CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-571

MEDICAL REVIEW(S)

CLINICAL REVIEW NDA 21-571

Medical Officer's Clinical Review #2
Original Application

Submitted:	February 12, 2004
Received:	February 12, 2004
Submitted:	February 19, 2004
Received:	February 19, 2004
Submitted:	February 25, 2004
Received:	February 26, 2004
Review completed:	February 27, 2004
Reviewer:	William Boyd, MD Clinical Team Leader
Proposed Name:	Iquix (levofloxacin ophthalmic solution 1.5%)
Sponsor:	Santen Incorporated 555 Gateway Drive Napa, CA 94558 (707) 256-2473 Contact: Lisa Ann Suchar

Submitted:

Final labeling text based on previous review and discussion with the sponsor. The labeling which follows is the sponsor's resubmission dated February 25, 2004.

The sponsor has accepted all labeling changes requested by the agency.

6 Draft Labeling Page(s) Withheld

5 mL fill in 5 cc container– NDC 65086-145-05

Storage:
Store at 15° – 25°C (59° – 77°F).

Rx Only.

Manufactured by:
Santen Oy, P.O. Box 33, FIN-33721 Tampere, Finland

Marketed by:
Vistakon Pharmaceuticals, LLC
Jacksonville, FL 32256, U.S.A.

Licensed from:
Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan

U.S. PAT. NO 5,053,407

February 2004 Version

Reviewer's Comments:

The submitted labeling is acceptable.

NDA 21-571, Iquix (levofloxacin ophthalmic solution 1.5%), is recommended for approval for the for the treatment of corneal ulcer caused by susceptible strains of bacteria.

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Medical Officer's Review of NDA 21-571
120-Day Safety Update

NDA 21-571
Medical Officer's Review

Submission Date: 8/22/03
Received Date: 8/25/03
Review Completed: 10/15/03

Proposed Trademark: Iquix

Generic Name: Levofloxacin ophthalmic solution 1.5%

Sponsor:
Santen Incorporated
555 Gateway Drive
Napa, CA 94558
(707) 256-2473
Contact: Lisa Ann Suchar, Ph.D.

Pharmacologic Category: Anti-infective (fluoroquinolone)

Proposed Indication: —

Dosage Form and Route of Administration: Ophthalmic solution for topical ocular administration

Submitted:

120-Day safety update stating that there has been no new safety information since the submission of original NDA 21-571 on April 30, 2003.

Reviewer's Comments:

Agree.

Lucious Lim, M.D., M.P.H.
Medical Officer

cc: NDA 21-571
HFD-550/Div Files
HFD-550/PM/Gorski
HFD-550/Biopharm/Chaurasia
HFD-550/Biostats/Choi

HFD-550/Chem/Khorshidi
HFD-550/Pharm/Mukherjee
HFD-550/MO/Lim
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10/15/03 11:22:11 AM
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Wiley Chambers
10/15/03 02:08:23 PM
MEDICAL OFFICER

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CLINICAL REVIEW of NDA 21-571

Original Application

Submitted:	April 30, 2003
Received:	May 1, 2003
Review completed:	December 19, 2003
Reviewer:	Lucious Lim, MD, MPH
Proposed Name:	Iquix (levofloxacin ophthalmic solution 1.5%)
Sponsor:	Santen Incorporated 555 Gateway Drive Napa, CA 94558 (707) 256-2473 Contact: Lisa Ann Suchar

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability

NDA 21-571 is recommended for approval for the treatment of bacterial corneal ulcer in patients 6 years of age and older with the labeling revisions included in this review.

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

No additional Phase 4 studies are recommended. There are no additional recommended risk management steps for this product.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Levofloxacin is a fluoroquinolone antibacterial agent. Quixin (levofloxacin ophthalmic solution) 0.5% is approved for the treatment of bacterial conjunctivitis in the United States. The same formulation (Oftaquix) is marketed in Finland. A preservative-free formulation (Cravit) is marketed in Japan. Levofloxacin ophthalmic solution (Iquix) 1.5% contains a higher concentration of the active drug substance as compared to Quixin and does not contain a preservative. Levofloxacin ophthalmic solution 1.5% (1.5% LVFX) targeted for the treatment bacterial corneal ulcer.

B. Efficacy

The submitted studies in NDA 21-571 are sufficient to establish efficacy for the use of 1.5% LVFX in the treatment of bacterial corneal ulcer in patients. The clinical cure rate for susceptible microorganisms ranges from 76%-82%. This lower than expected rate suggests that 1.5% LVFX should be administered more frequently than was given in the studies.

C. Safety

The submitted studies in NDA 21-571 demonstrate an acceptable safety profile with the use of 1.5% LVFX for the treatment of bacterial corneal ulcer. The most frequently recorded adverse events were headache and dysgeusia (taste perversion).

D. Dosing

The dosing regimen proposed in NDA 21-571 is —

E. Special Populations

No additional data on special populations are needed.

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Clinical Review

I. Introduction and Background

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

Iquix (levofloxacin ophthalmic solution) 1.5% is a fluoroquinolone antibacterial agent. It is an ophthalmic solution for topical ocular administration. The sponsor's proposed indication is — . The dosing regimen is as follows: —

[ ]

B. State of Armamentarium for Indication(s)

Levofloxacin is a fluoroquinolone antibacterial agent. Quixin (levofloxacin ophthalmic solution) 0.5% is approved for the treatment of bacterial conjunctivitis. There are six ophthalmic fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, gatifloxacin, levofloxacin, and moxifloxacin) approved in the United States for use in the treatment of bacterial conjunctivitis. Only ciprofloxacin and ofloxacin are currently approved for use in the treatment of bacterial corneal ulcers.

C. Important Milestones in Product Development

There were no important milestones in the development of this product.

D. Other Relevant Information

The drug substance was obtained by license for ophthalmic use from Daiichi Pharmaceutical Co., Ltd. in Japan. —

—

— . The RW Johnson NDAs 20-634 and 20-635 for Levaquin® Tablets and Levaquin® Injection are approved. Santen Inc. has permission to cross-reference these NDAs in support of this application.

This NDA also cross-references Santen Inc.'s NDA 21-199 for Quixin® (levofloxacin ophthalmic solution) 0.5%, a lower concentration of levofloxacin approved in the U.S. for the treatment of bacterial conjunctivitis. Two 0.5% levofloxacin ophthalmic solutions are available in Asia (Cravit®, a preservative-free formulation) and Europe (Oftaquix™, same formulation as Quixin®).

E. **Important Issues with Pharmacologically Related Agents**
There are no safety and effectiveness concerns associated with agents in this pharmacologic class.

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

Drug Product Composition

Ingredient	Percent (w/v)	mg/ml
Levofloxacin	1.50	15.0
Glycerin, USP		
Dilute HCl and/or dilute NaOH, NF	Adjust to target pH 6.5	
Purified water (or higher grade), USP		

Regulatory Drug Product Specification

Specification	Limit
Appearance	
Identification by UV*	Conforms to the standard
Identification by HPLC*	Retention time matches that of the reference standard
Related Substances	NMT NMT NMT NMT Other individual impurities: NMT Total impurities: NMT
	Not more than
Osmolality	
Acidity or Alkalinity	pH
Clarity and Color of Solution	
Assay	of label claim
	NMT NMT NMT
Sterility	Current USP or equivalent
Antimicrobial Preservative Effectiveness	Current USP or equivalent

*Performed at release

III. Human Pharmacokinetics and Pharmacodynamics

A. **Pharmacokinetics**
Agree with Clinical Pharmacology and Biopharmaceutics Review. See Review for detailed results.

B. Pharmacodynamics

Agree with Clinical Pharmacology and Biopharmaceutics Review. See Review for detailed results.

IV. Description of Clinical Data and Sources

A. Overall Data

Four clinical trials are evaluated in this Medical Officer's review. Studies 16-002 and 16-003 are the primary support of efficacy and contribute to the safety database. Studies 16-001 and 16-006 contribute to the safety database.

B. Tables Listing the Clinical Trials

See Table 1 for a descriptive summary of the clinical trials.

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Table 1 – Description of Clinical Data Sources

Protocol Number	Study Design	Treatment Duration	Patient Population	Treatment Groups	Dosing	No. Sites	No. Subjects Randomized/ Completed	Status
Phase 1 Studies								
Safety, tolerability, and pharmacokinetics (plasma) 16-001 U.S.	Single-center, randomized, double-blinded, parallel group, vehicle-controlled	21 days	Healthy adult volunteers	1.5% LVFX[1] (without BAK[2]) Vehicle (with BAK[2])	2 drops q AM OU on Day 1. 2 drops q 2 hrs OU (10 doses) on Days 2 – 8. 2 drops q 4 hrs OU (5 doses) on Days 8 – 9. 2 drops q AM OU on Day 16.	1 (U.S.)	30/28 (1:1)	Completed
Safety and pharmacokinetics (tears) 16-006 U.S.	Single-center, randomized, double-blinded, parallel group, active-controlled	16 days	Healthy adults volunteers	1.5% LVFX[1] (without BAK[2]) 0.3% OFLX[3] (with BAK[2])	1 drop q 2 hrs OU (10 doses) on Days 1 – 3. 1 drop QID OU on Days 4 – 14.	1 (U.S.)	125/123 (4:1)	Completed
Phase 2/3 Studies								
Safety and efficacy 16-002 North America	Multi-center, randomized, double-blinded, parallel group, active-controlled	Approx-imately 12 days	Adults and pediatric patients ≥ 2 years of age with suspected bacterial corneal ulcer	1.5% LVFX[1] (without BAK[2]) 0.3% OFLX[3] (with BAK[2])	1–2 drops in the study eye q 2 hrs while awake and approximately 4 and 6 hrs after retiring on Days 1– 3. 1-2 drop QID while awake on Day 4 through completion.	25 (U.S.) 2 (Canada) 1 (Puerto Rico)	237/203 (1:1)	Completed
Safety and efficacy 16-003 International	Multi-center, randomized, double-blinded, parallel group, active-controlled	Approx-imately 12 days	Adults ≥ 18 years of age with suspected bacterial corneal ulcer	1.5% LVFX[1] (without BAK[2]) 0.3% OFLX[3] (with BAK[2])	Same as study 16-003	1 (Brazil) 2 (India) 5 (Israel)	199/151 (1:1)	Completed

[1] levofloxacin ophthalmic solution [2] benzalkonium chloride [3] Ofloxacin ophthalmic solution

C. **Postmarketing Experience**
No post-marketing data are available for this concentration of levofloxacin ophthalmic solution.

D. **Literature Review**
There is no data in the published literature pertinent to the review of this submission.

V. Clinical Review Methods

A. **How the Review was Conducted**
This medical officer's review evaluated each of four clinical trials separately.

B. **Overview of Materials Consulted in Review**
The submission is submitted in paper CTD format.

C. **Overview of Methods Used to Evaluate Data Quality and Integrity**
The Division of Scientific Investigations audited two study sites (study sites # 65 and #70 for protocol 16-002).

D. **Were Trials Conducted in Accordance with Accepted Ethical Standards**
There is no evidence to indicate that the trials were not conducted in accordance with accepted ethical standards.

E. **Evaluation of Financial Disclosure**
Financial disclosure statements are submitted. There is no evidence to indicate that participation of the investigator who has financial arrangements with applicant affected the integrity of the findings.

VI. Integrated Review of Efficacy

A. **Brief Statement of Conclusions**
The submitted studies in NDA 21-571 are sufficient to establish efficacy for the use of 1.5% LVFX in —

B. **General Approach to Review of the Efficacy of the Drug**
The efficacy database consisted of one North American clinical trial (conducted in U.S., Canada, and Puerto Rico) in support of efficacy in patients ages 2 years and older and one international clinical trial (conducted in Brazil, India, and Israel) in support of efficacy in patients ages 18 years and older.

