

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-810**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
Submission Number	50-810
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Reviewer Name	Wiley A. Chambers, MD
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Established Name	Azithromycin ophthalmic solution
(Proposed) Trade Name	AzaSite
Therapeutic Class	Ophthalmic macrolide antibiotic
Applicant	Insite
Priority Designation	S
Formulation	Ophthalmic solution, 1%
Dosing Regimen	One drop in the affected eye twice daily for the first two days and then once daily for days three through seven
Indication	Treatment of bacterial conjunctivitis

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## **1 EXECUTIVE SUMMARY**

### **1.1 Recommendation on Regulatory Action**

It is recommended from a clinical prospective that NDA 50-810, AzaSite (azithromycin ophthalmic solution) be approved for the treatment of bacterial conjunctivitis with labeling revisions listed in this review.

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that AzaSite when dosed twice a day for two days followed by once a day for five additional days is superior to its vehicle and equivalent to tobramycin ophthalmic solution in the treatment of bacterial conjunctivitis.

### **1.2 Recommendation on Postmarketing Actions**

#### **1.2.1 Risk Management Activity**

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

#### **1.2.2 Required Phase 4 Commitments**

There are no recommended Phase 4 commitments.

#### **1.2.3 Other Phase 4 Requests**

There are no recommended Phase 4 commitments.

### **1.3 Summary of Clinical Findings**

#### **1.3.1 Brief Overview of Clinical Program**

AzaSite (azithromycin ophthalmic solution) is a topical ophthalmic azalide (macrolide) antibiotic indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: CDC coryneform group G, *Staphylococcus aureus*, *Streptococcus mitis* group, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

#### **1.3.2 Efficacy**

Efficacy of the drug substance, azithromycin has been demonstrated in multiple systemic indications. AzaSite was studied in two adequate and well controlled studies. In study 003, AzaSite demonstrated superiority to its vehicle and in study 004, AzaSite demonstrated equivalence to tobramycin ophthalmic solution.

### 3.3 Safety

Relative safety has been demonstrated in two adequate and well controlled studies. The most frequently reported adverse events were: worsening of the conjunctivitis, ocular irritation, conjunctival hyperemia and edema, ocular burning/stinging upon instillation of the drug product and headache.

#### 1.3.4 Dosing Regimen and Administration

AzaSite is recommended to be dosed twice a day for the first two days and then once a day for the next five days.

#### 1.3.5 Drug-Drug Interactions

There are no known drug-drug interactions.

#### 1.3.6 Special Populations

There are no considerations of special populations.

## 2 INTRODUCTION AND BACKGROUND

### 2.1 Product Information

Trade Name:	AzaSite (azithromycin ophthalmic solution)
Chemical Class:	Type 3 (new formulation)
Therapeutic Class:	Ophthalmic azalide antibiotic
Indication:	AzaSite™ is a topical ophthalmic preparation of an azalide anti-infective indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: CDC coryneform group G, <i>Staphylococcus aureus</i> , <i>Streptococcus mitis</i> group, <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> ,
Dosing Regimen:	One drop in the affected eye twice a day for the first two days and then once a day for the next five days

### 2.2 Currently Available Treatment for Indications

Ophthalmologic products currently approved for the treatment of bacterial conjunctivitis include tobramycin ophthalmic solution, gentamicin ophthalmic solution, erythromycin ophthalmic ointment, ciprofloxacin ophthalmic solution, ofloxacin ophthalmic solution, levofloxacin ophthalmic solution, norfloxacin ophthalmic solution, gatifloxacin ophthalmic solution and moxifloxacin ophthalmic solution.

### 2.3 Availability of Proposed Active Ingredient in the United States

Systemic formulations (oral suspension, tablets, and intravenous injections) of azithromycin have been approved for a variety of systemic anti-infective indications for over 15 years.

## 4 Important Issues with Pharmacologically Related Products

Ophthalmic anti-infectives are generally well tolerated and effective for bacterial conjunctivitis. There are no specific issues which warrant special attention.

## 2.5 Presubmission Regulatory Activity

End of Phase 2 Meetings were held on April 9, 2001, January 15, 2003, and April 27, 2005. Pre-NDA meetings were held on June 21, 2005, and April 26, 2006. At each of the meetings, the Agency provided general guidance, there were no scientific disagreements.

## 2.6 Other Relevant Background Information

A topical ophthalmologic solution of azithromycin is not approved for marketing anywhere in the world.

## 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

### 3.1 CMC (and Product Microbiology, if Applicable)

INGREDIENT	% W/W
Azithromycin Monohydrate, USP	1.0
Mannitol, USP	-
Citric Acid Anhydrous, USP	-
Sodium Citrate Dihydrate, USP	-
Poloxamer 407, NF	-
Benzalkonium Chloride, NF	0.003
Polycarbophil, USP	-
Sodium Chloride, USP	-
Edetate Disodium Dihydrate, USP	-
Sodium Hydroxide, 2N, NF	adjust to pH 6.3
Water For Injection, USP	-

b(4)

INGREDIENT	FUNCTION
Azithromycin Monohydrate, USP	Active drug substance.
Mannitol, USP	
Citric Acid Anhydrous, USP	
Sodium Citrate Dihydrate, USP	
Poloxamer 407, NF	
Benzalkonium Chloride, NF	
DuraSite®	
Polycarbophil, USP	Vehicle.
Sodium Chloride, USP	
Edetate Disodium Dihydrate, USP	
Sodium Hydroxide, 2N, NF	Used to adjust the pH of the final product.
Water For Injection, USP	Vehicle.

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Attribute	Method	Release
		1% Azithromycin
Identification (Azithromycin) HPLC Retention time	TM036	Off-White, hazy liquid
Identification (Azithromycin) UV/VIS	TM036	
Azithromycin content	TM036	
Chromatographic purity	TM036	
Appearance	TM423	
pH	TM601	
Osmolality	TM414	
Viscosity, 25°C	TM424	
Benzalkonium Chloride	TM046	
Particulates	TM425	
Sterility	IPGM101	Sterile

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Reviewer's Comments: *Acceptable.*

### 3.2 Animal Pharmacology/Toxicology

Reference is made to the Agency's findings for NDA 50-670, Azithromycin tablets. See Pharm/Tox Review for local ocular toxicity studies.

Reviewer's Comments: *No Pharmacology or Toxicology issues that are likely to impact on the safety or efficacy of this product have been identified.*

### 3.3 Product Name Review

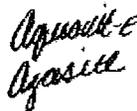
DMETS does not recommend the use of the name AzaSite. In reviewing the proprietary name, the primary concerns were relating to look-alike confusion with AzaSite are AquaSite and Aquavit-E. In addition, DMETS questions the sponsor's trend with using the suffix "site".

AquaSite was found to have look-alike and sound-alike similarities with AzaSite. AquaSite contains artificial tears and is indicated in the symptomatic treatment of dry eye. The dose of AquaSite solution is 1-2 drops instilled into affected eye(s) 3 or 4 times daily, as needed.

**Reviewer's Comments:** *AquaSite is not considered a potential concern because the product was a product marketed without an approved new drug application, was removed from the market and has not been marketed in several years.*

Aquavit-E was found to have look-alike similarities with AzaSite, when the modifier "E" is omitted from the name. Aquavit-E is a nutritional supplement used to treat Vitamin E deficiency.

The visual similarity of this name pair can be attributed to the fact both names begin with the letter "A" and contain the same trailing letters (-IT). Additionally, the letter "q" in Aquavit-E and the letter "z" in AzaSite can look alike when scripted (see below) since both are downstroke letters.



Aquavit-E  
Azasite

The products differ in dose (0.6 mL vs. 1 drop), strength (15 IU/0.3 mL vs. 1%), route of administration (oral vs. ophthalmic), dosage form (solution vs. ophthalmic drops), prescription status (over-the-counter vs. prescription) and indication for use (Vitamin E deficiency vs. bacterial conjunctivitis). However, Aquavit-E and AzaSite share an overlapping dosage form (solution) and a similar frequency of administration (once daily vs. once daily on days 3-7). In addition, both products are available in only one strength, which allows the prescriber to order either product without specifying a strength. Also, despite Aquavit-E's OTC status, it would not be unusual to see a prescription written for Aquavit-E as prescribers oftentimes write prescriptions for OTC medications for Medicaid, VA and Military Hospital patients or as reminders on prescription blanks. A prescription written for "Azasite -use as directed #1" may be misinterpreted for "Aquavit-E -use as directed #1" due to their familiarity with Aquavit-E. Aquavit-E's sponsor, Cypress Pharmaceutical, indicated that their product is kept behind the pharmacy counter or it must be special ordered if the pharmacy does not carry it. Additionally, we have concerns about the varying routes of administration, especially if the patient is anticipating an oral product but receives an ophthalmic product and vice versa. If the wrong product is dispensed, this may result in the inadvertent administration of the oral medication, since it comes with a dropper, in the eye. Therefore, DMETS believes the likelihood for confusion between Aquavit-E and AzaSite exists.

