

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22428Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Pre-Decisional Agency Information

Date: October 4, 2010

To: Lori Gorski, Project Manager
Division of Anti-Infective & Ophthalmology Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

Sheila Ryan, Pharm.D., Group Leader
Division of Drug Marketing, Advertising and Communications

Subject: Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution)
(b) (4)
NDA: 022428

DDMAC has reviewed the proposed package insert (PI) for Moxifloxacin AF (moxifloxacin hydrochloride ophthalmic solution) 0.5%, dated 9/23/2010, and we offer the following comments. Please feel free to contact me at (301)796-2653 with any questions or clarifications.

(b) (4)

2 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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/s/

CHRISTINE G CORSER
10/04/2010

DSI CONSULT: Request for Clinical Inspections

Date: July 7, 2010

To: Constance Lewin, MD, Branch Chief, GCP1
Tejashri Purohit-Sheth, MD., Branch Chief, GCP2
Jean Mulinde, Medical Officer, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: William Boyd, MD, Clinical Team Leader, 301-796-0686
Lucious, MD, Medical Reviewer, 301-796-0749
Division of Anti-Infective and Ophthalmology Products

From: Lori Gorski, Regulatory Health Project Manager, 301-796-0722
Division of Anti-Infective and Ophthalmology Products

Subject: Request for Clinical Site Inspections after a Complete Response

I. General Information

Application#: NDA 22-428

Sponsor/Sponsor contact information (to include phone/email):

Alcon

Attention: Ms. Karen Lankow, Associate Director, Regulatory Affairs
817-568-6494

Drug: Moxifloxacin Hydrochloride Ophthalmic Solution 0.5% as base

NME: No

Standard or Priority: Standard

Proposed indication: the treatment of bacterial conjunctivitis

Study Population < 18 years of age: Y

PDUFA: November 19, 2010

Action Goal Date: October 1, 2010

Inspection Summary Goal Date: September 15, 2010

II. Protocol/Site Identification

The following investigators are the high enrollers for this trial.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Dao, Jung MD Cornea Consultants of Arizona 3815 E. Bell Rd, #2500 Phoenix, AZ 85032 (602) 258-4321	C-07-40	49	the treatment of bacterial conjunctivitis
Ericksen, Corey DO Westside Medical 1477 N. 2000 W. Clinton, Utah 84015 (801) 774-8888	C-07-40	49	same
Khamis, Sherif MD San Fernando Valley Research Associates, Inc. 7111 Winnetka Ave., #14 Canoga Park, CA 91306 (818) 347-0065	C-07-40	49	same

III. Site Selection/Rationale

The three highest enrollers for Study C-07-40 are identified in the preceding table.

There are no specific safety or efficacy concerns for any of the sites in this clinical trial. There are no fraud or misconduct concerns currently identified at any of the investigational sites.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Routine Inspections as resources allow

Goal Date for Completion:

Request for Clinical Inspections

NDA 22-428

Page 3

If routine inspections are completed the Inspection Summary Results should be provided by September 15, 2010. We intend to issue an action letter on this application by October 1, 2010. The PDUFA due date for this application is **November 19, 2010**.

Should you require any additional information, please contact Lori Gorski at 301-796-0722 or William Boyd, MD at 301-796-0686.

Additional Information:

This is a paper NDA. The clinical portion of the application has been preliminarily reviewed and no issues have been identified to date to suggest a problem with data integrity.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22428	ORIG-1	ALCON PHARMACEUTICA LS LTD	MOXIFLOXACIN ALTERNATIVE FORMULATION OP

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/s/

LORI M GORSKI
07/09/2010
DSI consult request on resubmission

RPM FILING REVIEW

Application Information					
NDA # 22-428 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-			
Proprietary Name: (b) (4)					
Established/Proper Name: moxifloxacin hydrochloride					
Dosage Form: ophthalmic solution					
Strengths: 0.5% as base					
Applicant: Alcon Research Ltd.					
Agent for Applicant (if applicable):					
Date of Application: December 12, 2008					
Date of Receipt: December 15, 2008					
Date clock started after UN:					
PDUFA Goal Date: October 15, 2009		Action Goal Date (if different):			
Filing Date: February 13, 2009		Date of Filing Meeting: May 11, 2009			
Chemical Classification: 3					
Proposed indication: treatment of bacterial conjunctivitis					
Type of Original NDA:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)			
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html <i>and refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)			
Review Classification:		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted			
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>					
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>			
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device			
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):					
List referenced IND Number(s): IND 59,944					
Goal Dates/Names/Classification Properties		YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?		X			

Are the proprietary, established/proper, and applicant names correct in tracking system?	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system?	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes , explain in comment column.				
If affected by AIP , has OC/DMPQ been notified of the submission? If yes , date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?																				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).																				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>																				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X																	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X																			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?	X			Owned by Alcon
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input checked="" type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).			X	
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: x legible x English (or translated into English) x pagination x navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			X	