C. **Detailed Review of Trials by Indication**
Proposed Indication: —

Study #1 Protocol No. 16-002 Conducted 8/1/00 to 5/23/02

Title: A prospective, randomized, parallel-group, multi-center, double-masked trial comparing the efficacy and safety of 1.5% levofloxacin ophthalmic solution with 0.3% ofloxacin ophthalmic solution for treating bacterial keratitis.

Study Design: A multi-center, randomized, double-blinded, active-controlled, parallel-group study.

Test Drug Schedule: Patients received 1-2 drops of masked study medication in the study eye every 2 hours while awake, and approximately 4-6 hours after retiring, on Days 1 through 3, and then 4 times daily (approximately every 4 hours) while awake from Day 4 through study completion.

Investigator Number	Investigator	Number Randomized	
		1.5% LVFX	0.3% OFLX
064		6	7
080		7	4
065	**Dimitri T. Azar, M.D.** Boston, MA 02114 USA	13	12
026		4	1
068		3	3
096		2	3
089		1	0
081		4	5
104		1	1
035		4	2
066		1	2
101		4	6
038		3	4
006		0	1
042		4	4
088		2	2
059		3	4
097		4	3

		Number Randomized	
070	**John D. Sheppard, M.D.** Norfolk, VA 23507 USA	16	12
071		1	4
072		6	3
073		1	3
087		1	4
075		5	5
102		14	10
106	**Sonal S. Tuli, M.D.**[1] Gainesville, FL 23610 USA	0	0
049		3	3
009		6	6
095		2	2

[1] Dr. Tuli became principal investigator after Dr. [redacted] left the University of Florida. All patients enrolled at this site used Investigator No. 081.

Reviewer's Comments:

It is preferable to have at least 10 patients per arm per center.

Study Design

This was a multi-center, randomized, double-blinded, active-controlled, parallel-group study designed to evaluate the safety and efficacy of levofloxacin ophthalmic solution 1.5% (1.5% LVFX) for the treatment of bacterial corneal ulcers in patients 2 years of age or older.

Eligible patients who met all inclusion/exclusion criteria were randomized to receive 1.5% LVFX or Ofloxacin ophthalmic solution 0.3% (0.3% OFLX). Patients were instructed to instill 1-2 drops of masked study medication in the study eye every 2 hours while awake, and approximately 4-6 hours after retiring, on Days 1 through 3, and the 4 times a daily (approximately every 4 hours) while awake from Day 4 through completion of therapy. Treatment continued until the patients were considered cured or a treatment failure by the investigator. Medication was dispensed and dosing began on Day 1 (baseline, Visit 1). Follow-up visits were scheduled for Day 2 or 3 (Visit 2), Day 5 (±1), Day 8 (±1), Day 12 (±2), and Day 18 (±3). After clinical cure was noted, patients were evaluated again in 2 to 5 days at a confirmatory visit. A bacterial corneal culture was obtained at the baseline visit and a bacterial conjunctival culture was obtained at the confirmatory visit. Investigators had the option of continuing treatment with study medication after clinical cure was first noted if the investigators deemed it appropriate.

Study Medications

- Test Article – 1.5% LVFX (Formulation Number 1017S, Lot Nos. 00116/1 and 11001), containing 1.5% levofloxacin (15 mg/mL), glycerin, sodium hydroxide and/or hydrochloric acid to adjust pH, and purified water.
- Control Article – 0.3% OFLX (Formulation Number 1016S, Lot Nos. A1107, A3598, and 12165), containing 0.3% ofloxacin (3 mg.mL), 0.005% benzalkonium chloride (BAK), sodium chloride, and purified water.

Inclusion Criteria

Patients with all of the following conditions are eligible for participation in this study:

1. Patients (and legal guardian if patient is a minor) has given written informed consent to participate in the study.
2. Patient has a clinical diagnosis of suspected bacterial keratitis in one eye only (study eye) defined as an ulceration of the epithelium characterized by fluorescein staining with focal or diffuse suppurative stromal inflammation, cellular infiltration in the adjacent stroma with or without anterior chamber cellular reaction.
3. If patient is a female of childbearing potential, she must utilize a reliable contraceptive method [chemical contraceptive (oral, implantable, or injectable), spermicide with barrier, or IUD] throughout the study, and must have a negative urine pregnancy test prior to enrollment in this study.
4. Patient is 2 years of age or older.
5. Patient (and legal guardian if patient is a minor) understands the scope of the study and is willing to follow instructions and able to make all required study visits.
6. Patient has best-corrected ETDRS visual acuity of +1.0 logMAR (Snellen equivalent: 20/200) or better in the fellow eye.

Exclusion Criteria

Patients with any of the following conditions are not eligible for participation in this study:

1. Presence of suspected fungal, viral, or parasitic ocular infection in the study eye.
2. Females who are lactating, pregnant or are planning a pregnancy, or females of childbearing potential not using a reliable method of contraception.
3. Contact lens wear in the study eye during study period.
4. Use of any topical non-ocular or systemic antimicrobial (including subconjunctival injections) or steroid within 24 hours prior to enrollment into the study or during the study.
5. Use of topical ocular antimicrobial or steroid solution in the study eye within 2 hours prior to enrollment into the study or during the study. Patient should not have been on other pre-study antimicrobial therapy for corneal ulcer for >24 hours.
6. Patient with suspected bacterial endophthalmitis or bacterial scleritis.

7. Use of any systemic/topical investigational drug or device during the study or within 30 days before receipt of study medication. Patient cannot have previously been enrolled in this study.
8. Ocular surgery in the study eye within six weeks before the beginning of the study.
9. Cardiovascular or respiratory surgery within six weeks before the beginning of the study.
10. History of allergy or sensitivity to any quinolone or any component of the study medications, including the preservative BAK.
11. Current alcohol and/or drug abuse.
12. History of retinal detachment, diabetic retinopathy, or any retinal disease which may be progressive during the study.
13. Any history of uncontrolled chronic systemic disease (e.g., cardiovascular disease, hypertension, or diabetes).
14. Any history of autoimmune disease that the investigator feels may interfere with the study parameters (e.g., acquired immuno-deficiency syndrome or rheumatoid arthritis).
15. Any abnormality or presence of any significant illness that could interfere with the study.

Additionally, the investigator or medical monitor may declare any patient ineligible for any sound medical reason.

Efficacy Variables

The primary efficacy variable was clinical cure (i.e., complete re-epithelialization of the infected cornea and no progression from baseline of the stromal infiltrate) as judged by the investigator at the clinical cure visit (Endpoint).

Reviewer's Comments:

The agency does not agree with the primary efficacy variable as stated in the Final Study Report. The primary efficacy variable utilized in the review of this NDA is the assessment of clinical cure (i.e., complete re-epithelialization of the infected cornea and no progression from baseline of the stromal infiltrate) at Endpoint with confirmation at the Confirmatory Visit.

Secondary efficacy variables include cure rate at selected timepoints, cure rate at Endpoint by baseline epithelial defect size, time to clinical cure, investigator's clinical impression, treatment failures, relapse of cure, and corneal ulcer results.

Safety Variables

Safety variables include adverse events, best-corrected visual acuity (BCVA), ocular symptoms, biomicroscopic findings, and ophthalmoscopic findings.

Study Plan

Procedures	Visit 1	Visit 2	Contact	Follow-up Visits[1]	Confirmatory Visit
	Baseline, Day 1	Day 2 or 3	Day 3	Day 5±1, Day 8±1, Day 12±2, Day 18±3	48 hours to 5 days post clinical cure visit[2]
Informed consent, medical history, pregnancy test	X				
Query for adverse events		X		X	X
Visual acuity – ETDRS chart	X (OU)	X (SE)		X (SE)	X (OU)
Assessment of ocular symptoms	X (OU)	X (SE)		X (SE)	X (OU)
Administer unpreserved fluorescein stain	X (SE)	X (SE)		X (SE)	X (SE)
Assessment of ocular signs (biomicroscopy)	X (OU)	X (SE)		X (SE)	X (OU)
Measure and record defect and infiltrate	X (SE)	X (SE)		X (SE)	X (SE)
Photograph	X (SE)			X (SE at cure visit only)[1]	X (SE)
Bacteriologic culture	X (SE)				X (SE)
Ophthalmoscopy	X (OU)				X (OU)
Investigator's clinical impression		X (SE)		X (SE)	X (SE)
Dispense drug (as needed)	X	X		X	
Collect drug				X	X[2]
Contact patient re change in dosing regimen			X[3]		
Concomitant medications	X			X	
Exit form					X[4]

OU=both eyes. SE=study eye. [1]Clinical cure could be noted during any follow-up visit. If noted, a photograph was taken and the patient was scheduled for the Confirmatory Visit (2 to 5 days after cure visit). If clinical cure did not occur by Day 21 and/or treatment was continued, weekly follow-up visits were recommended. The last follow-up visit on treatment was the *Final Visit*. [2]If the investigator continued the patient on study medication after clinical cure was noted, the Confirmatory Visit was to still occur within 2 to 5 days of the cure visit. Drug was then collected at the end of treatment. [3]Contact was made if the patient did not visit the clinic on Day 3. [4]If treatment continued after the Confirmatory Visit, the exit form was completed when treatment ended.

Subject Disposition and Demographics

Two hundred thirty-seven (237) subjects enrolled in the study and 203 subjected completed the study.

Subject Disposition

	Number of Subjects		
	1.5% LVFX N (%)	0.3% OFLX N (%)	Total N (%)
Randomized	121	116	237
Discontinued prematurely	13 (10.7)	21(18.1)	34 (14.3)
Included in safety evaluations	120 (99.2)	114 (98.3)	234 (98.7)
Included in intent-to-treat efficacy analysis	121 (100.0)	116 (100.0)	237 (100.0)
Included in per protocol efficacy analysis	78 (64.5)	71 (61.2)	149 (62.9)

Negative baseline bacterial culture	35 (28.9)	36 (31.0)	71 (30.0)
Viral/Fungal/Parasitic growth	1 (0.008)	0 (0.000)	1 (0.004)

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Reason
006	2373	0.3% OFLX	Lost to follow-up
035	2363	0.3% OFLX	Treatment failure Adverse event – corneal perforation
	2364	0.3% OFLX	Treatment failure – eye pain
038	2055	1.5% LVFX	Treatment failure
042	2006	1.5% LVFX	Other – positive fungal culture
049	2439	0.3% OFLX	No follow-up data available
064	2333	1.5% LVFX	Adverse event – eyelid edema
	2334	1.5% LVFX	Lost to follow-up
	2606	1.5% LVFX	Treatment failure
	2335	0.3% OFLX	Treatment failure
	2529	0.3% OFLX	Other – positive chlamydial culture
	2530	0.3% OFLX	Treatment failure
	2607	0.3% OFLX	Lost to follow-up
	2608	0.3% OFLX	No follow-up data available
065	2477	1.5% LVFX	No follow-up data available
	2341	0.3% OFLX	Non-compliance
	2476	0.3% OFLX	Lost to follow-up
070	2022	1.5% LVFX	Other – investigator's decision (clinical entry criteria not met)
	2398	1.5% LVFX	Lost to follow-up
	2497	1.5% LVFX	Other – investigator's decision
	2023	0.3% OFLX	Other – increased signs and symptoms
	2399	0.3% OFLX	Non-compliance
071	2405	0.3% OFLX	Lost to follow-up
072	2102	0.3% OFLX	Treatment failure
	2411	0.3% OFLX	Adverse event – eye infection
075	2431	1.5% LVFX	Patient's decision not associated with adverse event
	2429	0.3% OFLX	Patient's decision not associated with adverse event
080	2047	1.5% LVFX	Lost to follow-up
	2518	1.5% LVFX	Treatment failure
	2609	0.3% OFLX	Treatment failure
087	2673	0.3% OFLX	Non-compliance
	2674	0.3% OFLX	Non-compliance
088	2460	1.5% LVFX	Lost to follow-up
101	6011	0.3% OFLX	Treatment failure