**Reviewer's Comments:** *There is disagreement with this assessment. The differences in dose, strength, route of administration, dosage form, prescription status and indication all contribute to a low risk of confusion.*

### Concerns with Proliferation of Sponsor's Name

DMETS questions if there may be a trend regarding the use of the suffix "site" which stems from the sponsor's name. In addition to the proposed name Azasite, we note that the sponsor "Insite" also utilized the suffix "site" for their (discontinued) product containing artificial tears (Aquasite). DMETS questions whether the sponsor intends to utilize the suffix "site" in conjunction with other names with subsequent applications. Post-marketing experience has shown confusion and resulting medication errors due to proliferation of names with a common prefix or suffix. One example of such confusion has been seen with products having the prefix "APO", manufactured in Canada by Apotex (see Appendix B for list of names with prefix "APO"). Consequently, DMETS has objected to the inclusion of the prefix "APO" for proprietary names proposed in this country since this practice may result in the introduction of numerous sound-alike/look-alike names. DMETS continues to object to proposals which would lead to proliferation of products with commonalities in nomenclature. DMETS believes that the entrance in the marketplace of different products which include common lettering, "site", would lead to confusion and result in additional look alike and/or sound alike medication errors. Therefore, subsequent names proposed for varying applications from this sponsor, including the suffix "site" should take into consideration the potential for this type of confusion.

**Reviewer's Comments:** *The use of a suffix "site" stemming from the sponsor's name might raise a concern for subsequent products to be confused with this product, but as this is the first product, there is a low potential for confusion.*

### 2.4 Statistical Labeling Comments

The Statistical Reviewer has recommend that the efficacy results of the non-inferiority study because of the difficulty in interpreting the efficacy results in the non-inferiority setting as discussed in the statistical review for this NDA. In addition, there is also a concern about the difference in dosing for the active-control study from the actual proposed dosing.

**Reviewer's Comments:** *The above recommendation has not been followed because the clinical comparison to tobramycin ophthalmic solution has clinical meaning even if it does not provide the opportunity to predict how AzaSite would have compared against a placebo. Comparison against a placebo was not the purpose of Study 004.*

## 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

### 4.1 Sources of Clinical Data

*Sources of clinical data used in this review were limited to the clinical studies submitted to this NDA. A Medline search was conducted. There was no additional relevant clinical information.*

## 4.2 Tables of Clinical Studies

Type of Study	Study	Objective(s) of the Study	No. of Subjects per arm (AzaSite/Control)	Study Design & Type of Control	Test Product; Dosage Regimen; Route of Administration	Duration
Phase 3	C-01-401-004	To compare the clinical and microbial efficacy and safety of AzaSite with tobramycin	365/378	Double-masked, active comparative, multicenter	AzaSite 1% ocular 2 drops daily x 2 days, then daily vs. tobramycin 4 drops daily	1 week
Phase 3	C-01-401-003	To compare the clinical and microbial efficacy and safety of AzaSite with placebo/vehicle	335/350	Double-masked, placebo controlled, multicenter	AzaSite 1% ocular 2 drops daily x 2 days, then daily vs. placebo	1 week
Phase 2	C-01-401-006	To compare the clinical and microbial efficacy and safety of AzaSite with placebo/vehicle	38/39	Double-masked, placebo controlled, multicenter	AzaSite 1% ocular 2 drops x 1 day, then 1 drop daily vs. placebo	1 week
Phase 1	C-01-401-001	To compare the safety of AzaSite with placebo/vehicle	18/18/18	Double-masked, placebo controlled	AzaSite 0.5% & 1% ocular 2 drops daily x 14 days vs. placebo	Two weeks

## 4.3 Review Strategy

*All submitted clinical studies were used in this review. A Medline search was also conducted. There was no additional relevant clinical information obtained from the literature.*

## 4.4 Data Quality and Integrity

Routine Division of Scientific Investigations audits were requested. Reports of the audits include descriptions of discrepancies between the source documentation and the line listings for the non-study eye. These discrepancies have been reviewed and determined to be a poor choice of terms rather than a true discrepancy. Non-study eyes that never had an infection and remained unchanged were listed as "cured." While this is not actually a cure and therefore not an appropriate term for the listing, the listings are never used in the efficacy evaluations because they were for the non-study eye. Random case report forms were reviewed. No issues of data integrity have been identified.

## 4.5 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

## 4.6 Financial Disclosures

The financial arrangements with clinical investigators and their supporting institutions were reviewed. Efficacy evaluations were performed including and excluding investigators with significant financial interests. The exclusion of investigators with significant financial interests does not significantly affect the results.

## CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

The data described in the following are derived from the Zithromax package insert. Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were:

$$AUC_{0-72} = 4.3 (1.2) \mu\text{g}\cdot\text{h}/\text{mL}$$

$$C_{\text{max}} = 0.5 (0.2) \mu\text{g}/\text{mL}$$

$$T_{\text{max}} = 2.2 (0.9) \text{ hours}$$

The applicant has elected not to perform any systemic absorption studies because the calculated level of systemic absorption (assuming 100% absorption) is low compared to orally administered azithromycin. The calculation modified by this reviewer for 100% is as follows:

Volume of eyedrop = 50  $\mu\text{L}$

Concentration of azithromycin in the eye drop = 1% = 10 mg/mL = 10  $\mu\text{g}/\mu\text{L}$

Assume bilateral administration, twice a day;

The total amount of azithromycin administered to the eyes is

$$50 \mu\text{L} \times 2 (\text{eyes}) \times 10 \mu\text{g}/\mu\text{L} \times 2 (\text{per day}) = 2000 \mu\text{g}$$

Volume of distribution = 30 L/kg

Weight of a normal female subject = 50 kg

Therefore, volume of distribution of a normal subject is:

$$30 \text{ L}/\text{kg} \times 50 \text{ kg} = 1500 \text{ L}$$

Assume 100% absorption, the maximum plasma concentration will be:

$$2000 \mu\text{g} / 1500 \text{ L} = 1.34 \mu\text{g}/\text{L} = 1.34 \text{ ng}/\text{mL}$$

The limit of quantification of the assay is reported to be 10 ng/mL, therefore a systemic absorption study would not be capable of detecting azithromycin.

The data from single dose studies indicated that tear levels reached a maximum within 0.5 hour to 1 hour. It dropped rapidly within five hours and then stayed flat during the next 6 to 20 hours. The tear concentration was dose-dependent with the 1% AzaSite, the tear concentration at the 24 hour time point at 13.2  $\mu\text{g}/\text{mL}$ .

### 5.2 Pharmacodynamics

The initial tear concentration of azithromycin is expected to be 5-8 mg/mL which is several orders of magnitude above the concentrations needed to kill the indicated bacteria.

### 5.3 Exposure-Response Relationships

There is no known exposure-response relationship. This is most likely due to the relatively high concentration of the antibiotic in relationship to the concentration needed to kill the indicated bacteria.

## 6 INTEGRATED REVIEW OF EFFICACY

### 6.1 Indication – Bacterial Conjunctivitis

The proposed indication is for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: CDC coryneform group G, *Staphylococcus aureus*, *Streptococcus mitis* group, *Streptococcus pneumoniae*, *Haemophilus influenzae*.

#### 6.1.1 Methods

Study	Objective(s) of the Study	No. of Subjects per arm (AzaSite/Control)	Study Design & Type of Control	Test Product; Dosage Regimen; Route of Administration	Duration
C-01-401-004	To compare the clinical and microbial efficacy and safety of AzaSite with tobramycin	365/378	Double-masked, active comparative, multicenter	AzaSite 1% ocular 2 drops daily x 2 days, then daily vs. tobramycin 4 drops daily	1 week
C-01-401-003	To compare the clinical and microbial efficacy and safety of AzaSite with placebo/vehicle	335/350	Double-masked, placebo controlled, multicenter	AzaSite 1% ocular 2 drops daily x 2 days, then daily vs. placebo	1 week

#### 6.1.2 General Discussion of Endpoints

Bacterial conjunctivitis is generally a self limited disease with a usual course of 7-14 days. The goal of therapy to reduce the duration of the illness and minimize the chances of infecting other individuals. Efficacy is recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials of at least 7 days in duration. Independence refers to different investigators and different geographic locations between the trials. Demonstration of efficacy is recommended to include evidence of statistical significance and clinical relevance. Clinical relevance or a clinical cure is recommended to be defined as the resolution of signs and symptoms (i.e. a score of 0, normal conjunctiva and no discharge) for the infected patients who meet the inclusion criteria of the protocol.

The following are recommended demonstrations of efficacy:

1. Statistically significant superiority in replicated studies to the product's vehicle in the cure of the signs and symptoms of bacterial conjunctivitis in clinically infected patients who meet the inclusion criteria.
2. An alternative approach for drug substances which have already demonstrated efficacy in another anti-infective indication is to show superiority to vehicle in one trial and equivalence to tobramycin or one of the approved fluoroquinolones dosed qid in another trial. Equivalence is defined as the having a two sided 95% confidence interval for the difference in cure rates of less than 15%.

