

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206307Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	December 9, 2014
<b>From</b>	William M. Boyd, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	206307
<b>Applicant</b>	Alcon Research, Ltd.
<b>Date of Submission</b>	April 25, 2014
<b>PDUFA Goal Date</b>	December 25, 2014
<b>Type of Application</b>	505(b)(1)
<b>Name</b>	XTORO (finafloxacin otic suspension) 0.3%
<b>Dosage forms / Strength</b>	Topical otic suspension
<b>Proposed Indication(s)</b>	Indicated for the treatment of acute otitis externa (AOE) caused by susceptible strains of <i>Pseudomonas aeruginosa</i> and <i>Staphylococcus aureus</i>
<b>Recommended:</b>	Recommended for Approval

### 1. Introduction

Finafloxacin is a new chemical entity, quinolone antimicrobial with activity against bacteria. Similar to other quinolones, finafloxacin's mechanism of action is inhibition of DNA gyrase and topoisomerase IV. Finafloxacin otic suspension is formulated for topical otic administration. It is a white to off-white, aqueous suspension that is a sterile, preserved, multidose product.

There are many topical otic drug products approved for the treatment of acute otitis externa. These treatments include topical otic anti-bacterials and topical otic anti-bacterial/corticosteroid combination products. There are approved quinolone antimicrobial otic drug products available containing ciprofloxacin, ciprofloxacin and hydrocortisone and ofloxacin.

### 2. Background

Finafloxacin otic suspension has been studied under IND 110576 which was opened in September 2011 with the submission of a protocol for Phase 1. On November 3, 2011, an End-of-Phase 1 meeting was held with the Agency in order to obtain agreement on the overall development plan. The Agency suggested any otowick use should be standardized. Additional guidance regarding the plan to pursue pediatric exclusivity was given.

In December 2011, a Special Protocol Assessment was submitted for the Phase 3 studies (C-10-018 and C-10-019). A Special Protocol Agreement Letter was issued in January 2012. The agreement included the following points:

- Treatment arms stratified for otowick use;
- Preplanned analyses to evaluate the interaction between otowick and cure;
- Evaluation of the *in vitro* activity of finafloxacin against clinical isolates associated with infections of the external auditory canal.

In April 2012, Alcon submitted a proposed pediatric study request (PPSR) for the treatment of acute otitis externa and a proposed partial pediatric waiver for patients younger than (b) (4) of age. A Pediatric Written Request was issued for finafloxacin in the treatment of acute otitis externa on February 22, 2013. Reports for the proposed study were to be submitted to the Agency by June 30, 2016. On September 27, 2013, a Pre-NDA meeting was held to obtain agreement on the details of the NDA submission.

### 3. CMC

From the Product Quality Review finalized 9/17/14:

Finafloxacin otic suspension, 0.3% is intended for treating otic bacterial infections in patients with Acute Otitis Externa. The recommendation dosage is four drops into the effected ear twice daily for 7 days.

Finafloxacin otic suspension, 0.3% will be packaged in 4 mL (sample size) and 8 mL (trade size) white low density polyethylene (LDPE) bottles, with (b) (4) white (b) (4) closures. The bottle's label instruction recommends to "store at 2°C to 25°C" and is assigned an expiration date of 104 weeks for 5 mL fill trade size and 78 weeks for 0.5 mL sample size.

#### DRUG SUBSTANCE

(*S, S*) – Finafloxacin, also known as AL-60371, is a new molecular entity that belongs to the quinolone family of antimicrobials. The molecule contains two chiral centers. The (*S, S*)- finafloxacin shows more than hundred fold greater antibacterial activity under neutral and acidic pH than its enantiomer, (*R, R*)-finafloxacin, against fluoroquinolone-susceptible pathogens. The name finafloxacin or AL-60371 in this review always refers to (*S, S*)-finafloxacin. Finafloxacin exists as a white to yellow powder or crystals. The drug substance is shown to exist in (b) (4) (b) (4) is present in the commercial batches of the drug substance. It is non-hygroscopic and has a melting point of about 300°C

Finafloxacin contains (b) (4) the drug substance that is used for the manufacturing of the drug product. AL-60371 has somewhat low solubility in water but comparatively improved solubility in buffers while the solubility in organic solvents varies considerably. The chiral purity of finafloxacin was assessed to be (b) (4) % using chiral HPLC method.

