3% ophthalmic solution with moxifloxacin 0.5% ophthalmic solution for the treatment of bacterial conjunctivitis in subjects from birth to 31 days of age.

A total of 171 eligible subjects were enrolled into the study and were randomized (1:1 treatment allocation ratio) to receive 6 days of treatment of gatifloxacin 0.3% ophthalmic solution (N=85) or moxifloxacin 0.5% ophthalmic solution (N=86). Subjects in both treatment groups received 1 drop of the assigned study medication TID in each eye clinically diagnosed with bacterial conjunctivitis starting on Day 1 and continuing through Day 6. If only one eye was qualified, this eye was the study eye. If both eyes were qualified, the study eye was the culture positive eye at baseline. If both eyes were qualified and culture positive at baseline or both eyes were qualified and culture negative at baseline, then the right eye was the study eye.

The study consisted of 5 or 6 scheduled visits. All subjects were to complete visits on Day 1 (baseline), Day 2, Day 3, Day 5, and Day 7. See the schedule of study visits and procedures for additional details.

The primary efficacy endpoint was clinical success rate, defined as the proportion of subjects with clearing of both conjunctival erythema and conjunctival discharge (i.e., both the conjunctival erythema and conjunctival discharge scores reached 0) in the study eye at Day 7.

Secondary efficacy measures included microbiological improvement and improvement in ocular signs, i.e., lid crusting, lid erythema, lid edema, conjunctival discharge, conjunctival erythema,conjunctival edema, and corneal appearance. A subject was considered to have microbiological improvement if all bacterial species present at Day 1 (baseline) was eradicated or reduced.

SCHEDULE OF VISITS AND PROCEDURES

	Scheduled Visits					
					Exit	
	Day 1 (Baseline)	**Day 2[a]**	**Day 3**	**Day 5[a]**	**Day 7[b]**	**Unqualified Eye Follow-up[c]**
Informed consent and privacy forms	X					
Medical and ophthalmic history	X					
Demographics (gender, race, date of birth)	X					
Concomitant medications/ concurrent procedures	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X
Vital signs (heart rate, respiratory rate, temperature)	X	X	X	X	X	X
Subject body weight	X	X	X	X	X	X
Ocular exam of both eyes	X		X		X[d]	X[d]
Ocular exam (required if an unqualified eye becomes clinically diagnosed with bacterial conjunctivitis)		X[e]		X[e]		
Conjunctival swab (qualified eye(s))[f]	X				X	
Conjunctival swab (unqualified eye -if this eye becomes clinically diagnosed with bacterial conjunctivitis)		X[g]	X[g]	X[g]		X
Serious medical events	X					
Randomization	X					
Instill first dose of study medication[h]	X					
Adverse events	X	X	X	X	X	X
Dispense study medication	X	X[i]	X[i]	X[i]		
Collect study medication from subjects exiting the study					X	X

a The Day 2 and Day 5 visits can be performed either by telephone or by office visit at the discretion of the investigator. If a telephone visit is performed for either of these visits the only assessment to be completed is the collection of adverse events.

b The Day 7 visit should occur between 12 hours (minimum) to 48 hours (maximum) after the last dose of study medication is administered in the qualified eye(s). If an unqualified eye becomes clinically diagnosed with bacterial conjunctivitis at Day 7, the subject should be exited from the study and treated off study based on standard of care. The Day 7 visit will be considered the exit visit for subjects who do not become clinically diagnosed with bacterial conjunctivitis in an unqualified eye prior to the Day 7 visit.

c An Unqualified Eye Follow-up visit(s) is required for subjects who become clinically diagnosed with bacterial conjunctivitis in an unqualified eye after the Day 1 visit and prior to the Day 7 visit. The subjects should be followed after Day 7 either by telephone or office visit(s) at the discretion of the investigator. These visit(s) should be performed every 2 days or less until the subject exits the study. The duration of treatment for the unqualified eye will be left to the discretion of the investigator, but should not exceed 6 days. The final Unqualified Eye Follow-up visit requires an office visit and will be considered the exit visit for subjects who become clinically diagnosed with bacterial conjunctivitis in an unqualified eye and should occur after the last dose of study medication is administered.

d The ocular exam at the Day 7 and the final Unqualified Eye Follow-up visit must be performed by the ophthalmologist.

e If an unqualified eye becomes clinically diagnosed with bacterial conjunctivitis after Day 1 and prior to Day 7, an ocular exam of both eyes is required to be performed on the day of diagnosis.