Additionally, in trials which include the test product's vehicle in one arm, it is recommended that the cure rate of the vehicle should not be numerically superior to the cure rate of the test product for the Intent-to-Treat population.

### 1.3 Study Design

The completed studies (003 and 004) were adequate and well controlled, randomized, double-masked, parallel group studies. In each case, AzaSite was administered twice a day for two days followed by once a day for the next 3-5 days. Study 003 included a comparison against the drug product's vehicle administered on the same schedule. Study 004 included a comparison against tobramycin ophthalmic solution. Tobramycin ophthalmic solution has been used as a reference standard for many bacterial conjunctivitis studies. The inclusion/exclusion criteria were essentially the same in these studies. The population were representative of the patients. They were patients who had presumed bacterial conjunctivitis at the beginning of the clinical study. To be included for efficacy results, the patient also had to have a conjunctival culture which identified bacteria in sufficient numbers to be considered clinically significant. The results of the microbial culture were not available prior to the initiation of treatment. Clinical evaluations were performed at baseline, day 3-4 and day 6-7. The primary efficacy variable is considered to be clinical resolution which is defined as the complete resolution of ocular discharge and conjunctival injection.

\*Final culture at least 12 hours last dose of drug product.

#### Group I - Threshold = 1 CFU/mL

Acinetobacter species  
Achromobacter species  
Citrobacter species  
Enterobacter species  
Other Enterobacteriaceae  
  Shigella species  
  Staphylococcus species  
Klebsiella species  
Moraxella species other than Moraxella catarrhalis  
Neisseria gonorrhoeae and other Neisseria species  
Proteus/Morganella species  
Pseudomonas aeruginosa and other Pseudomonas species  
Serratia marcescens  
Streptococcus Group A (beta hemolytic, Streptococcus pyogenes)  
Streptococcus pneumoniae

#### Group II - Threshold = 10 CFU/mL

Moraxella catarrhalis  
Staphylococcus aureus  
Streptococcus Group B (beta or nonhemolytic)  
Streptococcus Group C (alpha, beta or nonhemolytic)  
Streptococcus Group D  
Streptococcus Group G  
Viridans Streptococcus

#### Group III - Threshold = 100 CFU/mL

Bacillus species  
Micrococcus species  
Staphylococcus epidermidis  
Other coagulase-negative Staphylococcus species

#### Group IV - Threshold = 1000 CFU/mL

Corynebacterium species

	Visit 1	Visit 2	Visit 3
Assessment	Day 1	Day 3	Day 6
	(Eligibility/Baseline)	(+1 day) (Days 3-4)	(+1 day) (Days 6-7)
ICF/Assent	X		
Pregnancy Test	X		
History	X		
Clinical Assessment	X	X	X
Investigator Global Rating		X	X
Visual Acuity	X	X	X
Biomicroscopy	X	X	X
Ophthalmoscopy	X		X
Microbial Culture	X	X	X*
Dispense Diary	X		
Review Diary with Subject		X	X
Dispense Drug	X		
Instill Drug at Site	X	X	

**APPEARS THIS WAY ON ORIGINAL**

#### 6.1.4 Efficacy Findings - Clinical Resolution

Clinical Resolution is defined as absence of all three clinical signs: ocular discharge, bulbar conjunctival injection, and palpebral conjunctival injection.

Per Protocol with Last Observation Carried Forward (LOCF)

Study 003	AzaSite	Vehicle	
Visit 2 (Day 3-4)	N=124	N=137	P=0.14
Clinical Resolution	20 (16%)	13 (10%)	7% (-1, 15%)
Visit 3 (Day 6-7)	N=130	N=149	p=0.03
Clinical Resolution	82 (63%)	74 (50%)	13.4% (1.9, 25.0%) *

Study 004	AzaSite	Tobramycin	
Visit 2 (Day 3-4)	N=148	N=148	
	37 (25%)	38 (26%)	-0.7% (-10.6, 9.2%)**
Visit 3 (Day 6-7)	N=159	N=157	p=0.78
Clinical Resolution	127 (80%)	123 (78%)	1.5% (-7.4, 10.5%)*

\* Difference with 95% confidence interval

**Reviewer's Comments:** *Study 003 demonstrates superiority over the drug product's vehicle, and Study 004 demonstrates equivalence to tobramycin ophthalmic solution.*

**APPEARS THIS WAY ON ORIGINAL**

**Intent to Treat (i.e., not necessarily culture positive) – Clinical Resolution**

Study 003 Intent to Treat	AzaSite	Vehicle	
Visit 2 (Day 3-4)	N=301	N=322	p=0.31
Clinical Resolution	49 (16%)	43 (13%)	3% (-3, 9%)
Visit 3 (Day 6-7)	N=328	N=347	p=0.024
Clinical Resolution	203 (62%)	184 (53%)	9% (1,16%)

**Reviewer's Comments:** *Although not necessary to support approval, AzaSite was superior to its vehicle in the Intent-to-Treat population. The Intent-to-Treat population included patients who were suspected to have bacterial conjunctivitis but did not meet the criteria needed to confirm bacterial conjunctivitis.*

Study 004 Intent to Treat	AzaSite	Tobramycin	
Visit 2 (Day 3-4)	N=333	N=356	
Clinical Resolution	71 (21%)	76 (21%)	0% (-6.1, 6.1%)
Visit 3 (Day 6-7)	N=365	N=378	
Clinical Resolution	257 (70%)	260 (69%)	1% (-5, 8%)

**Reviewer's Comments:** *Clinical resolution was equivalent in the AzaSite and tobramycin ophthalmic solution populations.*

**Clinical Resolution by cultured organism (cured patients/total patients)**

Organism	Vehicle -003	AzaSite -003	AzaSite -004	Tobra -004
<i>A. calcoaceticus</i> - <i>A. baumannii</i>	1/1			
<i>Acinetobacter calcoaceticus</i>	0/1			
<i>Aerococcus viridans</i>	0/1		1/1	
<i>Agrobacterium radiobacter</i>				
<i>Brevibacterium casei</i>	1/1			
<i>Brevibacterium species</i>		0/1		
CDC coryneform group G	2/5	2/3	3/3	
<i>Chryseobacterium indologenes</i>	0/1			
<i>Corynebacterium bovis</i>				
<i>Corynebacterium propinquum</i>				1/1
<i>Corynebacterium species</i>	2/2	0/1		

Organism	Vehicle -003	AzaSite -003	AzaSite -004	Tobra -004
<i>Enterobacter cloacae</i>	1/1		0/1	0/1
<i>Enterobacter intermedius</i>		1/1		
<i>Enterococcus faecalis</i>			1/1	
<i>Escherichia hermannii</i>		1/1		
Gemella species	0/1			
<i>Haemophilus haemolyticus</i>				1/1
<i>Haemophilus influenzae</i>	24/38	29/39	51/57	45/48
<i>Haemophilus parainfluenzae</i>	0/1	1/1		
<i>Klebsiella oxytoca</i>	1/0			
<i>Klebsiella pneumoniae</i>			0/1	0/1
Micrococcus species	1/1			
<i>Moraxella catarrhalis</i>	1/3	2/4	1/1	
<i>Morganella morganii</i>	1/0			
<i>Neisseria meningitidis</i>				
<i>Neisseria mucosa</i>		0/1		
<i>Neisseria subflava</i>		0/1		
<i>Ochrobactrum anthropi</i>				
<i>Providencia rettgeri</i>		1/1		
<i>Pseudomonas aeruginosa</i>		1/2		
Rhodococcus species	0/1			
<i>Serratia marcescens</i>				1/1
Serratia species	1/1			
<i>Staphylococcus aureus</i>	11/21	19/23	12/17	15/20
<i>Staphylococcus auricularis</i>				
<i>Staphylococcus capitis</i>	1/1		1/1	
<i>Staphylococcus epidermidis</i>	7/13	3/5	4/4	4/4
<i>Staphylococcus haemolyticus</i>	1/1			
<i>Staphylococcus simulans</i>			1/1	
<i>Staphylococcus warneri</i>				1/1
<i>Stenotrophomonas maltophilia</i>	1/1	1/1		
<i>Stomatococcus mucilaginosus</i>			1/1	
<i>Streptococcus anginosus</i>		1/1		
<i>Streptococcus intermedius</i>				

Organism	Vehicle -003	AzaSite -003	AzaSite -004	Tobra -004
<i>Streptococcus mitis</i>	1/2		3/4	3/3
<i>Streptococcus mitis</i> group	1/4	2/7	3/3	1/2
<i>Streptococcus oralis</i>	3/6	1/1	2/3	2/2
<i>Streptococcus pneumoniae</i>	20/36	24/36	48/56	49/62
<i>Streptococcus pyogenes</i>	0/1			2/2
<i>Streptococcus salivarius</i>	2/3		1/1	1/1
<i>Streptococcus sanguis</i>	1/1			
<i>Streptococcus viridans</i>	1/1	1/1	1/1	

**Reviewer's Comments:** *Efficacy was demonstrated in patients with cultures positive for CDC coryneform group G, Staphylococcus aureus, Streptococcus mitis group, Streptococcus pneumoniae, and Haemophilus influenzae.*

### 6.1.5 Clinical Microbiology – Bacterial Eradication

Bacterial Eradication is defined as eradication of all pathogens above pathological threshold at baseline (Day 1).