Summary of Demographics

	Per Protocol			Intent-to-Treat		
	1.5% LVFX	0.3% OFLX	P-value[1]	1.5% LVFX	0.3% OFLX	P-value[1]
Number of Patients:	78	71		121	116	
AGE (years)			0.7041			0.0978
MEAN(SD)	40.4 (17.4)	39.4 (15.4)		42.9 (19.2)	38.9 (16.9)	
Median	35.5	37.0		39.0	36.5	

MIN-MAX	15-88	8-85		13-94	8-85	
>16 years: N (%)	76 (97.4)	67 (94.4)		117 (96.7)	109 (94.0)	
12-16 years: N (%)	2 (2.6)	3 (4.2)		4 (3.3)	5 (4.3)	
2-11 years: N (%)	0 (0.0)	1 (1.4)		0 (0.0)	2 (1.7)	
SEX: N (%)			0.7414			0.8969
Female	36 (46.2)	30 (42.3)		62 (51.2)	58 (50.0)	
Male	42 (53.8)	41 (57.7)		43 (35.5)	58(50.0)	
RACE: N (%)			1.0000			0.7876
Caucasian	48 (61.5)	44 (62.0)		78 (64.5)	72 (62.1)	
Non-Caucasian	30 (38.5)	27 (38.0)		43 (35.5)	44 (37.9)	
Black	9 (11.5)	12 (16.9)		13 (10.7)	16 (13.8)	
Asian	5 (6.4)	3 (4.2)		9 (7.4)	6 (5.2)	
Hispanic	13 (16.7)	7 (9.9)		18 (14.9)	15 (12.9)	
Asian Indian	2 (2.6)	3 (4.2)		2 (1.7)	4 (3.4)	
Other	1 (1.3)	1 (1.4)		1 (0.8)	2 (1.7)	
Not Recorded	0 (0.0)	1 (1.4)		0 (0.0)	1 (0.9)	

[1]P-value for age based on two-sample t-test. P-values for sex and race (non-Caucasian vs. Caucasian) based on Fisher's exact test.

Efficacy

Summary of Clinical Cure at Endpoint with Confirmation at the Confirmatory Visit* by Epithelial Defect Size at Baseline

Epithelial Defect Size at Baseline **Intent-to-Treat (ITT[b])**	Outcome	1.5% LVFX	0.3% OFLX	Lower 95% CI	P-value[a]
Mild (>0.0 – 1.0 mm^2)	Clinical cure	(45/53) 84.9%	(46/63) 77.8%		
Moderate (>1.0 – 4.0 mm^2)	Clinical cure	(39/50) 78.0%	(35/38) 92.1%		
Severe (>4.0 mm^2)	Clinical cure	(15/18) 83.3%	(7/15) 46.7%		
Total	Clinical cure	(99/121) 81.8%	(88/116) 75.9%	-4.4%	0.21
Epithelial Defect Size at Baseline **Per Protocol (PP[c])**	Outcome				
Mild (>0.0 – 1.0 mm^2)	Clinical cure	(32/36) 88.9%	(32/40) 80.0%		
Moderate (>1.0 – 4.0 mm^2)	Clinical cure	(25/30) 83.3%	(23/23) 100%		
Severe (>4.0 mm^2)	Clinical cure	(11/12) 91.7%	(6/8) 75.0%		
Total	Clinical cure	(68/78) 87.2%	(61/71) 85.9%	-9.7%	0.76
Epithelial Defect Size at Baseline **Modified Per Protocol (MPP[d])**	Outcome				
Total	Clinical cure	(34/41) 82.9%	(27/31) 87.1%	-20.7%	0.62

[a] Cochran-Mantel-Haenszel (CMH) statistic. $p<0.05$. [b] ITT=All patients who received treatment. [c] PP=All patients with a clinical and microbial diagnosis of bacterial corneal ulcer without a fungal, viral, or parasitic infection, who received treatment and had post-baseline data. [d] Subset of PP (exclude patients who had no baseline photos of lesion or lesion size was <2mm^2). * Defined as complete re-epithelialization of the infected cornea and lack of progression from baseline of the stromal infiltrate for two consecutive visits.

Reviewer's Comments:

This is the preferred efficacy analysis (confirmed cure). The modified per protocol (MPP) population is a subset of the per protocol (PP) population. The MPP population more adequately represents the" true" PP population. Thirty-seven (37) subjects treated with 1.5% LVFX and 40 subjects treated with 0.3% OFLX should have been excluded from the PP population for protocol violations (no baseline photos of lesion or lesion size <2mm^2) but were not excluded by sponsor.

1.5% LVFX appears to be equivalent to 0.3% OFLX in clinical efficacy. The clinical cure rate for 1.5% LVFX is 81.8% and 75.9% for 0.3% OFLX in the ITT population, 87.2% for1.5% LVFX and 85.9% for 0.3% OFLX in the PP population, and 82.9% for the 1.5% LVFX and 87.1% for 0.3% OFLX in the MPP population.

Summary of Clinical Cure at Endpoint* by Epithelial Defect Size at Baseline

Epithelial Defect Size at Baseline **Intent-to-Treat (ITT[b])**	Outcome	1.5% LVFX	0.3% OFLX	Lower 95.0% CI	P-value[a]
Mild (>0.0 – 1.0) mm^2	Clinical cure	(50/53) 94.3%	(55/63) 87.3%		
Moderate (>1.0 – 4.0 mm^2)	Clinical cure	(44/50) 88.0%	(38/38) 100.0%		
Severe (>4.0 mm^2)	Clinical cure	(15/18) 83.3%	(9/15) 60.0%		
Total	Clinical cure	(109/121) 90.1%	(102/116) 87.9%	-5.8%	0.53
Epithelial Defect Size at Baseline **Per Protocol (PP[c])**	Outcome				
Mild (>0.0 – 1.0 mm^2	Clinical cure	(35/36) 97.2%	(38/40) 95.0%		
Moderate (>1.0 – 4.0 mm^2)	Clinical cure	(28/30) 93.3%	(23/23) 100.0%		
Severe (>4.0 mm^2)	Clinical cure	(11/12) 91.7%	(7/8) 87.5%		
Total	Clinical cure	(74/78) 94.9%	(68/71) 95.8%	-7.7%	0.88
Epithelial Defect Size at Baseline **Modified Per Protocol (MPP[d])**	Outcome				
Total	Clinical cure	(38/41) 92.7%	(29/31) 93.5%	-12.6%	0.89

[a] Cochran-Mantel-Haenszel (CMH) statistic. p<0.05. [b] ITT=All patients who received treatment. [c] PP=All patients with a clinical and microbial diagnosis of bacterial corneal ulcer without a fungal, viral, or parasitic infection, who received treatment and had post-baseline data. * Defined as complete re-epithelialization of the infected cornea and lack of progression from baseline of the stromal infiltrate as judged by the investigator.

Reviewer's Comments:

Similar to the preferred efficacy analysis, 1.5% LVFX appears to be equivalent 0.3% OFLX in clinical efficacy. The clinical cure rate for 1.5% LVFX is 90.1% and 87.9% for 0.3% OFLX in

the ITT population, 94.9% for 1.5% LVFX and 95.8% for 0.3% OFLX in the PP population, and 92.7% for 1.5% LVFX and 93.5% for 0.3% OFLX in the MPP population.

Microbial Eradication Rates from Baseline to Final by Organism

Organism	1.5% LVFX	0.3% OFLX
GRAM-POSITIVE BACTERIA		
Aerococcus species	100.0% (1/1)	
Bacillus species	100.0% (3/3)	
Corynebacterium jeikeium	100.0% (1/1)	
Corynebacterium propinquum	100.0% (1/1)	100.0% (1/1)
Corynebacterium ulcerans		100.0% (1/1)
Corynebacterium species	100.0% (1/1)	100.0% (2/2)
Enterococcus faecalis	100.0% (1/1)	100.0% (1/1)
Gemella morbillorum	100.0% (1/1)	
Gemella species	100.0% (1/1)	
Rhodococcus equi	100.0% (1/1)	
Staphylococcus aureus	100.0% (8/8)	100.0% (6/6)
Staphylococcus capitis	83.3% (5/6)	100.0% (4/4)
Staphylococcus epidermidis	100.0% (33/33)	100.0% (31/31)
Staphylococcus lugdunensis	100.0% (3/3)	100.0% (2/2)
Staphylococcus saprophyticus	100.0% (1/1)	
Staphylococcus simulans	100.0% (1/1)	
Staphylococcus warneri	100.0% (3/3)	100.0% (7/7)
Stomatococcus mucilaginosus		100.0% (1/1)
Stomatococcus species	100.0% (2/2)	
Streptococcus dysgalactiae		100.0% (1/1)
Streptococcus mitis	100.0% (4/4)	100.0% (5/5)
Streptococcus oralis	100.0% (3/3)	100.0% (3/3)
Streptococcus pneumoniae	100.0% (1/1)	100.0% (2/2)
Streptococcus sanguis	100.0% (2/2)	100.0% (1/1)
Streptococcus (Viridans Group)		100.0% (1/1)
GRAM-NEGATIVE BACTERIA		
Achromobacter xylosoxidans		100.0% (1/1)
Aeromonas hydrophila		100.0% (1/1)
Haemophilus parainfluenzae	100.0% (1/1)	
Klebsiella pneumoniae	100.0% (1/1)	
Moraxella catarrhalis	100.0% (1/1)	
Moraxella osloensis		100.0% (1/1)
Moraxella species	100.0% (1/1)	100.0% (1/1)
Pantoea (Enterobacter) agglomerans		100.0% (1/1)
Pseudomonas aeruginosa	71.4% (5/7)	100.0% (3/3)
Pseudomonas stutzeri	100.0% (1/1)	
Serratia marcescens	100.0% (4/4)	100.0% (5/5)
Stenotrophomonas maltophilia	100.0% (1/1)	
ANAEROBES		
Propionibacterium acnes	100.0% (2/2)	

Numerator is the number of patients who had the organism eradicated, denominator is the number of patients who had the organism at baseline.

Reviewer's Comments:

Microbiological efficacy is demonstrated primarily against Staphylococcus aureus and Staphylococcus epidermidis.

Study #2 **Protocol No. 16-003** **Conducted 10/20/00 to 4/17/02**

Title: A prospective, randomized, parallel-group, multi-center, double-masked trial comparing the efficacy and safety of 1.5% levofloxacin ophthalmic solution with 0.3% ofloxacin ophthalmic solution for treating bacterial keratitis.

Study Design: Same as Protocol No. 16-002 except the study population was 18 years of age and older.

Test Drug Schedule: Same as in Protocol No. 16-002

Investigator Number	Investigator	Number Randomized	
		1.5% LVFX	0.3% OFLX
082		4	4
079		1	2
085		13	14
086		4	4
077		26	26
084		2	1
083		7	6
078		41	44

Reviewer's Comments:

It is preferable to have at least 10 patients per arm per center.

Study Design

The study design is identical to Protocol No. 16-002 except that the study population was at least 18 years of age.

Study Medications

- Test Article – 1.5% LVFX (Formulation Number 1017S, Lot Nos. 00116/1 and 11001), containing 1.5% levofloxacin (15 mg/mL), glycerin, sodium hydroxide and/or hydrochloric acid to adjust pH, and purified water.
- Control Article – 0.3% OFLX (Formulation Number 1016S, Lot Nos. A1107, A3598, and 12165), containing 0.3% ofloxacin (3 mg.mL), 0.005% benzalkonium chloride (BAK), sodium chloride, and purified water.