f At Day 1 conjunctival swabs will be obtained from the qualified eye(s) (clinically diagnosed eye(s) with bacterial conjunctivitis on Day 1) and sent to the reference laboratory for bacteria and Chlamydia testing. On Day 7, a conjunctival swab for bacteria will be obtained from the qualified eye(s) and sent to the reference lab for testing.

g If an unqualified eye becomes clinically diagnosed with bacterial conjunctivitis after the Day 1 visit and prior to the Day 7 visit, a conjunctival swab of the unqualified eye will be obtained prior to the instillation of study medication in the unqualified eye. A follow-up conjunctival swab will be obtained at the final Unqualified Eye Follow-up visit.

h Prior to the first dose of study medication, a medical history, ocular exam, and conjunctival swab will be obtained and the subject will be assessed for study eligibility. The subject will be observed for adverse events over the 30-minute period following instillation of the first dose of study medication.

i A second (2nd) bottle will be dispensed for an unqualified eye that becomes clinically diagnosed with bacterial conjunctivitis after Day 1

Data Source: Page 17 of the study protocol.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

Three analysis populations were defined: the modified Intent-to-Treat (mITT) population, which consists of all randomized subjects who were culture positive in at least one eye at baseline; the Intent-to-Treat (ITT) population, which consists of all randomized subjects regardless of the baseline culture results; and the safety population, which includes all treated subjects.

Of the 171 subjects enrolled into the study, 85 were randomized to the gatifloxacin 0.3% ophthalmic solution group and 86 were randomized to the moxifloxacin 0.5% ophthalmic solution group. A total of 95.3% (163/171) of subjects in the ITT population completed the 6-day treatment period: 83 in the gatifloxacin 0.3% ophthalmic solution group and 80 in the moxifloxacin 0.5% ophthalmic solution group. 8 of 171 (4.7%) enrolled subjects discontinued from the study, including 2 gatifloxacin and 6 moxifloxacin subjects. Only 1 subject discontinued due to an adverse event and no subjects discontinued due to lack of efficacy. 120 were culture positive at baseline and therefore included in the mITT population (56 gatifloxacin and 64 moxifloxacin). Subject disposition and subject completion status by analysis population are presented in Table 1 and Table 2, respectively.

Table 1: Subject Disposition, Study 198782-003

Category	Gatifloxacin 0.3%	Moxifloxacin 0.5%	Total
Randomized	85	86	171
ITT Population	85	86	171
mITT Population	56	64	120
Safety Population	85	86	171

Source: Applicant's CSR 198782-003

Table 2: Subject Completion Status, Study 198782-003

Category	ITT Population		mITT Population	
	Gatifloxacin 0.3% (N=85)	Moxifloxacin 0.5% (N=86)	Gatifloxacin 0.3% (N=56)	Moxifloxacin 0.5% (N=64)
Completed	83	80	56	61
Discontinued	2	6	0	3
Adverse Event	0	1	0	1
Ocular	0	0	0	0
Non-ocular	0	1	0	1
Lack of Efficacy	0	0	0	0
Lost to Follow-up	0	2	0	1
Personal Reasons	2	0	0	0
Protocol Violation	0	3	0	1
Other	0	0	0	0

Source: Applicant's CSR 198782-003, Tables 14.1-1.1 and 14.1-1.2

Overall for the ITT population, the mean age was 15.2 days (range 3 to 31 days) and mean weight was 3.76 kg. There were 112 males (65.5%) and 59 females (34.5%). The majority of the

population was non-Caucasian (53.8%). With the exception of gender, the distributions of these demographics and baseline characteristics were relatively even between two treatment groups.

Demographics and baseline characteristics for the mITT population were similar to those of the ITT population. Demographics and baseline characteristics for the ITT and mITT populations are presented in Table 3.

Table 3: Demographics and Baseline Characteristics, Study 198782-003

Characteristic	ITT Population		mITT Population	
	Gatifloxacin 0.3% (N = 85)	Moxifloxacin 0.5% (N = 86)	Gatifloxacin 0.3% (N = 56)	Moxifloxacin 0.5% (N = 64)
Age, days				
Mean (SD)	15.2 (6.59)	15.2 (6.05)	15.0 (6.41)	15.5 (5.92)
Sex, N (%)				
Male	48 (56.5)	64 (74.4)	30 (53.6)	48 (75.0)
Female	37 (43.5)	22 (25.6)	26 (46.4)	16 (25.0)
Race, N (%)				
Caucasian	43 (50.6)	36 (41.9)	30 (53.6)	24 (37.5)
Black	3 (3.5)	4 (4.7)	2 (3.6)	2 (3.1)
Asian	(5 (5.9)	3 (3.5)	2 (3.6)	2 (3.1)
Hispanic	32 (37.6)	40 (46.5)	22 (39.3)	34 (53.1)
Other	2 (2.4)	3 (3.5)	0 (0.0)	2 (1.7)
Weight, kg				
Mean (SD)	3.72 (0.539)	3.80 (0.602)	3.75 (0.550)	3.82 (0.661)