The drug substance is manufactured and tested by:

(b) (4)

**DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:**

**Table 3.2.P.1-1 Composition of Finafloxacin Otic Suspension (FID 119420)**

Component	Concentration % w/v	Function	Compendial Status
Finafloxacin (AL-60371)	0.3 <sup>a</sup>	Active	NOC <sup>b</sup>
Tyloxapol	(b) (4)	(b) (4)	USP
Hydroxyethyl Cellulose (b) (4)	(b) (4)	(b) (4)	NF
Sodium Chloride	(b) (4)	(b) (4)	USP
Magnesium Chloride (b) (4)	(b) (4)	(b) (4)	USP
Benzalkonium Chloride	(b) (4)	Preservative	NF
Sodium Hydroxide And / or Hydrochloric Acid	(b) (4)	Adjust pH	NF
Purified Water	(b) (4)	(b) (4)	USP

Note: FID = Formulation Identification Number

<sup>a</sup> Adjust for purity

<sup>b</sup> NOC = non-compendial

<sup>c</sup> Added as a (b) (4) % solution, based on assay.

The intended commercial packaging configuration is Alcon's (b) (4) package system which contains a white low density polyethylene (LDPE) bottle, (b) (4) and a white (b) (4) closure. A trade size of 5 mL filled in an 8 mL bottle and a sample size of 0.5 mL filled in an 4 mL bottle are proposed. In addition, a foil laminate pouch is used with the sample size to (b) (4)

(b) (4) The bottle (b) (4) sterilized by (b) (4) and the closure is sterilized (b) (4). The (b) (4) used for the construction of the bottle, (b) (4) and closure have been approved for use with other multiple ophthalmic and otic products and have been subjected to USP testing. Each filled unit will be placed inside a carton.

**PROPOSED REGULATORY SPECIFICATIONS:**

**Table 3.2.P.5.1-1 Regulatory Acceptance Specifications for Finaxofloxacin Otic Suspension**

<b>Test</b>	<b>Specification</b>
Finaxofloxacin (AL-60371) ID (HPLC) <sup>a</sup>	Positive
Finaxofloxacin (AL-60371) ID (TLC) <sup>a</sup>	Positive
Finaxofloxacin (AL-60371) Assay (HPLC)	90 - 110% of Label
Finaxofloxacin (AL-60371) Impurities (HPLC): <sup>b</sup> <div style="background-color: #cccccc; width: 100px; height: 15px; margin-bottom: 5px;"></div> Any Single Unspecified Impurity Total Impurities	NMT <sup>(b) (4)</sup> % of active NMT <sup>(b) (4)</sup> % of active NMT <sup>(b) (4)</sup> % of active NMT <sup>(b) (4)</sup> % of active
Benzalkonium Chloride ID (HPLC) <sup>a</sup>	Positive
Benzalkonium Chloride Assay (HPLC)	80 - 120% of Label
Appearance, Suspension: Color (Visual)	White to Off-White
Osmolality (Freezing Point Depression)	260 - 330 mOsm/kg
pH (pH Meter)	5.7 - 6.3
Viscosity (Brookfield Viscometer) CP42 LVT, 30 rpm	2 - 8 cps
Redispersibility (Visual or HPLC)	NMT <sup>(b) (4)</sup>
Dissolution	TBD*
Particle Size by <sup>(b) (4)</sup> : <div style="background-color: #cccccc; width: 100px; height: 15px; margin-bottom: 5px;"></div> <sup>(b) (4)</sup>	NLT <sup>(b) (4)</sup> <div style="background-color: #cccccc; width: 100px; height: 15px; margin-bottom: 5px;"></div> <sup>(b) (4)</sup> NMT <sup>(b) (4)</sup>
Sterility	Pass USP

<sup>a</sup> Release test only.  
<sup>b</sup> Report any single impurity <sup>(b) (4)</sup> % of label.  
 \* Alcon is in the process of developing method.

**FACILITIES INSPECTIONS:**

An overall facilities recommendation of “Acceptable” has been made by the Office of Compliance (8/8/2014).

CDTL Review  
 William M. Boyd, M.D.  
 NDA 206307  
 XTORO (finaxloxacn otic suspension) 0.3%

**EES Summary Report: overall acceptable.**

**FDA CDER EES  
 ESTABLISHMENT EVALUATION REQUEST  
 SUMMARY REPORT**

Application:	NDA 206307/000	Sponsor:	ALCON RES LTD
Org. Code:	590		6201 SOUTH FREEWAY
Priority:	1		FORT WORTH, TX 761342089
Stamp Date:	25-APR-2014	Brand Name:	FINAFLOXACIN (AL-60371)
PDUFA Date:	25-DEC-2014	Estab. Name:	
Action Goal:		Generic Name:	FINAFLOXACIN (AL-60371)
District Goal:	25-AUG-2014	Product Number; Dosage Form; Ingredient; Strengths	001; SUSPENSION, FINAFLOXACIN; 0.3%