Subject Disposition and Demographics

One hundred ninety-nine (199) subjects enrolled in the study and 151 subjects completed the study.

Subject Disposition

	Number of Subjects		
	1.5% LVFX N (%)	0.3% OFLX N (%)	Total N (%)
Randomized	98	101	199
Discontinued prematurely	24 (24.5)	24 (23.8)	48 (24.1)
Included in safety evaluations	97 (99.0)	100 (99.0)	197(99.0)
Included in intent-to-treat efficacy analysis	98 (100.0)	101 (100.0)	199 (100.0)
Included in per protocol efficacy analysis	69 (70.4)	62 (61.4)	131 (65.8)
Negative baseline bacterial culture	25 (25.5)	30 (29.7)	55 (27.6)
Viral/Fungal/Parasitic growth	1 (0.010)	0 (0.000)	1 (0.005)

Discontinued Patients and Reasons

Investigator	Patient	Treatment	Reason
077	3003	1.5% LVFX	Treatment failure
	3005	1.5% LVFX	Treatment failure
	3006	1.5% LVFX	Lost to follow-up
	3009	1.5% LVFX	Lost to follow-up
	3016	1.5% LVFX	Treatment failure Adverse event – corneal perforation
	3017	1.5% LVFX	Non-compliance
	3018	1.5% LVFX	Lost to follow-up
	3528	1.5% LVFX	Treatment failure
	3530	1.5% LVFX	Treatment failure
	3541	1.5% LVFX	Lost to follow-up
	3545	1.5% LVFX	Treatment failure
	3002	0.3% OFLX	Treatment failure
	3010	0.3% OFLX	Treatment failure
	3014	0.3% OFLX	Treatment failure Adverse event – corneal perforation
	3015	0.3% OFLX	Treatment failure

Investigator	Patient	Treatment	Reason
	3085	0.3% OFLX	Lost to follow-up
	3089	0.3% OFLX	Other*
	3525	0.3% OFLX	Other*
	3531	0.3% OFLX	Treatment failure
	3540	0.3% OFLX	Treatment failure
078	3046	1.5% LVFX	No follow-up data available
	3047	1.5% LVFX	Lost to follow-up
	3058	1.5% LVFX	Patient decision not associated with adverse event
	3060	1.5% LVFX	Treatment failure
	3068	1.5% LVFX	Treatment failure
	3070	1.5% LVFX	Lost to follow-up
	3553	1.5% LVFX	Patient decision not associated with adverse event
	3564	1.5% LVFX	Lost to follow-up
	3568	1.5% LVFX	Lost to follow-up
	3581	1.5% LVFX	Patient decision not associated with adverse event
	3025	0.3% OFLX	Treatment failure Adverse event – corneal perforation
	3032	0.3% OFLX	Treatment failure
	3042	0.3% OFLX	Treatment failure
	3045	0.3% OFLX	Treatment failure
	3048	0.3% OFLX	Other*
	3052	0.3% OFLX	Treatment failure
	3063	0.3% OFLX	Patient decision not associated with adverse event
	3071	0.3% OFLX	Treatment failure
	3074	0.3% OFLX	Patient decision not associated with adverse event
	3558	0.3% OFLX	Treatment failure Adverse event – corneal perforation
	3576	0.3% OFLX	No follow-up data available
	3582	0.3% OFLX	Patient decision not associated with adverse event
079	3503	1.5% LVFX	Lost to follow-up
082	3514	1.5% LVFX	Lost to follow-up
083	3496	1.5% LVFX	Adverse event – ocular discomfort
	3160	0.3% OFLX	Lost to follow-up
	3494	0.3% OFLX	Lost to follow-up
085	4005	0.3% OFLX	Treatment failure

*Concomitant fungal growth (1), worsening clinical condition (1), and investigator's discretion (1).

Summary of Demographics

	Per Protocol			Intent-to-Treat		
	1.5% LVFX	0.3% OFLX	P-value[1]	1.5% LVFX	0.3% OFLX	P-value[1]
Number of Patients:	69	62		98	101	
AGE (years)			0.5294			0.9542
MEAN(SD)	43.9 (14.4)	45.6 (16.5)		43.7 (14.7)	43.9 (16.3)	
Median	45.0	46.0		45.0	45.0	
MIN-MAX	20-71	18-84		20-79	18-84	
SEX: N (%)			0.2773			0.3002
Female	22 (31.9)	26 (41.9)		31 (31.6)	40 (39.6)	
Male	47 (68.1)	36 (58.1)		67 (68.4)	61 (60.4)	
RACE: N (%)			0.5144			0.7528
Caucasian	12 (17.4)	14 (22.6)		29 (29.6)	27 (26.7)	

Non-Caucasian	57 (82.6)	48 (77.4)		69 (70.4)	74 (73.3)	
Asian Indian	55 (79.7)	44 (71.0)		67 (68.4)	70 (69.3)	
Black	0 (0.0)	1 (1.6)		0 (0.0)	1 (1.0)	
Hispanic	2 (2.9)	3 (4.8)		2 (2.0)	3 (3.0)	

[1]P-value for age based on two-sample t-test. P-values for sex and race (non-Caucasian vs. Caucasian) based on Fisher's exact test.

Efficacy

Summary of Clinical Cure at Endpoint with Confirmation at the Confirmatory Visit* by Epithelial Defect Size at Baseline

Epithelial Defect Size at Baseline **Intent-to-Treat (ITT[b])**	Outcome	1.5% LVFX	0.3% OFLX	Lower 95.0% CI	P-value[a]
Mild (>0.0 – 1.0) mm^2	Clinical cure	(18/19) 94.7%	(16/19) 84.2%		
Moderate (>1.0 – 4.0 mm^2)	Clinical cure	(25/30) 83.3%	(25/29) 86.2%		
Severe (>4.0 mm^2)	Clinical cure	(31/49) 63.3%	(34/51) 66.7%		
Total	Clinical cure	(74/98) 75.5%	(77/101) 76.2%	-12.6%	0.90
Epithelial Defect Size at Baseline **Per Protocol (PP[c])**	Outcome				
Mild (>0.0 – 1.0 mm^2	Clinical cure	(8/8) 100.0%	(8/8) 100.0%		
Moderate (>1.0 – 4.0 mm^2)	Clinical cure	(18/21) 85.7%	(14/14) 100.0%		
Severe (>4.0 mm^2)	Clinical cure	(24/40) 60.0%	(29/40) 72.5%		
Total	Clinical cure	(50/69) 72.5%	(51/62) 82.3%	-24.0%	0.34
Epithelial Defect Size at Baseline **Modified Per Protocol (MPP[d])**	Outcome				
Total	Clinical cure	(41/58) 77.6%	(41/52) 78.8%	-24.3%	0.32

[a] Cochran-Mantel-Haenszel (CMH) statistic. $p<0.05$. [b] ITT=All patients who received treatment. [c] PP=All patients with a clinical and microbial diagnosis of bacterial corneal ulcer without a fungal, viral, or parasitic infection, who received treatment and had post-baseline data. [d] Subset of PP (exclude patients who had no baseline photos of lesion or lesion size was <2mm^2). * Defined as complete re-epithelialization of the infected cornea and lack of progression from baseline of the stromal infiltrate for two consecutive visits.

Reviewer's Comments:

This is the preferred efficacy analysis(confirmed cure). The modified per protocol (MPP) population is a subset of the per protocol (PP) population. The MPP population more adequately represents the" true" PP population. Eleven (11) subjects treated with 1.5% LVFX and 10 subjects treated with 0.3% OFLX should have been excluded from the PP population for protocol violations (no baseline photos were taken of any of the lesions; all lesion size <2mm^2 were excluded) but were not excluded by sponsor.

1.5% LVFX appears to be equivalent to 0.3% OFLX in clinical efficacy. The clinical cure rate for 1.5% LVFX is 75.5% and 76.2% for 0.3% OFLX in the ITT population, 72.5% for 1.5% LVFX and 82.3% for 0.3% OFLX in the PP population, and 77.6% for 1.5% LVFX and 78.8% for 0.3% OFLX in the MPP population.

Summary of Clinical Cure at Endpoint* by Epithelial Defect Size at Baseline

Epithelial Defect Size at Baseline **Intent-to-Treat (ITT[b])**	Outcome	1.5% LVFX	0.3% OFLX	Lower 95.0% CI	P-value[a]
Mild (>0.0 – 1.0) mm^2	Clinical cure	(18/19) 94.7%	(18/19) 94.7%		
Moderate (>1.0 – 4.0 mm^2)	Clinical cure	(27/30) 90.0%	(26/29) 89.7%		
Severe (>4.0 mm^2)	Clinical cure	(37/49) 75.5%	(39/53) 73.6%		
Total	Clinical cure	(82/98) 83.7%	(83/101) 82.2%	-8.9%	0.76
Epithelial Defect Size at Baseline **Per Protocol (PP[c])**	Outcome				
Mild (>0.0 – 1.0 mm^2	Clinical cure	(8/8) 100.0%	(8/8) 100.0%		
Moderate (>1.0 – 4.0 mm^2)	Clinical cure	(19/21) 90.5%	(14/14) 100.0%		
Severe (>4.0 mm^2)	Clinical cure	(28/40) 70.0%	(31/48) 64.6%		
Total	Clinical cure	(55/69) 79.7%	(53/62) 85.5%	-18.7%	0.67
Epithelial Defect Size at Baseline **Modified Per Protocol (MPP[d])**	Outcome				
Total	Clinical cure	(45/58) 77.6%	(43/52) 82.7%	-20.0%	0.50

[a] Cochran-Mantel-Haenszel (CMH) statistic. $p<0.05$. [b] ITT=All patients who received treatment. [c] PP=All patients with a clinical and microbial diagnosis of bacterial corneal ulcer without a fungal, viral, or parasitic infection, who received treatment and had post-baseline data. * Defined as complete re-epithelialization of the infected cornea and lack of progression from baseline of the stromal infiltrate as judged by the investigator.

Reviewer's Comments:

Similar to the preferred efficacy analysis, 1.5% LVFX appears to be equivalent to 0.3% OFLX in clinical efficacy. The clinical cure rate for 1.5% LVFX is 83.7% and 82.2% for 0.3% OFLX in the ITT population, 79.7% for 1.5% LVFX and 85.5% for 0.3% OFLX in the PP population, and 77.6% for 1.5% LVFX and 82.7% for 0.3% OFLX in the MPP population.

Microbial Eradication Rates from Baseline to Final by Organism

Organism	1.5% LVFX	0.3% OFLX
GRAM-POSITIVE BACTERIA		
Corynebacterium macginleyi	100.0% (1/1)	
Corynebacterium species	100.0% (2/2)	80.0% (4/5)
Rhodococcus aureus		100.0% (1/1)
Staphylococcus aureus	100.0% (2/2)	100.0% (3/3)
Staphylococcus capitis	0.0% (0/1)	100.0% (1/1)
Staphylococcus epidermidis	100.0% (2/2)	50.0% (2/4)
Staphylococcus hominis	100.0% (1/1)	
Staphylococcus lugdunensis	100.0% (1/1)	100.0% (1/1)
Staphylococcus, coagulase negative	100.0% (4/4)	100.0% (6/6)
Streptococcus equinus	0.0% (0/1)	
Streptococcus oralis	100.0% (1/1)	
Streptococcus pneumoniae	84.2% (16/19)	83.3% (15/18)
Streptococcus salivarius		100.0% (2/2)
Streptococcus, alpha-hemolytic	100.0% (1/1)	
Streptococcus (Viridans Group)	100.0% (1/1)	100.0% (1/1)
GRAM-NEGATIVE BACTERIA		
Aeromonas hydrophila		50.0% (1/2)
Aeromonas species	100.0% (1/1)	
Brevundimonas vesicularis	100.0% (1/1)	
Burkholderia cepacia		100.0% (1/1)
Citrobacter koseri		100.0% (1/1)
Escherichia coli	100.0% (1/1)	
Moraxella species	100.0% (1/1)	
Pasteurella species	0.0% (0/1)	
Pseudomonas aeruginosa	91.7% (11/12)	10.0% (14/14)
Pseudomonas luteola		100.0% (1/1)
Pseudomonas putida	100.0% (1/1)	
Serratia marcescens	100.0% (2/2)	100.0% (1/1)
Stenotrophomonas maltophilia		100.0% (1/1)
Weeksella virosa	100.0% (2/2)	
ANEROBES		
Propionibacterium acnes	0.0% (0/1)	

Numerator is the number of patients who had the organism eradicated, denominator is the number of patients who had the organism at baseline.