Source: Applicant's CSR 198782-003, Tables 10.1 and 10.2

3.1.3 Statistical Methodologies

The clinical success rates were compared between the treatment groups (gatifloxacin 0.3% ophthalmic solution versus moxifloxacin 0.5% ophthalmic solution) using the Pearson's chi-square test, or Fisher's exact test if at least 25% of the cells had an expected count of less than 5. A 2-sided 95% confidence interval (CI) for the treatment difference in success rate was constructed using the normal approximation for binary variables. The analysis of the endpoint based on mITT population was the primary analysis, whereas the analysis using the ITT population was considered as secondary.

The method of last observation carried forward (LOCF) was applied to impute missing values. For the mITT population, missing values were only imputed from the last post-baseline value if available. For the ITT population, missing values were imputed based on the last available observation, regardless of whether it was collected from a post-baseline visit.

Secondary efficacy measures included microbiological improvement and improvement in ocular signs, i.e., lid crusting, lid erythema, lid edema, conjunctival discharge, conjunctival erythema, conjunctival edema, and corneal appearance. Analyses on microbiological improvement were

performed using only the mITT population. Analyses on ocular signs were performed using both the mITT and ITT populations. The same LOCF approach was employed for secondary analyses as was used for the primary efficacy analysis.

3.1.4 Results and Conclusions

3.1.4.1 Clinical Success Rate

The primary efficacy analysis was the clinical success rate in the mITT population, which was defined as the proportion of subjects in each treatment group whose study eye achieved a score of 0 for both conjunctival erythema and conjunctival discharge on Day 7. Subjects treated with gatifloxacin 0.3% ophthalmic solution had a clinical success rate of 78.6% at Day 7 compared with a success rate of 84.4% in subjects treated with moxifloxacin 0.5% ophthalmic solution.

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Table 4: Number (%) of Subjects with Clinical Success, mITT Population, Study 198782-003

Visit	Gatifloxacin 0.3% (N = 56)	Moxifloxacin 0.5% (N = 64)	P-value [a]	Difference (95% CI) [b]
Day 3	17 (30.4%) (18.3%, 42.4%)	28 (43.8%) (31.6%, 55.9%)	0.131	-13.4% (-30.5%, 3.7%)
Day 7	44 (78.6%) (67.8%, 89.3%)	54 (84.4%) (75.5%, 93.3%)	0.412	-5.8% (-19.8%, 8.1%)

Source: Applicant's CSR 198782-003, Table 14.2-1.1

a. P-value was derived from a 2-sided Pearson's chi-square test.

b. 95% confidence interval (CI) was constructed using the normal approximation for binary variables.

3.1.4.2 Microbiological Cure Rate

The Applicant presented the results for microbiological improvement at Day 7. A subject was considered to have microbiological improvement if all bacterial species present at Day 1 (baseline) was eradicated or reduced. At Day 7, 94.6% of subjects treated with gatifloxacin 0.3% ophthalmic solution, compared to 92.2% of subjects treated with moxifloxacin 0.5% ophthalmic solution, achieved microbiological improvement, i.e., all bacterial species present at baseline were eradicated or reduced. The treatment difference was 2.5% (p-value=0.722; 95% confidence interval: -6.4%, 11.3%).

Microbiological cure rate for the eradication of baseline pathogens, instead of microbiological improvement as defined in this application by the Applicant, was presented in the approved labels of Vigamox® (moxifloxacin 0.5% ophthalmic solution) and Zymar® (gatifloxacin 0.3% ophthalmic solution). Therefore, the reviewer conducted the analysis of microbiological cure rate

at Day 7, which was associated with the eradication of all pathogens that were above the threshold at baseline. The microbiological cure rate was 83.9% (47/56) for gatifloxacin 0.3% ophthalmic solution and 82.8% (53/64) for moxifloxacin 0.5% ophthalmic solution. The treatment difference was 1.1% (p-value=0.870; 95% confidence interval: -12.2%, 14.5%).

3.1.4.3 Microbiological Response

Microbiological response was categorized as eradication, reduction, persistence, or proliferation. The eradication rates at Day 7 over all organisms, all gram-positive bacteria, all gram-negative bacteria, and the most common specific organisms in the study eye for the mITT population are shown in Table 5.