FDA Contacts:	M. CHELLIAH	Prod Qual Reviewer		3017961724
	V. PAWAR	Micro Reviewer	(HFD-805)	3017961587
	N. BHANDARI	Product Quality PM		2404023815
	M. PUGLISI	Regulatory Project Mgr	(HFD-520)	3017960791

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Overall Recommendation:	ACCEPTABLE	on 08-AUG-2014	by R. XU	( )	3017966187
	PENDING	on 12-MAY-2014	by EES_PROD		

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Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 DRUG SUBSTANCE RELEASE TESTER  
 DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-JUN-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT**

<b>Establishment:</b>	<b>CFN:</b> 1610287 <b>FEI:</b> 1610287 ALCON RESEARCH, LTD.	
<b>DMF No:</b>	FORT WORTH, , UNITED STATES 761342099	<b>AADA:</b>
<b>Responsibilities:</b>	DRUG SUBSTANCE RELEASE TESTER DRUG SUBSTANCE STABILITY TESTER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER	
<b>Profile:</b>	SUSPENSIONS AND EMULSIONS (NON PARENTERALS)	<b>OAI Status:</b> NONE
<b>Last Milestone:</b>	OC RECOMMENDATION	
<b>Milestone Date:</b>	08-AUG-2014	
<b>Decision:</b>	ACCEPTABLE	
<b>Reason:</b>	DISTRICT RECOMMENDATION	

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#### **4. Nonclinical Pharmacology/Toxicology**

From the original Pharmacology/Toxicology Review finalized 9/25/14:

From a Nonclinical Pharmacology/Toxicology perspective, approval of NDA 206307 is recommended; no safety-related approvability issues were identified.

The safety of the AOE indication is supported by two 14-day toxicology studies in New Zealand rabbits, both conducted in compliance with good laboratory practices (GLP). Following twice-daily topical otic dosing (4 drops/dose, ~30 µL drop size):

1. The first study detected minimal-to-mild local toxicity with fluroxacin hydroxide in phosphate buffer at pH 7.5. The high-dose (1.0% fluroxacin, ~ 2.18 mg/animal/day) was the no observed adverse effect level (NOAEL) for systemic toxicity. This study included clinical pathology (hematology, clinical chemistry, coagulation), and necropsy (organ weights, gross pathology and histopathology) for the ears (pinna and bulla), adrenals, brain, heart, kidney, liver, lungs, ovary, spleen and testes.

2. The second study tested flufenoxacin (free base). The NOAEL was the highest dose tested, 1.2% (~ 2.78 mg/animal/day). Clinical pathology was assessed, but necropsy was limited to the ears (external ear canal, tympanic membrane, bulla, middle ear ossicles, and Eustachian tube).

Patient dose	Rabbit doses	Exposure margin
0.3%, 4 drops twice daily for seven days	1.0%, 4 drops twice daily for 14 days (tolerable local effects, systemic NOAEL)	3.3-fold
	1.2% (NOAEL for local toxicity)	4-fold

Four studies were conducted to assess the toxicity of direct instillation of flufenoxacin suspension into the middle ear. Local toxicity, consistent with minimal-to-mild irritation, was detected.

In support of other indications, oral and intravenous (iv) safety pharmacology, pharmacokinetic, and general toxicity studies in rodents and dogs have been conducted.

Flufenoxacin was demonstrated to be mutagenic and clastogenic.

Nonclinical carcinogenicity studies were not conducted, and are not warranted for this indication (topical otic dosing for 7 days, systemic exposure following topical otic dosing is minimal). The results of the oral nonclinical fertility and embryofetal studies are not relevant to topical otic dosing, because these studies tested a range of doses with estimated systemic exposures more than one thousand-fold higher than the highest systemic exposure detected in patients following topical otic dosing.

Topical otic route or lower systemic dose studies to further investigate fertility and developmental toxicity are not warranted to support the AOE indication. The rat general toxicity studies identified the male reproductive system as a sensitive target of flufenoxacin. Consistent with this finding, the rat oral fertility study observed complete male infertility at 500 mg/kg/day. Three oral embryofetal studies were conducted; flufenoxacin was clearly teratogenic.