Reviewer's Comments:

Microbiological efficacy is demonstrated primarily against Streptococcus pneumoniae and Pseudomonas aeruginosa.

D. Efficacy Conclusions

The submitted studies in NDA 21-571 are barely sufficient to establish efficacy for the use of 1.5% LVFX in the treatment of bacterial corneal ulcers of susceptible microorganisms. The clinical cure rate for susceptible microorganisms ranges from 76%-82%. This rate is lower than expected and suggests that 1.5% LVFX should be given more frequently than was administered in the clinical study.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The submitted studies in NDA 21-571 demonstrate an acceptable safety profile with the use of 1.5% LVFX for the treatment of bacterial corneal ulcers. The most frequently reported adverse events were headache and dysgeusia (taste perversion).

B. Description of Patient Exposure

The safety database consists of 586 subjects from four clinical trials (Protocols 16-001, 16-002, 16-003, 16-006), 431 subjects with presumed bacterial corneal ulcer and 155 healthy adult volunteers. The number of subjects exposed to 1.5% LVFX was 331, 239 for 0.3% OFLX, and 16 for Vehicle of 1.5% LVFX.

C. Methods and Specific Findings of Safety Review

The safety database consists of safety data from four clinical trials, Protocols 16-001, 16-002, 16-003, and 16-006. The safety data from the four trials were reviewed individually.

Study #1 Protocol No. 16-001 Conducted 10/30/99 to 11/23/99

Title: A 21-day, randomized, double-masked, placebo-controlled, single-center study evaluating the safety, comfort, and pharmacokinetics of 1.5% levofloxacin ophthalmic solution in healthy adult volunteers

Test Drug Schedule:

Day 1	1 dose per eye once in the morning
Days 2-8	1 dose per eye every 2 hours (6AM-12 AM; 10 doses per day)
Days 9-15	1 dose per eye every 4 hours (8AM-12AM; 5 doses per day)
Day 16	1 dose per eye once in the morning

Safety

Adverse Events

Frequency and Incidence of Ocular and Non-ocular Adverse Events Occurring at Rates 1% and Greater

Coded Adverse Event	1.5% LVFX (N=16)	Vehicle (N=16)
	N (%)	N (%)
OCULAR		
Chemosis		1 (6.3)
Hyperemia eye		1 (6.3)
Itching eye		1 (6.3)

IOP decrease		1 (6.3)
Lid pain		1 (6.3)
Pain eye	2 (12.5)	2 (12.5)
Photophobia		1 (6.3)
Vision decrease	1 (6.3)	1 (6.3)
NON-OCULAR		
Body as a Whole		
Cellulitis	1 (6.3)	
Headache	7 (43.8)	1 (6.3)
Infection	1 (6.3)	
Injury accidental		1 (6.3)
Pain abdomen		1 (6.3)
Pain arm		1 (6.3)
Pain back	1 (6.3)	
Pain chest	1 (6.3)	1 (6.3)
Cardiovascular System		
Palpitation		1 (6.3)
Digestive System		
Constipation	1 (6.3)	
Diarrhea	1 (6.3)	
Dyspepsia		1 (6.3)
Nausea	2 (12.5)	1 (6.3)
Vomit	1 (6.3)	1 (6.3)
Musculo-skeletal System		
Joint disease	1 (6.3)	
Nervous System		
Insomnia		1 (6.3)
Respiratory System		
Cough increase		1 (6.3)
Hiccup	2 (12.5)	
Pharyngitis		2 (12.5)
Rhinitis	1 (6.3)	2 (12.5)
Special Senses		
Taste perversion	7 (43.8)	1 (6.3)
Urogenital System		
Leukorrhea		1 (6.3)
Urine abnormal	2 (12.5)	2 (12.5)

Visual Acuity

Change in Visual Acuity from Baseline to Final (Day 21±2) Visit

	Treatment Group	
Line Changes	1.5% LVFX N (%)	Vehicle N (%)
N	12	14
≥ 2 lines loss	0 (0.0)	0 (0.0)
1 line loss, No change, 1 line gain	11 (91.7)	24 (92.3)
≥ 2 lines gain	1 (8.3)	1 (7.1)

Vital Signs

Change from Baseline in Vital Sign Results

Visit		1.5% LVFX	Vehicle	Total
Number of Subjects		14	16	30
Systolic BP (mmHg)	Visit 11 (Day 21±2)			
	N	12	14	26
	Mean (SD)	-3.7 (11.9)	0.3 (8.7)	-1.5 (10.3)
Diastolic BP (mmHg)	Visit 11 (Day 21±2)			
	N	12	14	26
	Mean (SD)	-1.3 (6.0)	0.1 (8.9)	-.5 (7.6)
Heart Rate (bpm)	Visit 11 (Day 21±2)			
	N	12	14	26
	Mean (SD)	4.3 (11.9)	1.3 (13.8)	2.7 (12.8)

Biomicroscopy

Change from Baseline in Biomicroscopy Results
(lids, conjunctiva, cornea, anterior chamber, lens, iris)

Evaluation	Visit	Change	1.5% LVFX N (%)	Vehicle N (%)	Total N (%)
Lids	Baseline to Visit 11 (Day 21±2)	Number of Subjects	12	14	26
		Improved	0 (0.0)	0 (0.0)	0 (0.0)
		No Change	12 (100.0)	14 (100.0)	26 (100.0)
		Worse	0 (0.0)	0 (0.0)	0 (0.0)
Conjunctiva	Baseline to Visit 11 (Day 21±2)	Number of Subjects	12	14	26
		Improved	0 (0.0)	0 (0.0)	0 (0.0)
		No Change	12 (100.0)	14 (100.0)	26 (100.0)
		Worse	0 (0.0)	0 (0.0)	0 (0.0)
Cornea	Baseline to Visit 11 (Day 21±2)	Number of Subjects	12	14	26
		Improved	0 (0.0)	0 (0.0)	0 (0.0)
		No Change	12 (100.0)	14 (100.0)	26 (100.0)
		Worse	0 (0.0)	0 (0.0)	0 (0.0)
Anterior Chamber	Baseline to Visit 11 (Day 21±2)	Number of Subjects	12	14	26
		Improved	0 (0.0)	0 (0.0)	0 (0.0)
		No Change	12 (100.0)	14 (100.0)	26 (100.0)
		Worse	0 (0.0)	0 (0.0)	0 (0.0)
Lens	Baseline to Visit 11 (Day 21±2)	Number of Subjects	12	14	26
		Improved	0 (0.0)	0 (0.0)	0 (0.0)
		No Change	12 (100.0)	14 (100.0)	26 (100.0)
		Worse	0 (0.0)	0 (0.0)	0 (0.0)
Iris	Baseline to Visit 11 (Day 21±2)	Number of Subjects	12	14	26
		Improved	0 (0.0)	0 (0.0)	0 (0.0)
		No Change	12 (100.0)	14 (100.0)	26 (100.0)
		Worse	0 (0.0)	0 (0.0)	0 (0.0)

Worsening from Baseline in Biomicroscopy Results by Subject

Subject Number	Treatment	Evaluation	Change	EYE
1120	Vehicle	Conjunctiva	Normal to Moderate	OD

Intraocular Pressure

Summary of Intraocular Pressure

Visit	1.5% LVFX*	Vehicle	Total
Number of Subjects	14	16	30
Screening			
N	14	16	30
Mean (SD)	17.4 (2.8)	17.8 (1.8)	17.6 (2.3)
Visit 11 (Day 21)			
N	12	14	26
Mean (SD)	15.5 (3.0)	14.7 (2.8)	15.1 (2.9)

* The average of data from both eyes is used.

Ophthalmoscopy

All subjects had normal fundus examination at baseline and upon exit from the study.

Rose Bengal Staining

Change from Screening in Rose Bengal Staining

Change*	1.5% LVFX N (%)	Vehicle N (%)	Total N (%)
Number of subjects	12	14	26
No change	1 (91.7)	10 (71.4)	21 (80.8)
Worse	1 (8.3)	4 (28.6)	5 (19.2)

* The average of data from both eyes is used.

Study #2 Protocol No. 16-002

Safety

Adverse Events

Frequency and Incidence of Ocular and Non-ocular Adverse Events

Coded Adverse Event	**1.5% LVFX (N=120)**	**0.3% OFLX (N=114)**
	N (%)	N (%)
OCULAR		
Abnormal sensation in eye		1 (0.9)

Coded Adverse Event	1.5% LVFX (N=120)	0.3% OFLX (N=114)
Blepharitis		1 (0.9)
Chemosis	1 (0.8)	
Conjunctival hyperemia	1 (0.8)	
Conjunctivitis bacterial NOS	1 (0.8)	
Corneal erosion	1 (0.8)	
Corneal perforation		1 (0.9)
Corneal scar		1 (0.9)
Corneal ulcer	2 (1.7)	
Diplopia	1 (0.8)	
Erythema of eyelid	1 (0.8)	
Eye infection NOS		1 (0.9)
Eye infection staphylococcal	1 (0.8)	
Eye irritation	2 (1.7)	1 (0.9)
Eye pain	1 (0.8)	3 (0.9)
Eyelid edema	1 (0.8)	
Instillation site burning	1 (0.8)	1 (0.9)
Instillation site irritation		1 (0.9)
Instillation site pain	1 (0.8)	1 (0.9)
Vision blurred	1 (0.8)	2 (1.8)
Visual acuity reduced	1 (0.8)	
Vitreous floaters	1 (0.8)	
NON-OCULAR		
Gastrointestinal Disorders		
Dysgeusia	2 (1.7)	
Nausea		2 (1.8)
General Disorders and Administration Site Conditions		
Fatigue		1 (0.9)
Feeling hot	1 (0.8)	
Pyrexia	1 (0.8)	
Infections and Infestations		
Bladder infection NOS		1 (0.9)
Gastroenteritis viral NOS	1 (0.8)	
Influenza		1 (0.9)
Nasopharyngitis	1 (0.8)	1 (0.9)
Streptococcal infection NOS		1 (0.9)
Musculoskeletal and Connective Tissue Disorders		
Facial pain		1 (0.9)
Joint sprain		1 (0.9)
Nervous System Disorders		
Dizziness		1 (0.9)
Headache NOS	12 (10.0)	11 (9.6)
Tension headaches		1 (0.9)
Psychiatric Disorders		
Insomnia		1 (0.9)
Respiratory, Thoracic and Mediastinal Disorders		
Rhinorrhea	1 (0.8)	1 (0.9)
Throat irritation		1 (0.9)

Coded Adverse Event	1.5% LVFX (N=120)	0.3% OFLX (N=114)
Skin and Subcutaneous Tissue Disorders		
Blister	1 (0.8)	
Rash NOS	1 (0.8)	

Visual Acuity

Change in Visual Acuity (logMAR) from Baseline to Confirmatory Visit

	Treatment Group	
Line Changes	1.5% LVFX N (%)	0.3% OFLX N (%)
N	86	78
≥ 2 lines loss	4 (4.7)	6 (7.7)
1 line loss, No change, 1 line gain	52 (60.5)	48 (61.5)
≥ 2 lines gain	30 (34.9)	24 (30.8)