Study 003	AzaSite	Vehicle	
Visit 2 (Day 3-4)	N=124	N=134	<0.001
Bacterial Eradication	100 (81%)	82 (61%)	
Visit 3 (Day 6-7)	N=130	N=149	<0.001
Bacterial Eradication	115 (88%)	99 (66%)	22% (13, 31%)

Study 004	AzaSite	Tobramycin	
Visit 2 (Day 3-4)	N=148	N=145	
Bacterial Eradication	85%	90%	6% (-13%, 2%)
Visit 3 (Day 6-7)	N=159	N=157	
Bacterial Eradication	88%	94%	6% (-12%, 0)

### 6.1.6 Efficacy Conclusions

Adequate and well controlled studies (-003 and -004) support the efficacy of AzaSite for the treatment of bacterial conjunctivitis due to the following susceptible organisms: CDC coryneform group G, *Staphylococcus aureus*, *Streptococcus mitis* group, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

## 7 INTEGRATED REVIEW OF SAFETY

### 7.1 Methods and Findings

#### 7.1.1 Deaths

There were no deaths in the clinical studies.

#### 7.1.2 Other Serious Adverse Events

Two serious adverse events were reported, both in Vehicle-treated subjects. One, a corneal ulceration, and the other was a cerebrovascular accident unrelated to drug.

#### 7.1.3 Dropouts and Other Significant Adverse Events

##### 7.1.3.1 Overall profile of dropouts

	Study 003		Study 004	
	Vehicle	AzaSite	Azithromycin	Tobramycin
Randomized	350	335	365	378
Completed	317	313	343	367
Discontinued	33	22	22	11
Per Protocol	149	130	159	157
Intent-to-Treat	328	347	360	375
Efficacy Evaluable	124	107	137	131
Primary Reason for Discontinuation				
Adverse Event	5	2	9	8
Protocol Violation	4	1	4	0
Withdrew Consent	6	6	2	3
Lost to Follow-up	1	5	1	0
Lack of Efficacy	15	7	2	0
Treatment Unmasked	0	1	0	0
Other	2	0	4	0

##### 7.1.3.2 Adverse events associated with dropouts

Subjects who did not complete the Phase 3 studies					
Drug	Site	PtID	Age, Sex Race	Days	Comments
AzaSite	4023	1270	3/M/C	5	"ET09"; previously enrolled in study; subject #1041
AzaSite	4057	0897	45/F/C	4	Bacterial conjunctivitis spread to OD
AzaSite	4030	0133	52/M/C	3	Bilateral iritis
AzaSite	4001	0003	33/F/C	2	Conjunctivitis OD

Subjects who did not complete the Phase 3 studies

Drug	Site	PtID	Age, Sex Race	Days	Comments
AzaSite	4030	0470	26/F/C	3	Conjunctivitis OD
AzaSite	4016	0242	36/M/A	4	Herpes zoster
AzaSite	4004	0055	3/M/B	2	Irritability
AzaSite	4001	0260	1/F/C	3	Lack of compliance
AzaSite	3031	0361	57/F/C	2	Lack of efficacy
AzaSite	3040	0474	39/M/B	2	Lack of efficacy
AzaSite	3040	0476	51/F/C	2	Lack of efficacy
AzaSite	4048	0763	27/M/C	2	Lack of efficacy
AzaSite	3068	0814	32/F/C	2	Lack of efficacy
AzaSite	3070	0837	80/M/C	2	Lack of efficacy
AzaSite	4053	0845	54/M/H	3	Lack of efficacy
AzaSite	3040	0927	33/M/C	2	Lack of efficacy
AzaSite	3142	1702	15/F/H	4	Lack of efficacy
AzaSite	4030	0478	6/F/C		Lost to follow-up
AzaSite	3123	0768	7/M/B	2	Lost to follow-up
AzaSite	3140	1789	21/F/C	1	Lost to follow-up
AzaSite	3190	2270	3/F/H	2	Lost to follow-up
AzaSite	3198	2387	3/M/H	2	Lost to follow-up
AzaSite	3202	2414	5/F/H	3	Lost to follow-up
AzaSite	4007	0102	6/M/O	2	Otitis media-right ear
AzaSite	4002	0027	26/M/A	1	Protocol violation
AzaSite	3010	0113	51/F/C	2	Protocol violation
AzaSite	4023	0287	4/M/C	4	Protocol violation
AzaSite	4031	0481	43/M/C	2	Protocol violation
AzaSite	4062	0977	5/M/C	2	Protocol violation
AzaSite	4042	0658	73/M/C	1	Pt was dispensed expired investigational meds
AzaSite	3140	1673	43/M/C	1	Sinusitis
AzaSite	4003	1317	43/F/C	2	Subject's dog chewed study drug bottles, days 3-5
AzaSite	4008	1563	35/F/B	4	Throat infection & dehydration
AzaSite	3177	2114	33/M/H	2	Treatment involuntarily unmasked
AzaSite	4030	0136	8/F/B	3	Upper Respiratory Tract Infection
AzaSite	3001	0001	46/F/B	1	Withdrew consent
AzaSite	4003	0035	6/M/C	1	Withdrew consent
AzaSite	3009	0100	8/F/C	1	Withdrew consent
AzaSite	3022	0261	19/M/B	2	Withdrew consent
AzaSite	4035	0549	5/F/H		Withdrew consent
AzaSite	3123	1472	11/F/H	2	Withdrew consent
AzaSite	3123	1476	8/F/H	2	Withdrew consent
AzaSite	3190	2295	1/F/H	2	Withdrew consent
AzaSite	3068	1249	37/F/C	4	Worsening of conjunctivitis symptoms OS
Tobramycin	4003	0033	27/F/C	4	Allergic reaction to study drug
Tobramycin	4001	1687	13/F/C	3	Cat scratch fever
Tobramycin	4016	0244	34/M/B	2	Conjunctivitis OD
Tobramycin	4023	1637	9/M/C	1	Hemorrhagic viral conjunctivitis OS
Tobramycin	4065	1028	39/M/C	1	Nausea & vomiting
Tobramycin	4046	0733	52/M/C	2	Respiratory infection-treated with doxycycline
Tobramycin	4001	1683	25/M/A	2	Upper Respiratory Tract Infection required oral antibiotic

## Subjects who did not complete the Phase 3 studies

Drug	Site	PtID	Age, Sex Race	Days	Comments
Tobramycin	4006	0087	49/F/C	2	Vomiting & diarrhea-subject stopped med
Tobramycin	4002	0029	16/F/C	4	Withdrew consent
Tobramycin	4007	0103	47/F/C	2	Withdrew consent
Tobramycin	4030	1149	2/F/C	2	Withdrew consent
Vehicle	3007	0075	36/F/C	3	Conjunctivitis present opposite eye
Vehicle	3040	0473	31/F/C	2	Conjunctivitis spread to OD
Vehicle	3049	0578	62/F/C	3	Conjunctivitis spread to other eye
Vehicle	3040	0929	90/F/C	2	Corneal abrasion OS (became SAE corneal ulceration)
Vehicle	3070	0831	58/F/C	3	Development of herpes simplex keratitis
Vehicle	3038	0015	23/M/H	3	Lack of efficacy
Vehicle	3021	0248	36/M/C	2	Lack of efficacy
Vehicle	3036	0427	63/M/C	2	Lack of efficacy
Vehicle	3038	0449	60/M/C	4	Lack of efficacy
Vehicle	3142	0629	17/F/H	4	Lack of efficacy
Vehicle	3068	0815	33/M/C	2	Lack of efficacy
Vehicle	3073	0868	39/M/C	2	Lack of efficacy
Vehicle	3013	1058	52/M/C	3	Lack of efficacy
Vehicle	3003	1145	85/M/C	3	Lack of efficacy
Vehicle	3068	1250	33/F/C	3	Lack of efficacy
Vehicle	3011	1441	30/M/B	2	Lack of efficacy
Vehicle	3161	1975	3/M/H	2	Lack of efficacy
Vehicle	3182	2173	58/F/H	3	Lack of efficacy
Vehicle	3186	2222	13/F/H	2	Lack of efficacy
Vehicle	3198	2378	3/M/H	2	Lack of efficacy
Vehicle	3198	2370	59/M/H	2	Lost to follow-up
Vehicle	3029	0340	58/F/C	3	Protocol violation
Vehicle	3070	0829	23/M/O	3	Protocol violation
Vehicle	3010	1133	56/F/C	5	Protocol violation
Vehicle	3177	2113	38/M/H	1	Protocol violation
Vehicle	3035	0409	50/F/C	5	Cultures for visit 1 and visit 2 were invalid
Vehicle	3190	2277	1/F/H	2	Study drug expired
Vehicle	3038	0019	41/M/C	4	Withdrew consent
Vehicle	3007	0081	31/F/C	3	Withdrew consent
Vehicle	3018	0205	53/F/C		Withdrew consent
Vehicle	3024	1200	75/M/H	3	Withdrew consent
Vehicle	3108	1296	29/F/B	3	Withdrew consent
Vehicle	3177	2131	39/M/H	2	Withdrew consent