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			Studies 1 mo – 16 yrs included
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			Waiver for 0-1 month
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>		X		Name was submitted May 29, 2009
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>				
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>			X	
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted. NONE	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	X			
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	X			
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>			X	

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting? Date: April 8, 2008	X			Meeting canceled after Alcon received our draft responses
Any Special Protocol Assessments (SPAs)? Date: June 4, 2008	X			

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

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/s/

LORI M GORSKI
09/28/2009
RPM filing review

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 07-08-2009

TO: Lori Gorski, Regulatory Project Manager
Jennifer Harris, M.D., Medical Officer
Division of Anti-Infective and Ophthalmology Products

FROM: Jean Mulinde, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-428

APPLICANT: Alcon

DRUG: Moxifloxacin Alternative Formulation (moxifloxacin hydrochloride ophthalmic solution)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of [REDACTED] (b) (4) conjunctivitis in patients (b) (4) years or older.

CONSULTATION REQUEST DATE: 03/16/2009

DIVISION ACTION GOAL DATE: 08/01/2009

PDUFA DATE: 10/15/2009

I. BACKGROUND:

Moxifloxacin Alternative Formulation (moxifloxacin hydrochloride ophthalmic solution) is a sterile solution containing moxifloxacin hydrochloride, a fluoroquinolone antibiotic, for topical ophthalmic use. Moxifloxacin Alternative Formulation (Moxifloxacin AF) is a new moxifloxacin formulation containing a xanthum (b) (4) and a reduced dosing regimen, while still providing similar safety and efficacy to previously approved moxifloxacin ophthalmic formulations (Vigamox®). Other ophthalmic formulations of moxifloxacin (Vigamox®, approved by the FDA in April, 2003) have been shown, in general, to be safe and effective to treat bacterial conjunctivitis; however, Vigamox® is required to be dosed 3 times per day for 7 days. In the current NDA the sponsor proposes that Moxifloxacin AF may be used to treat bacterial conjunctivitis at a dose of one drop to the affected eye two times per day for 7 days.

To support approval, the Applicant has provided data from two pivotal clinical trials (Protocol C-04-38 and Protocol C-04-40), which they believe provide sufficient evidence for the safety and efficacy of twice-daily dosing of Moxifloxacin AF for the 7 days, for the treatment of bacterial conjunctivitis. Protocol C-04-38 is considered most crucial by the Review Division in supporting approval; therefore clinical investigator (CI) inspections have only been requested for this protocol.

PROTOCOL NUMBER: C-04-38 “AN EVALUATION OF THE SAFETY AND EFFICACY OF MOXIFLOXACIN AF OPHTHALMIC SOLUTION 0.5% FOR THE TREATMENT OF BACTERIAL CONJUNCTIVITIS IN THE USA”

This study was a multicenter, randomized (1 Moxifloxacin AF subject: 1 vehicle subject), placebo-controlled, parallel group comparison study that was conducted at 32 centers in the United States. Patients were enrolled in the study from November 3, 2005 through May 17, 2007 (Date of final study report: November 12, 2008).

The primary efficacy assessment in the study had two components, clinical and microbiological. The primary clinical efficacy variable was clinical cure, defined as when the sum of the ratings for the two cardinal ocular signs of bacterial conjunctivitis (i.e. bulbar conjunctival injection and conjunctival discharge/exudate) was zero at the Exit Visit [Test-of-Cure (TOC)]. The primary microbiological efficacy variable was microbiological success, defined as when the pre-therapy pathogens were eradicated at the Exit Visit (TOC).

The secondary efficacy variables included a comparison of findings for the eight individual signs and symptoms of bacterial conjunctivitis at each visit (bulbar conjunctival injection, conjunctival discharge/exudate, lid erythema, lid swelling, palpebral conjunctiva, foreign body sensation, tearing and photophobia).

A safety endpoint was not specifically defined by the protocol; it is presumed that a comparison of reported adverse events was the primary safety endpoint.

The sites requested for inspection were two of five centers that all appear to be operating under a umbrella site management organization called (b) (4). All five of these sites also utilized the same ophthalmologist group as sub-investigators to conduct ophthalmic examinations. The sum of enrollment at these five centers (>110 subjects) represented approximately 17% of the subjects enrolled in this study. Therefore, while this product is not a new molecular entity, field inspections of at least several of these associated sites was considered important to verify data for safety and efficacy, and to evaluate of conduct of this pivotal study. The two sites of the five that appear to be operating in association with (b) (4) which were chosen for inspection, were among those with the highest enrollment in the study and that have no prior inspection history.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol # Site # # of Subjects	Inspection Date	Final Classification
Shane G. Christensen, MD Foothill Family Clinic South 6360 South 3000 East, Suite 100 Salt Lake City, UT 84121	C-04-38 Site #2833 29 subjects	06/10/2009- 06/17/2009	Pending (Preliminary classification of VAI)
Randall L. Watson, MD (b) (4) Southwest Family Medicine 1575 West 7000 South West Jordan, UT 84084	C-04-38 Site #3319 23 subjects	05/18/2009- 05/28/2009	NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary, letter has not yet issued to the CI.