## 5. Clinical Pharmacology/Biopharmaceutics

From the original Biopharmaceutics Review finalized 9/25/14:

Based on 21 CFR § 320.22 (b)(1) and CFR § 320.22 (c), Biopharmaceutics is of the opinion that for good cause, the requirement for the submission of evidence of in vivo bioavailability or bioequivalence can be waived, because the proposed drug product is an otic intended only for local therapeutic effect. Therefore, the biowaiver request is granted.

The Applicant did not provide any dissolution data in their submission. However, the Applicant agreed to develop a dissolution testing method as a Post-Marketing Commitment (Seq. 0012 dated 09/19/2014).

From the Approval letter for this application:

We remind you of your postmarketing commitments:

2828-1            Submit the dissolution method development report with the complete data.

The timetable you submitted on September 19, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission:    05/2015

2828-2            Submit a proposal for the dissolution acceptance criterion and the complete supportive data. The selection of the proposed acceptance criterion should be based on the dissolution profile data (i.e., 10, 15, 20, 30, 45, and 60 minutes; N=12) from a minimum of 12 commercial batches and the stability data for registration batches.

The timetable you submitted on September 19, 2014, states that you will conduct this study according to the following schedule:

Proposal Submission:        08/2015  
Final Report Submission:    11/2015

From the original Clinical Pharmacology Review finalized 8/19/14:

To support the NDA, the applicant submitted two Phase 3 clinical studies (C-10-018 & C-10-019) assessing the safety and efficacy of Flaxifloxacin Otic Suspension, 0.3%. Two Phase 1 pharmacokinetics studies (C-10-007 & C-10-022) were also conducted:

- C-10-007: randomized, multidose, fixed sequence PK study (otic and oral) in healthy subjects.
- C-10-022: open-label, single-dose PK study in AOE patients.

Systemic exposure to flaxifloxacin was evaluated following single ototopical dose (4 drops per ear without otowick; 4 or 8 drops per ear with otowick) in AOE patients and multiple ototopical doses (4 drops per ear; BID for 7 days) in healthy subjects. Quantifiable (LLOQ of 0.05 ng/mL) flaxifloxacin concentrations of up to 0.0812 ng/mL were observed in plasma samples from only 2 of 14 healthy subjects at a total of 3 time points. Similarly, quantifiable flaxifloxacin concentrations of up to 0.234 ng/mL were observed in plasma samples from only 2 of 36 AOE patients. No PK parameters could be determined. Because of the limited systemic exposure following ototopical doses of Flaxifloxacin Otic Suspension, 0.3%, clinically significant drug-drug interactions are not expected.

## 6. Sterility Assurance

From the original Product Quality Microbiology Review finalized 9/17/14:

After Finafloxacin [redacted] (b) (4)

The applicant has met regulatory expectations for validating the process used to demonstrate container closure integrity of the subject container and the Antimicrobial Preservative Effectiveness of topical Finafloxacin Otic Suspension. It is to be noted, active ingredient is also an anti-microbial agent.

Regarding Sterilization/Depyrogenation of containers, closures, equipment and Components:

- The closures are sterilized by [redacted] (b) (4)
- The bottles [redacted] (b) (4) are sterilized [redacted] (b) (4). This contract sterilization facility and processes have been previously approved in numerous Alcon applications the most recent being NDA [redacted] (b) (4)

## 7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 10/2/14:

Study Identifier / Study Type	Study Objective	Study Design	Treatment Group	Dosing Regimen/ Duration	Endpoints
Study C-10-018 Phase 3	Evaluate the efficacy and safety of AL-60371 otic suspension 0.3% in the treatment of patients with AOE	Multicenter, double-masked, randomized, vehicle-controlled, parallel group study.  Enrolling patients 6 months of age or older with a clinical diagnosis of AOE of less than 4 weeks duration.	AL-60371 otic suspension 0.3% (N=347)  Vehicle (N=346)	4 drops, BID for 7 days	<i>1° Efficacy Endpoint:</i> Clinical cure at Day 11 (TOC)  <i>2° Efficacy Endpoint:</i> Microbiological success at Day 11 (TOC); Time to cessation of ear pain as reported by patient diary
Study C-10-019 Phase 3	Evaluate the efficacy and safety of AL-60371 otic suspension 0.3% in the treatment of patients with AOE	Multicenter, double-masked, randomized, vehicle-controlled, parallel group study.  Enrolling patients 6 months of age or older with a clinical diagnosis of AOE of less than 4 weeks duration.	AL-60371 otic suspension 0.3% (N=274)  Vehicle (N=275)	4 drops, BID for 7 days	<i>1° Efficacy Endpoint:</i> Clinical cure at Day 11 (TOC)  <i>2° Efficacy Endpoint:</i> Microbiological success at Day 11 (TOC); Time to cessation of ear pain as reported by patient diary

## Analyses of Endpoints

### Primary Efficacy Variable for Study C-10-18

The primary efficacy endpoint in this study was the proportion of patients who achieved clinical cure at the Test-of-Cure (Day 11) visit. A clinical cure was attained if the sum of the numerical scores for the signs and symptoms of AOE (tenderness, erythema, and edema) was 0 at Day 11.