1.1.3.3 Other significant adverse events

Phase 2 and 3 Adverse Event Table

	AzaSite (N=736)	Vehicle (N=389)	Tobramycin (N=378)
Number of Patients with at Least One AE	107 (15%)	42 (11%)	56 (15%)
Eye irritation	12 (1.6%)	1 (0.3%)	4 (1.1%)
Worsening bacterial conjunctivitis	10 (1.4%)	3 (0.9%)	8 (2.1%)
Headache	7 (1.0%)	8 (2.3%)	1 (0.3%)
Pharyngolaryngeal pain	6 (0.8%)	2 (0.6%)	2 (0.5%)
Conjunctival hyperaemia	6 (0.8%)	0	4 (1.1%)
Conjunctival oedema	4 (0.5%)	5 (1.4%)	1 (0.3%)
Eye discharge	4 (0.5%)	0	3 (0.8%)
Eye pruritus	4 (0.5%)	1 (0.3%)	2 (0.5%)
Instillation site burning	4 (0.5%)	2 (0.6%)	1 (0.3%)
Nasopharyngitis	4 (0.5%)	0	1 (0.3%)
Partial vision loss	4 (0.5%)	3 (0.9%)	1 (0.3%)
Upper respiratory tract infection	4 (0.5%)	0	2 (0.5%)
Conjunctivitis allergic	3 (0.4%)	0	0
Corneal erosion	3 (0.4%)	0	1 (0.3%)
Cough	3 (0.4%)	2 (0.6%)	1 (0.3%)
Instillation site stinging	3 (0.4%)	0	0
Pyrexia	3 (0.4%)	3 (0.9%)	3 (0.8%)
Visual acuity reduced	3 (0.4%)	1 (0.3%)	0
Asthenic conditions	2 (0.3%)	0	0
Blepharitis	2 (0.3%)	1 (0.3%)	0
Conjunctivitis viral	2 (0.3%)	2 (0.6%)	1 (0.3%)
Corneal staining	2 (0.3%)	0	2 (0.5%)
Diarrhoea	2 (0.3%)	0	3 (0.8%)
Ear infections	2 (0.3%)	0	0
Epistaxis	2 (0.3%)	0	2 (0.5%)
Eye redness	2 (0.3%)	1 (0.3%)	1 (0.3%)
Eyelid oedema	2 (0.3%)	3 (0.9%)	1 (0.3%)
Keratoconjunctivitis sicca	2 (0.3%)	0	1 (0.3%)
Nasal congestion	2 (0.3%)	0	0
Nausea	2 (0.3%)	0	2 (0.5%)
Otitis media	2 (0.3%)	0	0
Rash	2 (0.3%)	0	0
Sinusitis	2 (0.3%)	1 (0.3%)	2 (0.5%)
Vomiting	2 (0.3%)	0	3 (0.8%)
Back pain	1 (0.1%)	0	0
Bronchospasm	1 (0.1%)	0	0
Cellulitis	1 (0.1%)	0	0
Conjunctival haemorrhage	1 (0.1%)	0	3 (0.8%)
Conjunctivitis	1 (0.1%)	0	2 (0.5%)
Corneal infiltrates	1 (0.1%)	0	2 (0.5%)
Corneal oedema	1 (0.1%)	1 (0.3%)	0
Dehydration	1 (0.1%)	0	0
Dermatitis and eczema	1 (0.1%)	1 (0.3%)	1 (0.3%)

	AzaSite (N=736)	Vehicle (N=389)	Tobramycin (N=378)
Dermatitis contact	1 (0.1%)	0	1 (0.3%)
Dysgeusia	1 (0.1%)	0	0
Ear pain	1 (0.1%)	0	0
Entropion	1 (0.1%)	0	0
Eye injury	1 (0.1%)	0	0
Eye pain	1 (0.1%)	1 (0.3%)	0
Facial pain	1 (0.1%)	0	0
Fatigue	1 (0.1%)	0	0
Flank pain	1 (0.1%)	0	0
Herpes viral infections	1 (0.1%)	1 (0.3%)	0
Herpes zoster	1 (0.1%)	0	0
Influenza	1 (0.1%)	0	1 (0.3%)
Influenza viral infections	1 (0.1%)	0	1 (0.3%)
Instillation site irritation	1 (0.1%)	0	0
Iritis	1 (0.1%)	0	0
Irritability	1 (0.1%)	0	0
Lacrimation increased	1 (0.1%)	0	1 (0.3%)
Lymphadenopathy	1 (0.1%)	0	0
Malaise	1 (0.1%)	0	0
Nightmare	1 (0.1%)	0	0
Parasomnias	1 (0.1%)	0	0
Pharyngitis	2 (0.2%)	1 (0.3%)	0
Punctate keratitis	1 (0.1%)	1 (0.3%)	3 (0.8%)
Rhinorrhoea	1 (0.1%)	0	0
kin hypopigmentation	1 (0.1%)	0	0
Sputum abnormal	1 (0.1%)	0	0
Swelling face	1 (0.1%)	0	0
Throat irritation	1 (0.1%)	0	0
Total fluid volume decreased	1 (0.1%)	0	0
Vision blurred	1 (0.1%)	2 (0.6%)	1 (0.3%)
Abnormal sensation in eye	0	0	1 (0.3%)
Bartonella infections	0	0	1 (0.3%)
Cat scratch disease	0	0	1 (0.3%)
Cerebrovascular accident	0	1 (0.3%)	0
Chest pain	0	1 (0.3%)	0
Conjunctival follicles	0	0	1 (0.3%)
Corneal abrasion	0	1 (0.3%)	0
Corneal ulcer	0	1 (0.3%)	0
Dermatitis allergic	0	1 (0.3%)	0
Dyspepsia	0	0	1 (0.3%)
Eye disorder	0	2 (0.6%)	0
Eye swelling	0	1 (0.3%)	0
Frequent bowel movements	0	0	1 (0.3%)
Hypersensitivity	0	1 (0.3%)	0
Influenza like illness	0	0	1 (0.3%)
Keratitis herpetic	0	1 (0.3%)	0
Oculoglandular syndrome	0	0	1 (0.3%)
Orbital oedema	0	0	1 (0.3%)
araesthesia	0	1 (0.3%)	0

	AzaSite (N=736)	Vehicle (N=389)	Tobramycin (N=378)
Postnasal drip	0	0	2 (0.5%)
Respiratory tract infection	0	0	1 (0.3%)
Rhinitis allergic	0	0	1 (0.3%)

**Reviewer's Comments:** *There were relatively few reported adverse experiences (individual events all less than 2%). The most frequently reported adverse experiences were worsening of the conjunctivitis, ocular irritation, conjunctival hyperemia and edema, ocular burning/stinging upon instillation of the drug product and headache.*

#### 7.1.4 Other Search Strategies

All Adverse Events are reported in Section 7.1.1.3.

#### 7.1.5 Common Adverse Events

All Adverse Events are reported in Section 7.1.1.3.

##### 7.1.5.1 Eliciting adverse events data in the development program

All Adverse Events are reported in Section 7.1.1.3.

##### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All Adverse Events are reported in Section 7.1.1.3.

##### 7.1.5.3 Incidence of common adverse events

All Adverse Events are reported in Section 7.1.1.3.

##### 7.1.5.4 Common adverse event tables

All Adverse Events are reported in Section 7.1.1.3.

##### 7.1.5.5 Identifying common and drug-related adverse events

All Adverse Events are reported in Section 7.1.1.3.

##### 7.1.5.6 Additional analyses and explorations

All Adverse Events are reported in Section 7.1.1.3.

#### 7.1.6 Less Common Adverse Events

All Adverse Events are reported in Section 7.1.1.3.

#### 7.1.7 Laboratory Findings

There were no clinical chemistry, hematology or urinalysis assessments in these studies.

##### 7.1.7.1 Overview of laboratory testing in the development program

There were no clinical chemistry, hematology or urinalysis assessments in these studies.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values  
There were no clinical chemistry, hematology or urinalysis assessments in these studies.

7.1.7.3 Standard analyses and explorations of laboratory data  
There were no clinical chemistry, hematology or urinalysis assessments in these studies.

7.1.7.3.1 Analyses focused on measures of central tendency  
There were no clinical chemistry, hematology or urinalysis assessments in these studies.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal  
There were no clinical chemistry, hematology or urinalysis assessments in these studies.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities  
There were no clinical chemistry, hematology or urinalysis assessments in these studies.

7.1.7.4 Additional analyses and explorations  
There were no clinical chemistry, hematology or urinalysis assessments in these studies.

7.1.7.5 Special assessments  
There were no clinical chemistry, hematology or urinalysis assessments in these studies.

#### **7.1.8 Vital Signs**

There were no clinically significant changes in vital signs.