Table 5: Eradication Rates at Day 7 for the Most Common Organisms Present in Study Eyes at Baseline, mITT Population, Study 198782-003

Organism	Gatifloxacin 0.3% (N=56)	Moxifloxacin 0.5% (N=64)
All organisms [a]	N = 86 79 (91.9%)	N = 98 89 (90.8%)
Gram-positive bacteria [a]	N =74 67 (90.5%)	N = 83 75 (90.4%)
Gram-negative bacteria [a]	N = 12 12 (100.0%)	N = 15 14 (93.3%)
Haemophilus influenzae [b]	N = 2 2 (100.0%)	N = 6 5 (83.3%)
Staphylococcus aureus [b]	N = 4 3 (75.0%)	N = 5 5 (100.0%)
Staphylococcus epidermidis [b]	N = 17 12 (70.6%)	N = 22 16 (72.7%)
Streptococcus mitis [b]	N = 7 6 (85.7%)	N = 7 7 (100.0%)
Streptococcus mitis group [b]	N = 15 15 (100.0%)	N = 10 9 (90.0%)
Streptococcus oralis [b]	N = 8 8 (100.0%)	N = 11 11 (100.0%)

Source: Applicant's CSR 198782-003, Table 11-3
Note: The specific bacteria included in this table were present in more than 5 subjects' study eyes within 1 treatment group at baseline.

a. For each bacterial classification at each visit, the sample size equals the number of species above pathological threshold at baseline with an evaluable response at the follow-up visit; multiple species were included for a single study eye.
b. The sample size within species is the number of subjects with a culture above pathological threshold for this species in the study eye at baseline with an evaluable response at the follow-up visit.

3.1.4.4 Efficacy Conclusions

(b) (4)

3.2 Evaluation of Safety

The overall incidence of adverse events was lower in subjects treated with gatifloxacin 0.3% ophthalmic solution (19.0%) compared with moxifloxacin 0.5% ophthalmic solution (23.3%).

(b) (4)

(b) (4) No subjects in the gatifloxacin treatment group experienced a serious adverse event.

See medical review for additional details.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Of 171 patients enrolled in the study, there were 112 males (65.5%) and 59 females (34.5%). More than half of the population was non-Caucasian (53.8%), of which the majority is Hispanic. The efficacy analysis was performed for subgroups defined by gender (male vs. female) and race. Due to the small number of patients in races other than Caucasian and Hispanic, separate subgroups of race are defined as Caucasian vs. non-Caucasian and Hispanic vs. non-Hispanic. Since the study was conducted in patients from birth to 31 days of age, the subgroup analysis by age is not applicable.

4.1 Gender, Race and Age

Similar clinical success rates were observed for male subjects who received gatifloxacin 0.3% ophthalmic solution or moxifloxacin 0.5% ophthalmic solution. Female subjects who received moxifloxacin 0.5% ophthalmic solution had higher clinical success rate than the female subjects who received gatfloxacin 0.3% ophthalmic solution. Breslow-Day test for homogeneity of the odds ratios comparing male and female subjects yields a p-value of 0.129 (b) (4)

Table 6: Subgroup analysis of clinical success rate by gender, mITT Population, Study 198782-003

Variable/Category	Gatifloxacin 0.3%	Moxifloxacin 0.5%	P-value [a]	Difference (95% CI) [b]
Gender				
Male	83.3% (25/30)	81.3% (39/48)	0.816	2.1% (-15.2%, 19.4%)
Female	73.1% (19/26)	93.8% (15/16)	0.127	-20.7% (-41.4%, 0.1%)
Race				
Caucasian	80.0% (24/30)	79.2% (19/24)	1.000	0.8% (-20.8%, 22.5%)
Non-Caucasian	76.9% (20/26)	87.5% (35/40)	0.319	-10.6% (-29.7%, 8.6%)
Hispanic	77.3% (17/22)	85.3% (29/34)	0.491	-8.0% (-29.2%, 13.2%)
Non-Hispanic	79.4% (27/34)	83.3% (25/30)	0.688	-3.9% (-23.0%, 15.1%)

a. P-value was derived from a 2-sided Pearson's chi-square test or Fisher's exact test if ≥ 25% of the cells had expected counts less than 5.
b. 95% confidence interval (CI) was constructed using the normal approximation for binary variables.

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4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

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5.2 Conclusions and Recommendations

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Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 21493	SUPPL 9	ALLERGAN INC	ZYMAR (GATIFLOXACIN) OPHTHALMIC SOLUTION

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