The primary efficacy analysis population was the **pathogen positive subset** of the ITT population which was defined as all patients who received study medication and had cultures positive for *Pseudomonas aeruginosa* and/or *Staphylococcus aureus* at baseline in the study ear.

**Table 6.1.4-1**  
**Primary Efficacy - Clinical Cures at Day 11 (TOC)**  
**ITT Population – Pathogen Positive Subset**

	Finafloxacin	Vehicle	Delta	95% CI <sup>a</sup>	p value <sup>b</sup>
<b>Pathogen Positive Subset - PMITT</b>					
<b>Day 11 n/N (%)</b>	<b>104/145 (71.7%)</b>	<b>46/138 (33.3%)</b>	<b>38.4</b>	<b>(27.6, 49.1)</b>	<b>&lt;0.0001</b>

a 95% confidence interval based on a non-stratified analysis; b Test = stratified CMH

The study met its primary efficacy endpoint. Finafloxacin was superior to vehicle in the proportion of patients who achieved clinical cure in the pathogen positive subset of the ITT population at Day 11 (TOC visit). The treatment group difference was statistically significant.

Microbiological success required that all pretherapy bacteria were absent from the exit otic specimen obtained at Day 11.

**Table 6.1.5-1**  
**Secondary Efficacy – Microbiological Success at Day 11 (TOC)**  
**ITT Population – Pathogen Positive Subset**

	Finafloxacin	Vehicle	Delta	95% CI <sup>a</sup>	p value <sup>b, c</sup>
<b>Pathogen Positive Subset - PMITT</b>					
<b>Day 11 n/N (%)</b>	<b>97/145 (66.9%)</b>	<b>18/138 (13.0%)</b>	<b>53.9</b>	<b>(44.4, 63.4)</b>	<b>&lt;0.0001</b>

a 95% confidence interval based on a non-stratified analysis;  
 b adjusted p-value based on Hommel's method of multiplicity correction;  
 c unadjusted p-value based on a stratified CMH.

The proportion of patients who achieved microbiological success in the pathogen positive subset of the ITT population at Day 11 (TOC visit) was greater in the finafloxacin group compared to the vehicle group. This difference was statistically significant as well.

Cessation of ear pain was considered to have occurred at the first time point for which ear pain was absent (morning or evening) and did not subsequently return. Day 1 was used as the starting point for this time to event analysis.

**Table 6.1.5-3**  
**Secondary Efficacy – Time to Cessation of Ear Pain**  
**ITT Population – Pathogen Positive Subset**

	Finafloxacin N=138	Vehicle N=128	p value <sup>b</sup>
Median (SE)	4.0 (0.2)	7.0 (0.4)	<0.0001
Mean	4.8	7.3	
Min, Max	(1.5, 13.0)	(1.5, 13.5)	

a 95% confidence interval based on a non-stratified analysis; b Test = stratified CMH

The time to cessation of ear pain was shorter by 2.5 days in the Finafloxacin group compared to the Vehicle group in the Pathogen Positive subset of the ITT population. This treatment group difference was statistically significant.

### Primary Efficacy Variable for Study C-10-19

The primary efficacy endpoint in this study was the proportion of patients who achieved clinical cure at the Test-of-Cure (Day 11) visit. A clinical cure was attained if the sum of the numerical scores for the signs and symptoms of AOE (tenderness, erythema, and edema) was 0 at Day 11.

The primary efficacy analysis population was the **pathogen positive subset** of the ITT population which was defined as all patients who received study medication and had cultures positive for *Pseudomonas aeruginosa* and/or *Staphylococcus aureus* at baseline in the study ear.