7.1.8.1 Overview of vital signs testing in the development program  
There were no clinically significant changes in vital signs.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons  
There were no clinically significant changes in vital signs.

7.1.8.3 Standard analyses and explorations of vital signs data  
There were no clinically significant changes in vital signs.

7.1.8.4 Additional analyses and explorations  
There were no clinically significant changes in vital signs.

#### **7.1.9 Electrocardiograms (ECGs)**

No ECG data was collected in the studies performed., nor is it required.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results  
No ECG data was collected in the studies performed.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons  
No ECG data was collected in the studies performed.

7.1.9.3 Standard analyses and explorations of ECG data.  
No ECG data was collected in the studies performed.

7.1.9.4 Additional analyses and explorations  
No ECG data was collected in the studies performed.

**7.1.10 Immunogenicity**  
Azithromycin is not expected to be immunogenic.

**7.1.11 Human Carcinogenicity**  
No human carcinogenicity studies were conducted.

**7.1.12 Special Safety Studies**  
No special safety studies were conducted or are considered necessary.

**7.1.13 Withdrawal Phenomena and/or Abuse Potential**  
There is no abuse potential expected from topical ophthalmic antibacterial drug products.

**7.1.14 Human Reproduction and Pregnancy Data**  
No studies in humans on the effects of ophthalmic azithromycin on reproduction or pregnancy were conducted. The systemic level of absorption of azithromycin is undetectable by current methodologies.

**7.1.15 Assessment of Effect on Growth**  
No studies of the effect on growth have been performed.

**7.1.16 Overdose Experience**  
No overdose experience is available.

**7.1.17 Postmarketing Experience**  
The drug product is not approved or marketed in any country.

## **7.2 Adequacy of Patient Exposure and Safety Assessments**

See Section 4.2. The Patient Exposure and Safety Assessments were adequate.

**APPEARS THIS WAY ON ORIGINAL**

## 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety in Phase 3

	Study 003		Study 004	
	Vehicle	AzaSite	AzaSite	Tobramycin
Randomized	350	335	365	378
Completed	317	313	343	367
Discontinued	33	22	22	11
Per Protocol	149	130	159	157
Intent-to-Treat	328	347	360	375
Efficacy Evaluable	124	107	137	131
<b>Primary Reason for Discontinuation</b>				
Adverse Event	5	2	9	8
Protocol Violation	4	1	4	0
Withdrew Consent	6	6	2	3
Lost to Follow-up	1	5	1	0
Lack of Efficacy	15	7	2	0
Treatment Unmasked	0	1	0	0
Other	2	0	4	0

7.2.1.1 Study type and design/patient enumeration  
See Section 4.2.

### 7.2.1.2 Demographics

Summary of demographics pooled across studies C-01-401-003 and C-01-401-004			
	AzaSite (N=698)	Tobramycin (N=378)	Vehicle (N=350)
<b>Age</b>			
Mean age (Range)	28.5 (1-87)	27.8 (1-93)	31.0 (1-96)
0-11 years	224 (32.1%)	126 (33.3%)	94 (26.9%)
12-64 years	417 (59.7%)	226 (59.8%)	216 (61.7%)
>=65 years	57 (8.2%)	26 (6.9%)	40 (11.4%)
<b>Sex</b>			
Male	276 (39.5%)	161 (42.6%)	139 (39.7%)
Female	422 (60.5%)	217 (57.4%)	211 (60.3%)
<b>Race</b>			
Caucasian	404 (57.9%)	244 (64.6%)	179 (51.1%)
African American	59 (8.5%)	40 (10.6%)	29 (8.3%)
Hispanic	198 (28.4%)	75 (19.8%)	128 (36.6%)
Others	37 (5.3%)	19 (5.0%)	14 (4.1%)
<b>3 Color (Hue)</b>			

Summary of demographics pooled across studies C-01-401-003 and C-01-401-004			
	AzaSite (N=698)	Tobramycin (N=378)	Vehicle (N=350)
Dark	416 (59.6%)	205 (54.2%)	204 (58.3%)
Hazel	74 (10.6%)	45 (11.9%)	28 (8.0%)
Light	208 (29.8%)	128 (33.9%)	118 (33.7%)
<b>Region</b>			
Non-US	88 (12.6%)	35 (9.3%)	62 (17.7%)
US	610 (87.4%)	343 (90.7%)	288 (82.3%)

### 7.2.1.3 Extent of exposure (dose/duration)

	C-01-401-003		C-01-401-004	
	AzaSite	Vehicle	AzaSite	Tobramycin
<b>Treatment Exposure</b>	N=333	N=350	N=365	N=378
Mean (SD) Days of Treatment	4.8 (0.7)	4.8 (0.7)	4.9 (0.6)	4.9 (0.5)
Min, Max Days of Treatment	1,5	1,7	1,6	1,7
<b>Total Number of Doses</b>	329	347	361	375

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There were no secondary clinical data sources contributing significant new information.

### 7.2.2.1 Other studies

There were no secondary clinical data sources contributing significant new information.

### 7.2.2.2 Postmarketing experience

There is no postmarketing information available.

### 7.2.2.3 Literature

A Medline search was conducted. No significant new information was available.

## 7.2.3 Adequacy of Overall Clinical Experience

The clinical studies were adequate for evaluation of the new drug product.

## 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal testing is necessary. Adequate in vitro testing has been performed.

## **7.2.5 Adequacy of Routine Clinical Testing**

The clinical testing performed in the studies were adequate for evaluation of the new drug product.

## **7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup**

The systemic exposure is below the level of detection. It is not possible to measure the metabolism, clearance or interaction.

## **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**

Evaluations are considered adequate. No further testing is recommended.

## **7.2.8 Assessment of Quality and Completeness of Data**

The data is considered adequate and complete.

## **7.2.9 Additional Submissions, Including Safety Update**

*No additional new information has been submitted that would alter the conclusions of this review.*

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

*There were relatively few reported adverse experiences (individual events each reported less than 2%). The most frequently reported adverse experiences were worsening of the conjunctivitis, ocular irritation, conjunctival hyperemia and edema, ocular burning/stinging upon instillation of the drug product and headache.*

## **7.4 General Methodology**

### **7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence**

#### **7.4.1.1 Pooled data vs. individual study data**

Pooled data is presented because of the small number of adverse events reported.

#### **7.4.1.2 Combining data**

Pooled data is presented because of the small number of adverse events reported.

### **7.4.2 Explorations for Predictive Factors**

#### **7.4.2.1 Explorations for dose dependency for adverse findings**

There is no evidence for dose dependency for adverse findings.

#### **7.4.2.2 Explorations for time dependency for adverse findings**

There is no evidence for time dependency for adverse findings.

#### **7.4.2.3 Explorations for drug-demographic interactions**

There is no evidence for drug-demographic interactions.

#### 7.4.2.4 Explorations for drug-disease interactions

There is no evidence of drug-disease interactions.

#### 7.4.2.5 Explorations for drug-drug interactions

There is no evidence of drug-drug interactions.

#### 7.4.3 Causality Determination

It is not possible to assess causality because the reported events could be due to any component of the drug product including the active ingredient, the preservative or some other component of the vehicle of the drug product.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

The proposed dosing regimen (twice daily for two days followed by once daily) is a reduction of the dosing regimen listed for other products approved for the treatment of bacterial conjunctivitis (three to four times per day). The applicant theorizes that less frequent dosing is needed because of properties of the vehicle which prolong retention of the drug product in the eye. No formal comparisons between once, twice, three or four times per day dosing has been performed with this or other drug products. In support of the proposed dosing regimen, the drug product is superior to its vehicle dosed at the same frequency and equivalent to tobramycin ophthalmic solution when the tobramycin was dosed four times per day.

### 8.2 Drug-Drug Interactions

There are no known drug-drug interactions.

### 8.3 Special Populations

There are no relevant special populations.

### 8.4 Pediatrics

Age		Study 103		Study 104	
		Vehicle	Azithromycin	Azithromycin	Tobramycin
1	Clinical Resolution	60% (9/15)	75% (9/12)	85% (17/20)	90% (9/10)
	Bacterial Eradication	67% (10/15)	83% (10/12)	80% (16/20)	80% (8/10)
2	Clinical Resolution	75% (9/12)	70% (7/10)	100% (13/13)	73% (11/15)
	Bacterial Eradication	83% (10/12)	80% (8/10)	69% (9/13)	80% (12/15)
3	Clinical Resolution	63% (5/8)	63% (5/8)	79% (11/14)	90% (9/10)
	Bacterial Eradication	75% (6/8)	100% (8/8)	93% (13/14)	100% (10/10)
4	Clinical Resolution	33% (1/3)	83% (5/6)	77% (10/13)	75% (9/12)
	Bacterial Eradication	33% (1/3)	100% (6/6)	85% (11/13)	100% (12/12)
5	Clinical Resolution	50% (3/6)	40% (2/5)	67% (6/9)	100% (9/9)

## OVERALL ASSESSMENT

### 9.1 Conclusions

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that AzaSite when dosed twice a day for two days followed by once a day for five additional days is superior to its vehicle and equivalent to tobramycin ophthalmic solution in the treatment of bacterial conjunctivitis.