Biomicroscopy

Change from Baseline in Biomicroscopy Results (flare, cells, conjunctival discharge, palpebral injection, bulbar injection, limbus, lens, iris)

Evaluation	Visit	Change	Treatment Group		P-value[1]
			1.5% LVFX N (%)	0.3 OFLX N (%)	
Flare Grading	Final Visit	Number of Subjects	120	113	
		Improved	6 (5.0)	11 (9.7)	
		No Change	114 (95.0)	102 (90.3)	0.2099
		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	105	96	
		Improved	5 (4.8)	11 (11.5)	
		No Change	100 (95.2)	85 (88.5)	0.1162
		Worse	0 (0.0)	0 (0.0)	
Cell Grading	Final Visit	Number of Subjects	120	113	
		Improved	13 (10.8)	11(9.7)	
		No Change	107 (89.2)	102 (90.3)	0.8319
		Worse	0 (0.0)	0(0.0)	
	Confirmatory Visit	Number of Subjects	105	96	
		Improved	11 (10.5)	9 (9.4)	
		No Change	94 (89.5)	87 (90.6)	0.8184
		Worse	0 (0.0)	0 (0.0)	
Conjunctival Discharge	Final Visit	Number of Subjects	119	114	
		Improved	12 (10.1)	9 (7.9)	
		No Change	107 (89.9)	105 (92.1)	0.6500

		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	105	96	
		Improved	12 (11.4)	7 (7.3)	
		No Change	93 (88.6)	89 (92.7)	0.3453
		Worse	0 (0.0)	70 (0.0)	
Palpebral Conjunctival Injection	Final Visit	Number of Subjects	120	114	
		Improved	37 (30.8)	37 (32.5)	
		No Change	82 (68.3)	77 (67.5)	0.9427
		Worse	1 (0.8)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	105	96	
		Improved	37 (35.2)	34 (35.4)	
		No Change	68 (64.8)	62 (64.6)	1.0000
		Worse	0 (0.0)	0 (0.0)	
Bulbar Conjunctival Injection	Final Visit	Number of Subjects	120	114	
		Improved	60 (50.0)	48(42.1)	
		No Change	60 (50.0)	66 (57.9)	0.2401
		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	105	96	
		Improved	60 (57.1)	51 (53.1)	
		No Change	45 (57.1)	45 (46.9)	0.5738
		Worse	0 (0.0)	0 (0.0)	
Limbus	Final Visit	Number of Subjects	119	113	
		Improved	41 (34.5)	41(36.3)	
		No Change	78 (65.5)	72 (63.7)	0.7851
		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	105	96	
		Improved	40 (38.1)	40 (41.7)	
		No Change	65 (61.9)	56 (58.3)	0.6659
		Worse	0 (0.0)	0 (.0)	
Lens	Final Visit	Number of Subjects	118	113	
		Improved	1 (0.8)	0 (0.0)	
		No Change	117 (99.2)	112 (99.1)	0.7401
		Worse	0 (0.0)	1 (0.9)	
	Confirmatory Visit	Number of Subjects	104	96	
		Improved	0 (0.0)	0 (0.0)	
		No Change	104 (100.0)	95 (99.0)	0.4800
		Worse	0 (0.0)	1 (1.0)	
Iris	Final Visit	Number of Subjects	120	112	
		Worse	0 (0.0)	2 (1.8)	0.2320
		Not Worse	120 (100.0)	110 (98.2)	
	Confirmatory Visit	Number of Subjects	105	96	
		Worse	0 (0.0)	1 (1.0)	0.4776
		Not Worse	105 (100.0)	95 (99.0)	

[1]P-value based on Fisher's Exact test.

Ocular Symptoms

Change from Baseline in Ocular Symptoms
(tearing, photophobia, itching, foreign body sensation, discomfort)

Evaluation	Visit	Change	Treatment Group		P-value[1]
			1.5% LVFX N (%)	0.3 OFLX N (%)	
Tearing	Final Visit	Number of Subjects	97	100	
		Improved	52 (53.6)	59 (59.0)	
		No Change	45 (46.4)	40 (40.0)	0.4300
		Worse	0 (0.0)	1 (1.0)	
	Confirmatory Visit	Number of Subjects	106	95	
		Improved	50 (47.2)	45 (47.4)	
		No Change	56 (52.8)	50 (52.6)	1.0000
		Worse	0 (0.0)	0 (0.0)	
Photophobia	Final Visit	Number of Subjects	117	113	
		Improved	65 (55.6)	65(57.5)	
		No Change	52 (44.4)	46 (40.7)	0.4101
		Worse	0 (0.0)	2 (1.8)	
	Confirmatory Visit	Number of Subjects	106	95	
		Improved	67 (63.2)	61 (64.2)	
		No Change	39 (36.8)	34 (35.8)	1.0000
		Worse	0 (0.0)	0 (0.0)	
Itching	Final Visit	Number of Subjects	114	112	
		Improved	14 (12.3)	17 (15.2)	
		No Change	100 (87.7)	93(83.0)	0.3390
		Worse	0 (0.0)	2(1.8)	
	Confirmatory Visit	Number of Subjects	104	95	
		Improved	12 (11.5)	16 (16.8)	
		No Change	92 (88.5)	78 (82.1)	0.2634
		Worse	0 (0.0)	1 (1.1)	
Foreign Body Sensation	Final Visit	Number of Subjects	117	113	
		Improved	53 (45.3)	54 (47.8)	
		No Change	64 (54.7)	59 (52.2)	0.7916
		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	106	95	
		Improved	51 (48.1)	53 (55.8)	
		No Change	55 (51.9)	42 (44.2)	0.3229
		Worse	0 (0.0)	0 (0.0)	
Discomfort	Final Visit	Number of Subjects	117	112	
		Improved	69 (59.0)	63 (56.3)	
		No Change	47 (40.2)	48 (42.9)	0.8437
		Worse	1 (0.9)	1 (0.9)	
	Confirmatory Visit	Number of Subjects	106	95	
		Improved	67 (63.2)	61 (64.2)	
		No Change	39 (36.8)	34 (35.8)	1.0000
		Worse	0 (0.0)	0 (0.0)	

[1]P-value based on Fisher's Exact test.

Ophthalmoscopy

Summary of Ophthalmoscopy Results
(retina, macula, choroid, vitreous, optic nerve)

Evaluation	Visit	Result	Treatment Group	
			1.5% LVFX	0.3% OFLX
Retina	Baseline	Number of Subjects	108	96
		Normal	104 (96.3)	93 (96.9)
		Abnormal	4 (3.7)	3 (3.1)
	Confirmatory Visit	Number of Subjects	82	75
		Normal	80 (97.6)	73 (97.3)
		Abnormal	2 (2.4)	2 (2.7)
Macula	Baseline	Number of Subjects	107	95
		Normal	107 (100.0)	92 (96.8)
		Abnormal	0 (0.0)	3 (3.2)
	Confirmatory Visit	Number of Subjects	82	75
		Normal	82 (100.0)	72 (96.0)
		Abnormal	0 (0.0)	3 (4.0)
Choroid	Baseline	Number of Subjects	108	95
		Normal	107 (99.1)	95 (100.0)
		Abnormal	1 (0.9)	0 (0.0)
	Confirmatory Visit	Number of Subjects	82	75
		Normal	81 (98.8)	75 (100.0)
		Abnormal	1 (1.2)	0 (0.0)
Vitreous	Baseline	Number of Subjects	108	95
		Normal	107 (99.1)	94 (98.9)
		Abnormal	1 (0.9)	1 (1.1)
	Confirmatory Visit	Number of Subjects	82	75
		Normal	81 (98.8)	74 (98.7)
		Abnormal	1 (1.2)	1 (1.3)
Optic Nerve	Baseline	Number of Subjects	108	96
		Normal	102 (94.4)	94 (97.9)
		Abnormal	6 (5.6)	2 (2.1)
	Confirmatory Visit	Number of Subjects	82	75
		Normal	78 (95.1)	74 (98.7)
		Abnormal	4 (4.9)	1 (1.3)

Study #3 Protocol No. 16-003

Safety

Adverse Events

Frequency and Incidence of Ocular and Non-ocular Adverse Events
Occurring at Rates 1% or Greater

Coded Adverse Event	**1.5% LVFX (N=97)**	**0.3% OFLX (N=100)**
	N (%)	N (%)
OCULAR		
Conjunctivitis	1 (1.0)	

Coded Adverse Event	1.5% LVFX (N=97)	0.3% OFLX (N=100)
Corneal perforation	2 (2.1)	3 (3.0)
Instillation site stinging	1 (1.0)	1 (1.0)
Ocular discomfort	1 (1.0)	
Vision blurred	1 (1.0)	
NON-OCULAR		
Gastrointestinal Disorders		
Dysgeusia	2 (2.1)	
General Disorders and Administration/ Site Conditions		
Pyrexia	1 (1.0)	1 (1.0)
Musculoskeletal and Connective Tissue Disorders		
Back pain		1 (1.0)
Nervous System Disorders		
Headache NOS	2 (2.1)	
Somnolence	1 (1.0)	
Skin and Subcutaneous Tissue Disorders		
Rash NOS		1 (1.0)

Visual Acuity

Change in Visual Acuity (logMAR) from Baseline to Confirmatory Visit

	Treatment Group	
Line Changes	1.5% LVFX N (%)	0.3% OFLX N (%)
N	65	67
≥ 2 lines loss	0 (0.0)	0 (0.0)
1 line loss, No change, 1 line gain	33 (50.8)	26 (38.8)
≥ 2 lines gain	32 (49.2)	41 (61.2)

Biomicroscopy

Change from Baseline in Biomicroscopy Results (flare, cells, conjunctival discharge, palpebral injection, bulbar injection, limbus, lens, iris)

Evaluation	Visit	Change	Treatment Group		P-value[1]
			1.5% LVFX N (%)	0.3 OFLX N (%)	
Flare Grading	Final Visit	Number of Subjects	94	94	
		Improved	39(41.5)	44 (46.8)	
		No Change	55 (58.5)	50 (53.2)	0.5570
		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	74	75	
		Improved	37 (50.0)	43 (57.3)	

		No Change	37(50.0)	32 (42.7)	0.4133
		Worse	0 (0.0)	0 (0.0)	
Cell Grading	Final Visit	Number of Subjects	96	97	
		Improved	41 (42.7)	42 (43.3)	
		No Change	55 (57.3)	55 (56.7)	1.0000
		Worse	0 (0.0)	0(0.0)	
	Confirmatory Visit	Number of Subjects	75	76	
		Improved	38 (50.7)	41 (53.9)	
		No Change	37 (49.3)	35 (46.1)	0.7455
		Worse	0 (0.0)	0 (0.0)	
Conjunctival Discharge	Final Visit	Number of Subjects	97	99	
		Improved	26 (26.8)	24 (24.2)	
		No Change	71 (73.2)	75 (75.8)	0.7441
		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	75	77	
		Improved	18 (24.0)	21 (27.3)	
		No Change	57 (76.0)	56 (72.7)	0.7119
		Worse	0 (0.0)	0 (0.0)	
Palpebral Conjunctival Injection	Final Visit	Number of Subjects	97	99	
		Improved	30 (30.9)	26 (26.3)	
		No Change	67 (69.1)	73 (73.7)	0.5282
		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	75	77	
		Improved	36 (48.0)	28 (36.4)	
		No Change	39 (52.0)	49 (63.6)	0.1887
		Worse	0 (0.0)	0 (0.0)	
Bulbar Conjunctival Injection	Final Visit	Number of Subjects	97	99	
		Improved	31 (32.0)	25(25.3)	
		No Change	66 (68.0)	74 (74.7)	0.3439
		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	75	77	
		Improved	35 (46.7)	28 (36.4)	
		No Change	40 (53.3)	49 (63.6)	0.2492
		Worse	0 (0.0)	0 (0.0)	
Limbus	Final Visit	Number of Subjects	97	99	
		Improved	29 (29.9)	25(25.3)	
		No Change	68 (70.1)	73 (73.7)	0.5237
		Worse	0 (0.0)	1 (1.0)	
	Confirmatory Visit	Number of Subjects	75	77	
		Improved	29 (38.7)	31 (40.3)	
		No Change	46 (61.3)	46 (59.7)	0.8694
		Worse	0 (0.0)	0 (.0)	
Lens	Final Visit	Number of Subjects	86	89	
		Improved	0 (0.0)	1 (1.1)	
		No Change	86 (100.0)	88 (98.9)	1.0000

		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	69	70	
		Improved	0 (0.0)	0 (0.0)	
		No Change	69 (100.0)	70 (100.0)	NA
		Worse	0 (0.0)	0 (0.0)	
Iris	Final Visit	Number of Subjects	93	95	
		Worse	1 (1.1)	1 (1.1)	1.0000
		Not Worse	92 (98.9)	94(98.9)	
	Confirmatory Visit	Number of Subjects	74	75	
		Worse	0 (0.0)	0 (0.0)	NA
		Not Worse	74 (100.0)	75 (100.0)	

[1]P-value based on Fisher's Exact test.