**Table 6.2.4-1**  
**Primary Efficacy - Clinical Cures at Day 11 (TOC)**  
**ITT Population – Pathogen Positive Subset**

	Finafloxacin	Vehicle	Delta	95% CI <sup>a</sup>	p value <sup>b</sup>
<b>Pathogen Positive Subset – PMITT</b>					
<b>Day 11 n/N (%)</b>	<b>101/147 (68.7%)</b>	<b>52/130 (40.0%)</b>	<b>28.7</b>	<b>(17.4, 40.0)</b>	<b>&lt;0.0001</b>

a 95% confidence interval based on a non-stratified analysis; b Test = stratified CMH

The study met its primary efficacy endpoint. Finafloxacin was superior to vehicle in the proportion of patients who achieved clinical cure in the pathogen positive ITT population at Day 11 (TOC visit). The treatment group difference was statistically significant.

Microbiological success required that all pretherapy bacteria were absent from the exit otic specimen obtained at Day 11.

**Table 6.2.5-1**  
**Secondary Efficacy – Microbiological Success at Day 11 (TOC)**  
**ITT Population – Pathogen Positive Subset**

	Finafloxacin	Vehicle	Delta	95% CI <sup>a</sup>	p value <sup>b, c</sup>
<b>Pathogen Positive Subset – PMITT</b>					
<b>Day 11 n/N (%)</b>	97/147 (66.0%)	15/130 (11.5%)	54.4	(45.0, 63.9)	<0.0001

- a 95% confidence interval based on a non-stratified analysis;
- b Adjusted p-value based on Hommel’s method of multiplicity correction;
- c Unadjusted p-value based on a stratified CMH.

The proportion of patients who achieved microbiological success in the Pathogen Positive subset of the ITT population at Day 11 (TOC visit) was greater in the Finafloxacin group compared to the Vehicle group. This difference was statistically significant.

Cessation of ear pain was considered to have occurred at the first time point for which ear pain was absent (morning or evening) and did not subsequently return. Day 1 was used as the starting point for this time to event analysis.

**Table 6.2.5-3**  
**Secondary Efficacy – Time to Cessation of Ear Pain**  
**ITT Population – Pathogen Positive Subset**

	Finafloxacin N=138	Vehicle N=128	p value <sup>a</sup>
<b>Median (SE)</b>	3.0 (0.2)	6.5 (0.3)	<0.0001
<b>Mean</b>	4.0	7.0	
<b>Min, Max</b>	(1.0, 13.0)	(1.5, 12.5)	

- a Adjusted, Cox proportional hazard model for treatment comparison.

The time to cessation of ear pain was shorter by 3 days in the Finafloxacin group compared to the Vehicle group pathogen positive subset of the ITT population. This treatment group difference was statistically significant.

### Additional Efficacy Issues/Analyses

The following table includes information on the proportion of patients who achieved clinical cure for selected bacterial microorganisms that were cultured at baseline. Only bacterial microorganisms observed at baseline in at least 5 study ears when combining the studies and treatments are included.

Patients who had more than one microorganism in the study ear at baseline are included in the row for each microorganism and were counted more than once within the table. Some patients had more than one isolate recovered for a specific microorganism. In these cases, the patient is only counted one time for that microorganism.

**Table 6.2.10-1**  
**Clinical Cures at Day 11 (TOC) by Baseline Microorganism in the Study Ear**  
**ITT Population – Culture Positive Subset**  
**Studies C-10-018 and C-10-019 Pooled**

Organism	Finafloxacin N=550		Vehicle N=543	
	Total N	Clinical Cures n (%)	Total N	Clinical Cures n (%)
<i>Bacillus cereus</i>	6	3 (50.0%)	3	2 (66.7%)
<i>Corynebacterium amycolatum</i>	12	6 (50.0%)	10	6 (60.0%)
<i>Corynebacterium auris</i>	16	13 (81.3%)	8	3 (37.5%)
<i>Enterococcus casseliflavus</i>	5	4 (80.0%)	0	---
<i>Enterococcus faecalis</i>	28	15 (53.6%)	20	10 (50.0%)
<i>Micrococcus</i> species	7	6 (85.7%)	2	0 (0.0%)
<b><i>Staphylococcus aureus</i><sup>a</sup></b>	<b>82</b>	<b>56 (98.3%)</b>	<b>71</b>	<b>29 (40.8%)</b>
<i>Staphylococcus auricularis</i>	101	78 (77.2%)	92	63 (68.5%)
<i>Staphylococcus capitis</i>	60	43 (71.7%)	83	45 (54.2%)
<i>Staphylococcus caprae</i>	27	25 (92.6%)	36	22 (61.1%)
<i>Staphylococcus epidermidis</i>	157	108 (68.8%)	155	75 (48.4%)
<i>Staphylococcus haemolyticus</i>	13	8 (61.5%)	10	5 (50.0%)
<i>Staphylococcus hominis</i>	8	6 (75.0%)	14	8 (57.1%)
<i>Staphylococcus lugdunensis</i>	7	4 (57.1%)	10	3 (30.0%)
<i>Staphylococcus pasteurii</i>	5	5 (100.0%)	3	2 (66.7%)