### 9.2 Recommendation on Regulatory Action

It is recommended from a clinical prospective that NDA 50-810, AzaSite (azithromycin ophthalmic solution) be approved for the treatment of bacterial conjunctivitis with labeling revisions listed in this review.

### 9.3 Recommendation on Postmarketing Actions

#### 9.3.1 Risk Management Activity

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

#### 9.3.2 Required Phase 4 Commitments

There are no recommended Phase 4 studies.

#### 9.3.3 Other Phase 4 Requests

There are no additional Phase 4 requests.

### 9.4 Labeling Review

See Appendix 10.2 for recommended changes to the labeling.

### 9.5 Comments to Applicant

*The Original Submission contains an error in Table 24, Line 1 of Study 004. The corrected results are included in this review, but the submitted application should be corrected.*

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

Study 003 A study to evaluate the clinical and microbial efficacy and safety of 1.0% AzaSite compared to Vehicle in the treatment of bacterial conjunctivitis. (Enrolled/Culture Positive/Cure)

## Clinical Review

Wiley A. Chambers, MD

NDA 50-810

AzaSite (azithromycin ophthalmic solution), 1%

Page 33 of 55

Site #	Investigator	Study Location	AzaSite	Vehicle
3001	Abrams, Marc, M.D.	Cleveland, OH 44115	4/1/0	8/4/2
3003	Bacharach, Jason, M.D.	Petaluma, CA 94954	5/1/1	7/1/0
3004	Berdy, Gregg, M.D.	Creve Coeur, MO 63141	0	0
3005	Branch, James D., M.D.	Winston-Salem, NC 27101	13/6/4	17/8/6
3007	Cerise, Donald, M.D.	Metairie, LA 70006	3/1/0	5/2/0
3008	Chace, Richard, M.D.	Portsmouth, NH 03801	0	0
3009	Coronado, Tomas, M.D.	San Antonio, TX 98205	11/5/4	12/4/3
3010	Crampton, H. Jerome, M.D.	Andover, MA 01810	3/3/1	3/3/2
3011	DuBiner, Harvey B., M.D.	Morrow, GA 30260	3/2/2	6/3/3
3012	Eiferman, Richard, M.D.	Louisville, KY 40205	7/0/0	8/2/0
3013	Ericson, Lamont, M.D.	Layton, UT 84041	9/4/2	11/3/1
3014	Evans, Richard, M.D.	San Antonio, TX 78240	2/2/0	1/1/1
3015	Forstot, S. Lance, M.D.	Littleton, CO 80120	0	0
3016	Friedland, Beth, M.D.	Durham, NC 27713	0	0
3017	Galentine, Paul, M.D.	Charlotte, NC 28211	0/0/0	1/1/0
3018	Geffin, Joel, M.D.	Waterbury, CT 06708		
3019	Gonzales, Casimiro, M.D.	Cudahy, CA 90201	3/3/0	3/1/0
3020	Helms, Harold J., Jr., M.D., Ph.D.	Birmingham, AL 35205	0	0
3021	Henderson, Thomas, M.D., FACS	Austin, TX 78704	4/1/1	2/0/0
3022	Kanengiser, Bruce, M.D.	Piscataway, NJ 08854	21/10/3	20/13/4
3023	Koffler, Bruce, M.D.	Lexington, KY 40509	0	0
3024	Kostick, Alexandra, M.D., FACS, FRCS	Palm Coast, FL 32137	6/1/1	6/1/1
3025	Kurata, Fred, M.D.	Los Angeles, CA 90013	0	0
3027	Leung, Richard, M.D.	San Diego, CA 92123	0	2
3028	Lewis, Angela, M.D.	Zachary, LA 70791	0	0
3029	Liu, James, M.D.	San Jose, CA 95124	0/0/0	1/1/0
3030	Long, Douglas, M.D.	Milwaukee, WI 53209	0	1
3031	Mansouri, Arash, M.D.	Fredericksburg, VA 22405	1/0/0	2/1/0
3032	Mitchell, Elizabeth, M.D.	Memphis, TN 38119	3/2/2	4/1/1
3033	Moran, C. Thomas, M.D.	Louisville, KY 40205	3/2/1	2/0/0
3035	Olander, Kenneth, M.D., Ph.D.	Maryville, TN 37803	1	1
3036	Perez-Ortiz, Don, M.D.	Tampa, FL 33603	21/6/5	19/4/2
3037	Rotberg, Michael, M.D.	Charlotte, NC 28210	2/0/0	6/3/2
3038	Rubin, Jay M., M.D.	San Antonio, TX 78209	7/3/3	6/2/1
3039	Salamon, Samuel, M.D.	Cleveland, OH 44115	0	0
3040	Schenker, Howard, M.D.	Rochester, NY 14618	10/2/0	9/3/0
3041	Goyal, Dinesh, M.D.	Minneapolis, MN 55402	0	0
3042	Shulman, David, M.D.	San Antonio, TX 78209	3	1
3043	Silverstein, Steven M., M.D.	Kansas City, MO 64133	2/1/0	2/1/1
3044	Stevenson, O. Dara, M.D.	New Orleans, LA 70119	0	1
3045	Wapner, Francis J., M.D.	Salt Lake City, UT 84124	17/11/11	14/6/3
3047	Au, Yue Kong, M.D.	Bossier City, LA 71111	0	0
3048	McGarey, David, M.D., PC	Flagstaff, AZ 86001	0	2
3049	Bohn, Barry, M.D.	Lafayette, LA 70506	8/2/1	8/3/2

## Clinical Review

Wiley A. Chambers, MD

NDA 50-810

AzaSite (azithromycin ophthalmic solution), 1%

Site #	Investigator	Study Location	AzaSite	Vehicle
3051	Rowe, Jonathan, M.D.	Kalamazoo, MI 49048	0	0
3053	Smith, Lindley, M.D.	Richmond, VA 23220	0	0
3054	Sutton, James, M.D.	Ocean Springs, MS 39564	8/2/2	7/7/5
3055	Yaros, Michael, M.D.	Cherry Hill, NJ 08003	3/2/1	3/1/1
3056	Call, Newel Branson, M.D.	Salt Lake City, UT 84102	0	0
3057	Davis, Richard, M.D.	Huntington, NY 11743	0	0
3058	DeLuise, Vincent, M.D.	Waterbury, CT 06708	1/0/0	1/1/1
3059	Desmond, Brian, M.D.	Bend, OR 97701	1	1
3060	O'Rourke, Melinda, M.D.	Wheat Ridge, CO 80033	1	0
3061	Schneider, Ellen, M.D.	Metairie, LA 70006	0	0
3062	Tharp, Andrew, M.D.	Evansville, IN 47714	0	0
3063	Wittpenn, John, Jr., M.D.	Stonybrook, NY 11790	0	0
3064	Newman, Gordon, M.D.	Dallas, TX 75240	0	0
3065	Felch, James, M.D.	Nashville, TN 37203	0/0/0	1/1/0
3066	Jackson, Alan, M.D.	Salt Lake City, UT 84107	0	0
3067	Groat, Robert, M.D.	Greensboro, NC 27401	1	1
3068	Williams, Robert, M.D.	Louisville, KY 40217	5/1/1	5/1/0
3070	Silverstein, Bruce, M.D.	Redding, CA 96002	4/1/0	4/1/0
3072	Mayo, Mark, M.D.	Pasadena, TX 77504	1	0
3073	Sanders, Marc, M.D.	Houston, TX 77004	2/1/0	3/0/0
3082	Kibirige, Mustapha, M.D.	Houston, TX 77002	2	1
3083	Ho, Charles, M.D.	Marietta, GA 30062	0	0
3084	Martinez, Carlos, M.D.	Long Beach, CA 90808	1/1/1	0/0/0
3085	Way, David, M.D.	New Braunfels, TX 78130	0	0
3092	Watson, Susan A., M.D.	Rocky Mount, NC 27804	1	2
3093	Kim, Tae, M.D.	Cerritos, CA 90703	0	0
3108	Rubin, Mark, M.D.	Ormond Beach, FL 32174	9/0/0	6/1/0
3123	DeLeon, Jesse, M.D.	Paramount, CA 90723	17/9/7	17/12/7
3124	Harral, Russell, M.D.	Jonesboro, AR 72401	6/0/0	6/2/2
3133	Ackerman, Stacey, M.D.	Philadelphia, PA 19148	0/0/0	1/1/1
3135	Heller, Warren Harvey M.D.	Phoenix, AZ 85003	9/5/1	9/5/0
3140	Tepedino, Michael, M.D.	High Point, NC 27262	5/2/2	7/3/2
3141	Dao, Jung, M.D.	Phoenix, AZ 85032	10/5/5	8/4/3
3142	Davitt, William, M.D.	El Paso, TX 79904	12/6/3	11/8/4
3144	Wiggins, Robert Earl, Jr., M.D.	Asheville, NC 28803	0	0
3145	Dugel, Raj, M.D.	Torrance, CA 90503	0	0
3148	Piccione, Richard J., M.D.	Lafayette, LA 70508	0	0
3151	Foley, John A.	Exmore, VA 23350	1/1/1	0/0/0
3155	Sultana, Nighat, M.D.	The Woodlands, TX 77380	1	1
3161	Feris-Iglesias, Jesús M., M.D.	Sto. Domingo, D.N., Dominican Republic	4/4/3	3/3/2
3162	Stern-Diaz, Herbert S., M.D.	Santo Domingo, R.D., Dominican Republic	3	3
3163	Thormann-Peynado, Monica C., M.D.	Santo Domingo, D.N., 008, Dominican Republic	7/4/4	8/5/0