Ocular Symptoms

Change from Baseline in Ocular Symptoms
(tearing, photophobia, itching, foreign body sensation, discomfort)

Evaluation	Visit	Change	Treatment Group		P-value[1]
			1.5% LVFX N (%)	0.3 OFLX N (%)	
Tearing	Final Visit	Number of Subjects	97	100	
		Improved	52 (53.6)	59 (59.0)	
		No Change	45 (46.4)	40 (40.0)	0.4300
		Worse	0 (0.0)	1 (1.0)	
	Confirmatory Visit	Number of Subjects	74	77	
		Improved	42 (43.2)	56 (72.7)	
		No Change	32 (56.8)	21 (27.3)	0.0429
		Worse	0 (0.0)	0 (0.0)	
Photophobia	Final Visit	Number of Subjects	97	100	
		Improved	65 (67.0)	61(61.0)	
		No Change	32 (33.0)	39 (39.0)	0.4582
		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	74	77	
		Improved	55 (74.3)	56 (72.7)	
		No Change	19 (25.7)	21 (27.3)	0.8554
		Worse	0 (0.0)	0 (0.0)	
Itching	Final Visit	Number of Subjects	97	100	
		Improved	20 (20.6)	13 (13.0)	
		No Change	77 (79.4)	87 (87.0)	0.1830
		Worse	0 (0.0)	0(0.0)	
	Confirmatory Visit	Number of Subjects	74	77	
		Improved	11 (14.9)	10 (13.0)	
		No Change	63 (85.1)	67 (87.0)	0.8162
		Worse	0 (0.0)	0 (0.0)	
Foreign Body Sensation	Final Visit	Number of Subjects	97	100	

		Improved	38 (39.2)	33 (33.0)	
		No Change	59 (60.8)	66 (66.0)	0.4582
		Worse	0 (0.0)	1 (1.0)	
	Confirmatory Visit	Number of Subjects	74	77	
		Improved	33 (44.6)	29 (37.7)	
		No Change	41 (55.4)	48 (62.3)	0.4119
		Worse	0 (0.0)	0 (0.0)	
Discomfort	Final Visit	Number of Subjects	97	100	
		Improved	70 (72.2)	66 (66.0)	
		No Change	27 (27.8)	34 (34.0)	0.3601
		Worse	0 (0.0)	0 (0.0)	
	Confirmatory Visit	Number of Subjects	74	77	
		Improved	55 (74.3)	61 (79.2)	
		No Change	19 (25.7)	16 (20.8)	0.5638
		Worse	0 (0.0)	0 (0.0)	

[1]P-value based on Fisher's Exact test.

Ophthalmoscopy

Summary of Ophthalmoscopy Results
(retina, macula, choroid, vitreous, optic nerve)

			Treatment Group	
Evaluation	Visit	Result	1.5% LVFX	0.3% OFLX
Retina	Baseline	Number of Subjects	42	47
		Normal	39 (92.9)	45 (95.7)
		Abnormal	3 (7.1)	2 (4.3)
	Confirmatory Visit	Number of Subjects	55	62
		Normal	52 (94.5)	59 (95.2)
		Abnormal	3 (5.5)	3 (4.8)
Macula	Baseline	Number of Subjects	42	46
		Normal	40 (95.2)	44 (95.7)
		Abnormal	2 (4.8)	2 (4.3)
	Confirmatory Visit	Number of Subjects	54	62
		Normal	52 (96.3)	60 (96.8)
		Abnormal	2 (3.7)	2 (4.3)
Choroid	Baseline	Number of Subjects	42	46
		Normal	41 (97.6)	45 (97.8)
		Abnormal	1 (2.4)	1 (2.2)
	Confirmatory Visit	Number of Subjects	54	61
		Normal	53 (98.1)	61 (100.0)
		Abnormal	1 (1.9)	0 (0.0)
Vitreous	Baseline	Number of Subjects	42	47
		Normal	42 (100.0)	46 (97.9)
		Abnormal	0 (0.0)	1 (2.1)
	Confirmatory Visit	Number of Subjects	54	61
		Normal	54 (100.0)	61 (100.0)
		Abnormal	0 (0.0)	0 (0.0)
Optic Nerve	Baseline	Number of Subjects	42	45
		Normal	41 (97.6)	44 (97.8)
		Abnormal	1 (2.4)	1 (2.2)
	Confirmatory Visit	Number of Subjects	55	63
		Normal	54 (98.2)	62 (98.4)
		Abnormal	1 (1.8)	1 (1.6)

Study #4 **Protocol No. 16-006** **Conducted 04/20/02 to 05/13/02**

Title: A randomized, double-masked, single-center trial evaluating safety and mean drug concentration in tears following topical administration of 1.5% levofloxacin ophthalmic solution or 0.3% ofloxacin ophthalmic solution in healthy adult volunteers with asymptomatic eyes

Study Design: A 16-day randomized, double-masked, active-controlled, single-center safety and pharmacokinetic study in healthy adult volunteers

Test Drug Schedule:

Day 0	1 dose (two drops) per eye
Days 1-3	2 drops in each eye every 2 hours while awake and at approximately four and six hours after retiring
Days 4-14	2 drops in each eye four times daily (approximately every 4 hours) while awake

Safety

Adverse Events

Frequency and Incidence of Ocular and Non-ocular Adverse Events
Occurring at Rates 1% and Greater

Coded Adverse Event	1.5% LVFX (N=100)	0.3% OFLX (N=25)
	N (%)	N (%)
OCULAR		
Asthenopia	1 (1.0)	2 (8.0)
Dry eye NOS	1 (1.0)	
Eyelid margin crusting		1 (4.0)
NON-OCULAR		1 (4.0)
Gastrointestinal Disorders		
Abdominal pain upper		1 (4.0)
Diarrhoea NOS	2 (2.0)	
Dysgeusia	14 (14.0)	1 (4.0)
Dyspepsia	3 (3.0)	
Loose stools	1 (1.0)	
Nausea	3 (3.0)	1 (4.0)
Oral mucosal blistering	1 (1.0)	
Throat irritation	3 (3.0)	
Vomiting NOS	1 (1.0)	
General Disorders and Administration Site Conditions		
Fatigue	1 (1.0)	
Pyrexia	1 (1.0)	
Musculoskeletal and Connective Tissue Disorders		

Coded Adverse Event	1.5% LVFX (N=100)	0.3% OFLX (N=25)
Muscle twitching	1 (1.0)	
Nervous System Disorders		
Headache NOS	11 (11.0)	3 (12.0)
Respiratory, Thoracic and Mediastinal Disorders		
Lower respiratory tract infection NOS	1 (1.0)	
Nasal congestion	2 (2.0)	
Skin and Subcutaneous Tissue Disorders		
Dermatitis contact	1 (1.0)	
Pruritus NOS		1 (4.0)

Visual Acuity

Change in Visual Acuity (logMAR) from Baseline to Final (Day 15) Visit

	Treatment Group	
Line Changes	1.5% LVFX N (%)	0.3% OFLX N (%)
N	100	25
≥ 2 lines loss	4 (4.0)	1 (4.0)
1 line loss, No change, 1 line gain	94 (94.0)	23 (92.0)
≥ 2 lines gain	2 (2.0)	1 (4.0)

Ocular Symptoms

One subject (1.0%) in the 1.5% LVFX treatment group experienced a clinically significant worsening (increased of at least two units) of burning/stinging from baseline to endpoint (Day 15).

Summary of Ocular Symptoms Results

			Treatment			
			1.5% LVFX N (%)		0.3% OFLX N (%)	
Evaluation	Visit	Change	OD	OS	OD	OS
Burning/Stinging	Baseline	Normal	99 (99.0)	99 (99.0)	25 (100.0)	25 (100.0)
		Mild	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
	Day 15	Normal	84 (84.0)	84 (84.0)	21 (84.0)	21 (84.0)
		Mild	14 (14.0)	14 (14.0)	4 (16.0)	4 (16.0)
		Moderate	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Tearing	Baseline	Absent	100 (10.0)	100 (100.0)	2 (100.0)	25 (100.0)
	Day 15	Absent	95 (95.0)	94 (94.0)	23 (92.0)	23 (92.0)
		Mild	4 (4.0)	5 (5.0)	2 (8.0)	2 (8.0)
Photophobia	Baseline	Absent	100 (100.0)	100 (100.0)	25 (100.0)	25 (100.0)
	Day 15	Absent	97 (97.0)	97 (97.0)	25 (100.0)	25 (100.0)
		Mild	2 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)
Itching	Baseline	Absent	100 (100.0)	100 (100.0)	24 (96.0)	24 (96.0)
		Mild	0 (0.0)	0 (0.0)	1 (4.0)	1 (4.0)

	Day 15	Absent	86 (86.0)	85 (85.0)	24 (96.0)	24 (96.0)
		Mild	13 (13.0)	14 (14.0)	1 (4.0)	1 (4.0)
Foreign Body Sensation	Baseline	Absent	99 (99.0)	99 (99.0)	25 (100.0)	25 (100.0)
		Mild	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
	Day 15	Absent	95 (95.0)	95 (95.0)	23 (92.0)	23 (92.0)
		Mild	4 (4.0)	4 (4.0)	2 (8.0)	2 (8.0)
Discomfort	Baseline	Absent	100 (100.0)	100 (100.0)	25 (100.0)	25 (100.0)
	Day 15	Absent	98 (98.0)	98 (98.0)	24 (96.0)	24 (96.0)
		Mild	1 (1.0)	1 (1.0)	1 (4.0)	1 (4.0)

Biomicroscopy

Summary of Biomicroscopy Results

			Treatment			
			1.5% LVFX N (%)		0.3% OFLX N (%)	
Evaluation	Visit	Change	OD	OS	OD	OS
Lids	Baseline	Normal	99 (99.0)	99 (99.0)	25 (100.0)	25 (100.0)
		Mild	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
	Day 15	Normal	98 (98.0)	98 (98.0)	25 (100.0)	25 (100.0)
		Mild	2 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)
Conjunctiva	Baseline	Normal	97 (97.0)	95 (95.0)	24 (96.0)	24 (96.0)
		Mild	3 (3.0)	5 (5.0)	1 (4.0)	1 (4.0)
	Day 15	Normal	96 (96.0)	93 (93.0)	25 (100.0)	25 (100.0)
		Mild	3 (3.0)	6 (6.0)	0 (0.0)	0 (0.0)
Cornea	Baseline	Normal	100 (100.0)	100 (100.0)	25 (100.0)	25 (100.0)
	Day 15	Normal	99 (99.0)	99 (99.0)	25 (100.0)	25 (100.0)
Anterior Chamber	Baseline	Normal	100 (100.0)	100 (100.0)	25 (100.0)	25 (100.0)
	Day 15	Normal	99 (99.0)	99 (99.0)	25 (100.0)	25 (100.0)
Lens	Baseline	Normal	95 (95.0)	97 (97.0)	24 (96.0)	25 (100.0)
		Mild	5 (5.0)	3 (3.0)	1 (4.0)	0 (0.0)
	Day 15	Normal	93 (93.0)	95 (95.0)	24 (96.0)	25 (100.0)
		Mild	6 (6.0)	4 (4.0)	1 (4.0)	0 (0.0)
Iris	Baseline	Normal	100 (100.0)	100 (100.0)	25 (100.0)	25 (100.0)
	Day 15	Normal	99 (99.0)	99 (99.0)	25 (100.0)	25 (100.0)

Ophthalmoscopy

All subjects had normal fundus examination at baseline and upon exit from the study.