1. Randall L. Watson, MD

(b) (4)
Southwest Family Medicine
1575 West 7000 South
West Jordan, UT 84084
Protocol C-04-38, Site #3319

a. What was inspected:

This inspection was conducted in accordance with Compliance Program 7348.811 between 05/18/2009-05/28/2009. A total of 29 subjects were screened, 29 subjects were enrolled and 26 completed the study. Records for all 23 enrolled subjects were reviewed to verify appropriate completion of inform consent documents, that subjects met eligibility criteria, primary endpoint outcomes, concomitant medication use, and completeness of adverse event reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to

the inspection.

b. General observations/commentary:

The inspection of Dr. Watson’s site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued. During the inspection, however, several examples of discrepancies between (b) (4) microbiology reports and microbiology findings recorded in line listings were identified. These discrepancies are summarized in the following table.

Subject	Visit	Source Document (b) (4) a Report	NDA Line Listings
2702	Exit	Haemophilus influenzae	Haemophilus Influenzae
		Corynebacterium sp.	Streptococcus vestibularis
2718	Day 1	Corynebacterium macginleyi	Corynebacterium macginleyi
		Streptococcus cristatus	Streptococcus cristatus
		Haemophilus influenzae	(no third organism listed)
2721	Exit	Cornebacterium sp.	Paenibacillus timonensis

c. Assessment of data integrity:

With the exception of microbiology data noted in the preceding table, data derived from Dr. Watson’s site are considered acceptable. Errors present in microbiology line listings do not represent a regulatory violation attributable to the clinical investigator; rather they appear to be errors that occurred in some way with transfer of data between (b) (4) and the Applicant or in generation of line listings by the Applicant. The review division should consider following up with the Applicant regarding the above identified discrepancies.

2. Shane G. Christensen, MD

Foothill Family Clinic South
6360 South 3000 East, Suite 100
Salt Lake City, UT 84121
Protocol C-04-38, Site #2833

a. What was inspected:

This inspection was conducted in accordance with Compliance Program 7348.811 between 06/10/2009-06/17/2009. A total of 29 subjects were screened, 29 subjects were enrolled and 26 completed the study. Records for all 29 enrolled subjects were reviewed to verify appropriate completion of informed consent documents, that subjects met eligibility criteria, primary endpoint outcomes, and completeness of adverse event reporting. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary:

The inspection of Dr. Christensen's site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator for:

- i. Failure to maintain adequate investigational drug disposition records with respect to dates, quantity, and use by subjects [21 CFR 312.62(a)]. Specifically, test article dispensing logs did not document return of test product (missing return dates, receiver initials, and units returned) for 2 subjects, the return date was inaccurate for one subject, and for 13 subjects the incorrect "Ship ID" (date supplies shipped to site) was recorded on the test article dispensing log. **(DSI Note: While the incorrect "Ship ID" was recorded for 13 subjects, FDA investigators were able to determine from alternate documentation at the site that these subjects did actually receive the correct randomized therapy.)**
- ii. Failure to ensure that the investigation was conducted according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, performing a fundus examination that consisted of only a red reflex assessment for a 10 year old (Subject #205) when the protocol required that retina/macula/choroid and optic nerve assessments be performed on children aged 5 years and older.
- iii. Failure to prepare or maintain adequate case histories with respect to data pertinent to the investigation [312.62(b)]. Specifically, for:
 - a) The Day 3 Ocular Signs source documents and case report form (CRF) for Subject #226 contain conflicting information for conjunctival discharge/exudate (source document -1/Mild, CRF – 0/Normal) and lid erythema (source document – 0/Normal, CRF 1/Mild).
 - b) The Day 4 Ocular Symptoms source document and CRF for Subject #207 contain conflicting information (source document – foreign body sensation, tearing, and photophobia are listed as mild, CRF shows same as absent).
 - c) Day 1 Ocular Signs source documents and case report form (CRF) for Subject #216 contain conflicting information for OD lid swelling (source document - Mild, CRF – absent).

c. **Assessment of data integrity:**

Although regulatory violations were noted, it is unlikely that they significantly affect overall reliability of primary safety and efficacy data from the site.

Note: Observations noted above are based on communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, Protocol C-04-38 appears to have been conducted adequately and the data in support of the NDA appear reliable.

The final classification of the Clinical Investigator inspection of Dr. Watson is No Action Indicated (NAI).

The preliminary classification of the Clinical Investigator inspection of Dr. Christensen is VAI. While regulatory violations occurred at this site, the primary safety and efficacy data from this site are considered reliable. Upon receipt of the EIR for Dr. Christensen an addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIR.

{See appended electronic signature page}

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/s/

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