Site #	Investigator	Study Location	AzaSite	Vehicle
3164	Vázquez-Díaz, Jose Alfredo, M.D.	Ponce, Puerto Rico 00716	1/0/0	3/2/0
3177	Gonzalez-Trevino, Juan Luis, M.D.	Monterrey N.L., C.P. 64020 Mexico	5/0/0	3/1/0
3181	Aseff-Zamorano, Alejandro Jose, M.D.	Monterrey, N.L. 64010, Mexico	1/1/1	4/2/0
3182	Galdamez Coronado, Sergio Anibal, M.D.	Guatemala 01009, Guatemala	0/0/0	2/1/1
3186	Rosales-Andrino, Guillermo Estuardo, MD	Guatemala 01010, Guatemala	4/0/0	4/2/2
3190	Montiel-Viesca, Francisco Jose, M.D.	Guatemala 01009, Guatemala	13/9/7	15/6/3
3198	Rodriguez-Solares, Adib Federico, M.D.	Guatemala 01011, Guatemala	14/6/1	13/7/3
3202	Lechuga-Ortiz, Fausto Miguel, M.D.	La Paz, Baja California Sur 23090, Mexico	2/1/0	2/0/0
3210	Arellanes-Garcia, Maria de Lourdes, M.D.	Mexico, D.F. Deleg. Coyoacan, Mexico	0	0
3211	Leal-Leyva, Roberto, MD	Chihuahua, 31020, Mexico	1	1

Study 004 - A study to evaluate the clinical and microbial efficacy and safety of AzaSite compared to 0.3% tobramycin ophthalmic solution in the treatment of bacterial conjunctivitis (Enrolled/Culture Positive/Cure)

Site #	Investigator	Study Location	AzaSite	Tobramycin
4001	Amin, Pranav, MD	Yuba City, CA 95991	16/11/9	17/9/6
4002	Aquavella, James, MD	Rochester, NY 14642	3/1/1	5/1/1
4003	Bowe, Brian, MD	Wenatchee, WA 98801	4/2/1	5/1/1
4004	Caldwell, Delmar, MD	New Orleans, LA 70112	4/0/0	6/1/1
4005	Colby, Kathryn, MD	Boston, MA 02114	0	0
4006	Dao, Jung, MD	Phoenix, AZ 85032	29/12/10	32/11/8
4007	Davitt, William, MD	El Paso, TX 79904	24/10/5	24/15/13
4008	Dawson, Peter S., MD	Houston, TX 77008	10/3/2	9/3/1
4010	Hector, Richard, MD	Bradenton, FL 34209	2/1/0	1/0/0
4011	Insler, Michael S., MD	New Orleans, LA 70112	0/0/0	1/1/0
4013	Katzman, Barry, MD	San Diego, CA 92115	9/4/2	10/1/0
4014	Lichtenstein, Steven, MD	Louisville, KY 40202-1747	0	0
4015	Lipka, Andrew, MD	Princeton, NJ 08540	0	0
4016	Macy, Jonathan I, MD	Los Angeles, CA 90048	7/3/3	6/1/1
4020	O'Brien, Terrence, MD	Lutherville, MD 21093	0	0
4021	O'Neal, Kevin, MD, PhD	Raleigh, NC 27604	1/1/1	0/0/0
4022	Paul, Matthew, MD	Danbury, CT 06810	3/2/2	1/0/0
4023	Protzko, Eugene, MD	Bel Air, MD 21014	66/41/40	68/36/33
4024	Puglisi, John, MD	North Miami Beach, FL 33169	1/0/0	1/0/0
4025	Rapoza, Peter, MD	Boston, MA 02114	1/1/1	1/0/0
4026	Reidy, Robert, MD	Albuquerque, NM 87102	0	0
4028	Spector, Steve, MD	West Palm Beach, FL 33407	3/0/0	4/0/0
4029	Stein, Emil, MD	Las Vegas, NV 89119	5/3/1	4/1/0
4030	Tepedino, Michael, MD	High Point, NC 27262	49/23/19	50/24/19
4031	Thomas, Robert A., MD	Phoenix, AZ 85020	1/0/0	0/0/0
4033	Welborn, Julius W., MD	Greenville, SC 29607	9/3/3	9/2/2
4034	Bray, William, MD	Spokane, WA 99204	2/1/0	4/1/0
4034				

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Site #	Investigator	Study Location	AzaSite	Tobramycin
4035	Yee, Richard, MD	Houston, TX 77030	10/4/4	10/5/5
4036	Levy, Norman, MD, PhD	Gainesville, FL 32605	6/4/4	7/1/1
4037	Lappin, Michael, MD	Santa Ana, CA 92705	0	0
4038	Alder, John, MD	Murray, UT 84107	0/0/0	1/1/0
4039	Cowden, John, MD	Columbia, MO 65212	7/3/1	6/3/2
4040	Hagen, Kerry, MD	Portland, OR 97209	4/1/0	2/0/0
4041	Petras, Christodoulos M., MD	Richmond, VA 23229	0	0
4042	D'Aversa, Gerard, MD	Valley Stream, NY 11581	1/0/0	1/0/0
4043	Donshik, Peter, MD	Bloomfield, CT 06002	0	0
4044	Doshi-Carnavale, Sima, MD	Lynbrook, NY 11563	1/0/0	0/0/0
4045	Perry, Henry, MD	Rockville Centre, NY 11570	0	0
4046	Bauman, Alan, MD	Kansas City, MO 64132	2/0/0	4/2/0
4047	Chang, Alexander, MD	Pittsburg, PA 15220	0	0
4048	Denison, Chad, MD	Hutchison, KS 67502	6/0/0	4/2/1
4049	Hasty, Ben, MD	Panama City, FL 32405	2/0/0	2/0/0
4050	Held, Evan, MD	Huntington Station, NY 11746	0	0
4051	Muller, Laura, MD	New Port Richey, FL 34652	0	0
4052	Phillips, Michael, MD	Greenville, SC 29605	1/0/0	3/1/0
4053	Shugarman, Richard, MD	Lake Worth, FL 33461	2/1/0	4/1/0
4054	Shuster, Alan, MD	Jupiter, FL 33458	5/0/0	5/4/2
4056	Weinberger, Irving, MD	Pittsburg, PA 15228	0	0
4057	Berdy, Gregg, MD	Creve Coeur, MO 63141	6/4/3	8/4/4
4058	Chiappetta, Jason, MD	Richmond, VA 23226	0	0
4059	Johnson, Anthony P., M.D.	Greenville, SC 26907	3/3/2	3/1/1
4060	Kurata, Fred, MD	Los Angeles, CA 90013	14/3/2	14/5/4
4062	Wiggins, Robert, MD	Asheville, NC 28803	5/2/2	5/2/2
4063	Fishburn, Jon, MD	Boise, ID 83704	0	0
4064	Peterseim, M. Millicent, MD	Charleston, SC 29403	0	0
4065	Helms, Harold, MD	Birmingham, AL 35205	3/0/0	2/1/1
4077	Katz, Randy, MD	Boynton Beach, FL 33426	0	0
4078	Elliott, Steven, MD	Evansville, IN 47714	0/0/0	1/1/0
4151	Slon-Hitti, Claudio, MD	San Jose, Costa Rica	16/4/4	17/7/6
4152	Avila-Aguero, Maria, MD	San Jose, Costa Rica	0	0
4153	Tovar Rivera, Mariano, MD	San Jose, Costa Rica	2/1/1	2/2/2
4154	Jimenez-Fonseca, Elisa, MD	San José, Costa Rica	0	0
4162	Leal-Leyva, Roberto, MD	Chihuahua, Chihuahua, 31020, Mexico	1/0/0	1/0/0
4163	Porrás-Mendoza, Luis Carlos, MD	Chihuahua, Chihuahua 31238, Mexico	11/7/4	11/6/5
4166	Arellanes-García, Lourdes, MD	Mexico, D.F. 04030, Mexico	2/0/0	4/0/0
4168	Vasquez Hernandez, Roberto Javier, MD	Panama City, Republic of Panama	1/0/0	0/0/0
4170	Luciani-Chiu, Kathia, MD	Panama City, Republic of Panama	0	0
4171	Castrejon Alba, Maria Mercedes, MD	Panama City, Republic of Panama	0	0
4172	Suarez Fernandez, Marixel, MD	Panama City, Republic of Panama	0	0

19 Page(s) Withheld

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