Organism	Finafloxacin N=550		Vehicle N=543	
	Total N	Clinical Cures n (%)	Total N	Clinical Cures n (%)
<i>Staphylococcus simulans</i>	5	3 (60.0%)	6	3 (50.0%)
<i>Staphylococcus warneri</i>	21	16 (76.2%)	9	7 (77.8%)
<i>Streptococcus agalactiae</i>	6	2 (33.3%)	3	2 (66.7%)
<i>Streptococcus mitis</i>	9	8 (88.9%)	12	4 (33.3%)
<i>Streptococcus species</i>	8	7 (87.5%)	7	5 (71.4%)
<i>Turicella otitidis</i>	119	86 (72.3%)	131	77 (58.8%)
<i>Achromobacter xylosoxidans</i>	5	4 (80.0%)	4	1 (25.0%)
<i>Escherichia coli</i>	9	6 (66.7%)	8	2 (25.0%)
<i>Klebsiella pneumonia</i>	7	4 (57.1%)	11	2 (18.2%)
<i>Proteus mirabilis</i>	11	8 (72.7%)	7	4 (57.1%)
<b><i>Pseudomonas aeruginosa</i><sup>a</sup></b>	<b>230</b>	<b>163 (70.9%)</b>	<b>219</b>	<b>76 (34.7%)</b>
<i>Stenotrophomonas maltophilia</i>	16	12 (75.0%)	4	2 (50.0%)

Sample sizes presented in the headers represent the number of evaluable subjects for this analysis set.

Subjects with multiple pathogens at baseline are included in the row for each pathogen.

N= number of patients with that organism present above threshold in the study eye at baseline

a The applicant considers *Staphylococcus aureus* and *Pseudomonas aeruginosa* the etiological agents of AOE.

In order to determine the relevance of the clinical cures of microorganisms cultured at baseline other than *Staphylococcus aureus* and *Pseudomonas aeruginosa*, a modified culture positive subset of the ITT analysis set was defined. This ITT subset includes patients who were culture positive at baseline but not for *Staphylococcus aureus* or *Pseudomonas aeruginosa*.

Bacterial microorganisms from patients who had one or both of the primary pathogens isolated at baseline from the study ear were excluded from the following table.

Bacterial microorganisms observed at baseline in at least 5 - 9 study ears for which finafloxacin achieved  $\geq 80\%$  clinical cure rate are included. Bacterial microorganisms observed in at least 10 study ears for which finafloxacin achieved a higher clinical cure rate are also included.

**Table 6.2.10-2  
 Clinical Cures at Day 11 (TOC) by Baseline Microorganism in the Study Ear  
 ITT Population – Modified Culture Positive Subset  
 Studies C-10-018 and C-10-019 Pooled**

Organism	Finafloxacin N=550		Vehicle N=543	
	Total N	Clinical Cures n (%)	Total N	Clinical Cures n (%)
<i>Corynebacterium auris</i>	9	8 (88.9%)	4	2 (50.0%)
<i>Staphylococcus capitis</i>	45	33 (73.3%)	63	36 (57.1%)
<i>Staphylococcus caprae</i>	16	14 (87.5%)	21	15 (71.4%)
<i>Staphylococcus epidermidis</i>	91	66 (72.5%)	92	51 (55.4%)
<i>Staphylococcus warneri</i>	13	10 (76.9%)	8	6 (75.0%)
<i>Turicella otitidis</i>	67	47 (70.1%)	80	53 (66.3%)

Sample sizes presented in the headers represent the number of evaluable subjects for this analysis set.  
 Patients with multiple microorganisms at baseline are included in the row for each microorganism.  
 N= number of patients with that organism present above threshold in the study eye at baseline

Finafloxacin achieved clinical cure for the above organisms which produced acute otitis externa in the absence of the *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

With the exception of *Turicella otitidis*, the clinical cure rates for the above microorganisms (e.g., 72.5 – 88.9%) are greater than the clinical cure rate for the pathogen positive subset of the ITT population (e.g., 68.7 71.7%).