Rose Bengal Staining

Summary of Rose Bengal Staining Results

		Treatment			
		1.5% LVFX N (%)		0.3% OFLX N (%)	
Visit	Change	OD	OS	OD	OS
Screening	Normal	100 (100.0)	100 (100.0)	25 (100.0)	25 (100.0)
Day15	Normal	99 (99.0)	99 (99.0)	25 (100.0	25 (100.0)

D. Adequacy of Safety Testing

The safety database from the four submitted clinical studies in NDA 21-571 is adequate.

E. Summary of Critical Safety Findings and Limitations of Data

1.5% LVFX is considered safe when used as labeled.

VIII. Dosing, Regimen, and Administration Issues

The proposed dosing regimen is supported by the clinical efficacy studies; however since the cure rate is low, the dosing range in the studies should be considered a minimum.

IX. Use in Special Populations

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

Sponsor's analyses on the effects of gender are adequate. No significant differences have been observed.

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

Sponsor's analyses on the effects of age, and ethnicity on safety and efficacy are adequate. No significant differences have been observed.

C. Evaluation of Pediatric Program

Applicant submitted a request dated January 10, 2003 for a full waiver of pediatric studies. At the time of the request, the Pediatric Final Rule was not in effect. Since the Pediatric Rule now has been re-instituted, a waiver down to the age of 6 years is appropriate. For children between the ages of 6 and 15 years, it is the Agency's view that safety and efficacy data could be reliably extrapolated from the existing clinical database.

D. Comments on Data Available or Needed in Other Populations

No additional data in other special populations are needed.

X. Conclusions and Recommendations

A. Conclusions

The submitted studies in NDA 21-571 are sufficient to establish efficacy for the use of 1.5% LVFX in [redacted]

B. Recommendations

NDA 21-571 is recommended for approval for [redacted] with the labeling revisions included in this review.

XI. Appendix

A. Other Relevant Materials

Summary of Frequency and Incidence of Ocular and Non-ocular Adverse Events
(Protocol Nos. 16-001, 16-002, 16-003, 16-006)

Coded Adverse Event	1.5% LVFX (N=333)	0.3% OFLX (N=239)	Vehicle (N=16)
	N (%)	N (%)	N (%)
OCULAR			
Abnormal sensation in eye		1 (0.4)	
Asthenopia	1 (0.3)	2 (0.8)	
Blepharitis		1 (0.4)	
Chemosis	1 (0.3)		1 (6.3)
Conjunctival hyperemia	1 (0.3)		1 (6.3)
Conjunctivitis bacterial NOS	2 (0.6)		
Corneal erosion	1 (0.3)		
Corneal perforation	2 (0.6)	4 (1.7)	
Corneal scar		1 (0.4)	
Corneal ulcer	2 (0.6)		
Diplopia	1 (0.3)		
Dry eye NOS	1 (0.3)		
Erythema of eyelid	1 (0.3)		
Eye infection NOS		1 (0.4)	
Eye infection staphylococcal	1 (0.3)		
Eye irritation	2 (0.6)	1 (0.4)	
Eye pain	3 (0.9)	3 (1.3)	2 (12.5)
Eyelid edema	1 (0.3)		
Eyelid margin crusting		1 (0.4)	
Eyelid pain			1 (6.3)
Instillation site burning	1 (0.3)	1 (0.4)	
Instillation site irritation		1 (0.4)	
Instillation site pain	1 (0.3)	1 (0.4)	
Instillation site stinging	1 (0.3)	1 (0.4)	
IOP decrease			1 (6.3)
Itching eye			1 (6.3)
Ocular discomfort	1 (0.3)		
Photophobia			1 (6.3)
Vision blurred	2 (0.6)	2 (0.8)	
Visual acuity reduced	2 (0.6)		1 (6.3)
Vitreous floaters	1 (0.3)		
NON-OCULAR			
Body as a Whole			
Injury accidental			1 (6.3)

Coded Adverse Event	1.5% LVFX (N=333)	0.3% OFLX (N=239)	Vehicle (N=16)
Cardiovascular Disorders			
Pain chest	1 (0.3)		1 (6.3)
Palpitation			1 (6.3)
Gastointestinal Disorders			
Abdominal pain		1 (0.4)	
Constipation	1 (0.3)		
Diarrhea	3 (0.9)		
Dyspepsia	3 (0.9)		1 (6.3)
Loose stools	1 (0.3)		
Nausea	5 (1.5)	2 (0.8)	1 (6.3)
Oral mucosal blistering	1 (0.3)	1 (0.4)	
Vomit	2 (0.6)		1 (6.3)
General Disorders and Administration Site Conditions			
Fatigue	1 (0.3)	1 (0.4)	
Feeling hot	1 (0.3)		
Pyrexia	3 (0.9)	1 (0.4)	
Infections and Infestations			
Bladder infection NOS		1 (0.4)	
Gastroenteritis viral NOS	1 (0.3)		
Infection	1 (0.3)		
Influenza		1 (0.4)	
Nasopharyngitis	1 (0.3)	1 (0.4)	2 (12.5)
Streptococcal infection NOS			
Musculoskeletal and Connective Tissue Disorders			
Arm pain			1 (6.3)
Back Pain	1 (0.3)	1 (0.4)	
Facial pain		1 (0.4)	
Joint disease	1 (0.3)		
Joint sprain		1 (0.4)	
Muscle twitching	1 (0.3)		
Nervous System Disorders			
Dizziness		1 (0.4)	
Headache NOS	32 (9.6)	14 (5.9)	
Somnolence	1 (0.3)		
Tension headaches		1 (0.4)	
Psychiatric Disorders			
Insomnia		1 (0.4)	1 (6.3)
Respiratory, Thoracic and Mediastinal Disorders			
Cough increase			1 (6.3)
Hiccup	2 (0.6)		
Lower respiratory tract infection	1 (0.3)		
Nasal congestion	2 (0.6)		
Rhinitis	1 (0.3		2 (12.5)
Rhinorrhea	1 (0.3)	1 (0.4)	
Throat irritation	3 (0.9)	1 (0.4)	
Skin and Subcutaneous Tissue Disorders			

Coded Adverse Event	1.5% LVFX (N=333)	0.3% OFLX (N=239)	Vehicle (N=16)
Blister	1 (0.3)		
Cellulitis	1 (0.3)		
Dermititis contact	1 (0.3)		
Pruritus NOS		1 (0.4)	
Rash NOS	1 (0.3)	1 (0.4)	
Special Senses			
Dysgeusia (taste perversion)	25 (7.5)	1 (0.4)	1 (6.3)
Urogenital Disorders			
Leukorrhea			1 (6.3)
Urine abnormal	2 (0.6)		2 (12.5)

Summary of Microbial Eradication Rates by Final Organism
Protocol Nos. 16-002 and 16-003

Organism	1.5% LVFX	0.3% OFLX
GRAM-POSITIVE BACTERIA		
Aerococcus species	100.0% (1/1)	
Bacillus species	100.0% (3/3)	
Corynebacterium jeikeium	100.0% (1/1)	
Corynebacterium macginleyi	100.0% (1/1)	
Corynebacterium propinquum	100.0% (1/1)	100.0% (1/1)
Corynebacterium ulcerans		100.0% (1/1)
Corynebacterium species	100.0% (3/3)	83.3% (5/6)
Enterococcus faecalis	100.0% (1/1)	100.0% (1/1)
Gemella morbillorum	100.0% (1/1)	
Gemella species	100.0% (1/1)	
Rhodococcus aureus		100.0% (1/1)
Rhodococcus equi	100.0% (1/1)	
Staphylococcus aureus	100.0% (10/10)	100.0% (9/9)
Staphylococcus capitis	71.4% (5/7)	100.0% (5/5)
Staphylococcus epidermidis	100.0% (35/35)	94.3% (33/35)
Staphylococcus hominis	100.0% (1/1)	
Staphylococcus lugdunensis	100.0% (4/4)	100.0% (3/3)
Staphylococcus saprophyticus	100.0% (1/1)	
Staphylococcus simulans	100.0% (1/1)	
Staphylococcus warneri	100.0% (3/3)	100.0% (7/7)
Staphylococcus, coagulase negative	100.0% (4/4)	100.0% (6/6)
Stomatococcus mucilaginosus		100.0% (1/1)
Stomatococcus species	100.0% (2/2)	
Streptococcus dysgalactiae		100.0% (1/1)
Streptococcus equines	0.0% (0/1)	
Streptococcus mitis	100.0% (4/4)	100.0% (5/5)
Streptococcus oralis	100.0% (4/4)	100.0% (3/3)
Streptococcus pneumoniae	85.0% (17/20)	85.0% (17/20)
Streptococcus sanguis	100.0% (2/2)	100.0% (1/1)
Streptococcus salivarius		100.0% (2/2)
Streptococcus, alpha-hemolytic	100.0% (1/1)	
Streptococcus (Viridans Group)	100.0% (1/1)	100.0% (2/2)

GRAM-NEGATIVE BACTERIA		
Achromobacter xylosoxidans		100.0% (1/1)
Aeromonas hydrophila		66.7% (2/3)
Aeromonas species	100.0% (1/1)	
Brevundimonas vesicularis	100.0% (1/1)	
Burkholderia cepacia		100.0% (1/1)
Citrobacter koseri		100.0% (1/1)
Escherichia coli	100.0% (1/1)	
Haemophilus parainfluenzae	100.0% (1/1)	
Klebsiella pneumoniae	100.0% (1/1)	
Moraxella catarrhalis	100.0% (1/1)	
Moraxella osloensis		100.0% (1/1)
Moraxella species	100.0% (2/2)	100.0% (1/1)
Pantoea (Enterobacter) agglomerans		100.0% (1/1)
Pasteurella species	0.0% (0/1)	
Pseudomonas aeruginosa	84.2% (16/19)	100.0% (17/17)
Pseudomonas luteola		100.0% (1/1)
Pseudomonas putida	100.0% (1/1)	
Pseudomonas stutzeri	100.0% (1/1)	
Serratia marcescens	100.0% (6/6)	100.0% (6/6)
Stenotrophomonas maltophilia	100.0% (1/1)	100.0% (1/1)
Weeksella virosa	100.0% (2/2)	
ANEROBES		
Propionibacterium acnes	66.7% (2/3)	

Numerator is the number of patients who had the organism eradicated, denominator is the number of patients who had the organism at baseline.

Reviewer's Comments:

Microbiological efficacy is demonstrated primarily against Staphylococccus aureus, Staphylococcus capitis, Staphylococcus epidermidis, Streptococcus pneumoniae, Pseudomonas aeruginosa, and Serratia marcescens.

B. Individual More Detailed Study Reviews (If performed)

None.

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