### Clinical Microbiology

From the Clinical Microbiology Review finalized 9/26/14:

In the combined AOE studies (C-10-018 and C-10-019), there were a total of 2746 pretherapy isolates recovered from the affected ear(s) of randomized patients, 71.05% (1951) of the pre-therapy isolates were gram-positive, 26.7% (732) were gram-negative and 2.3% (63) were yeast or fungi. Of the 2379 pre-therapy isolates, 560 were considered to be the etiological AOE pathogens of which 405 (72.3%) were *Pseudomonas aeruginosa* and 155 (27.7%) were *Staphylococcus aureus* isolates. Table 39 shows the clinical cure and microbiological response rates by pathogen, however, it is important to note that all of the organisms were mixed culture with either a *P. aeruginosa* or *S. aureus* isolate.

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Table 39: Clinical Outcomes and Microbiological Outcomes by baseline pathogen (PP-MITT population)

	Clinical Cure at Test-of-Cure Visit (TOC)				Microbiological Outcome at Test of Cure Visit			
	Finaxofacin		Vehicle		Finaxofacin		Vehicle Control	
	N	(%)	N	(%)	N	(%)	N	(%)
<b>Gram-Positive</b>								
<i>Bacillus cereus</i>	6	(50.0)	3	(66.7)	6	(100)	3	(100)
<i>Bacillus species</i>	4	(75.0)	1	(0)	3	(100)	2	(100)
<i>Bacillus flexus</i>	--	--	--	--	--	--	--	--
<i>Bacillus megaterium</i>	--	--	--	--	--	--	--	--
<i>Bacillus pumilus</i>	--	--	--	--	--	--	--	--
<i>Bacillus subtilis</i>	--	--	--	--	1	(100)	0	(0)
<i>Brevibacterium schreibleri</i>	--	--	--	--	--	--	--	--
<i>Corynebacterium amycolatum</i>	12	(50.0)	10	(60)	9	(77.8)	8	(62.5)
<i>Corynebacterium auris</i>	16	(81.3)	8	(37.5)	12	(83.3)	5	(60.0)
<i>Corynebacterium jeikeium</i>	--	--	--	--	2	(100.0)	--	--
<i>Corynebacterium propinquum</i>	--	--	--	--	1	(100.0)	2	(100.0)
<i>Corynebacterium pseudodiphtheriticum</i>	--	--	--	--	1	(100.0)	1	(100.0)
<i>Corynebacterium species</i>	40	(75.0)	46	(45.7)	30	(96.8)	37	(81.0)
<i>Enterococcus casseliflavus</i>	5	(80.0)	--	--	2	(100.0)	--	--
<i>Enterococcus faecalis</i>	28	(53.6)	20	(50)	17	(94.1)	15	(66.7)
<i>Enterococcus gallinarum</i>	--	--	--	--	2	(100.0)	--	--
<i>Clemella morbillorum</i>	--	--	--	--	1	(100.0)	--	--
<i>Kocuria rhizophila</i>	--	--	--	--	1	(100.0)	1	(100.0)
<i>Kocuria varians</i>	--	--	--	--	1	(100.0)	--	--
<i>Micrococcus luteus</i>	2	(100.0)	5	(60)	1	(100.0)	3	(100.0)
<i>Micrococcus species</i>	7	(85.7)	2	(0)	3	(100.0)	1	(100.0)
<i>Staphylococcus aureus</i>	82	(68.3)	71	(40.8)	72	(87.8)	44	(60.3)
<i>Staphylococcus auricularis</i>	101	(77.2)	92	(68.5)	48	(90.5)	41	(65.9)
<i>Staphylococcus capitis</i>	60	(71.7)	83	(54.2)	25	(92)	17	(62.2)
<i>Staphylococcus caprae</i>	27	(92.6)	36	(61.1)	11	(81.8)	27	(55.6)
<i>Staphylococcus cohnii</i>	3	(66.7)	3	(33.3)	3	(100.0)	2	(80.0)
<i>Staphylococcus epidermidis</i>	157	(68.8)	155	(48.4)	89	(85.4)	99	(74.7)
<i>Staphylococcus haemolyticus</i>	13	(61.5)	10	(50)	8	(100.0)	7	(85.7)
<i>Staphylococcus hominis</i>	8	(75.0)	14	(57.1)	5	(100.0)	10	(100.0)
<i>Staphylococcus lugdunensis</i>	7	(57.1)	10	(30)	4	(75.0)	8	(100.0)
<i>Staphylococcus pasteuri</i>	5	(100.0)	3	(66.7)	3	(100.0)	1	(100.0)
<i>Staphylococcus simulans</i>	5	(60.0)	6	(50)	6	(100.0)	6	(66.7)
<i>Staphylococcus species</i>	22	(68.2)	20	(35)	10	(100.0)	15	(86.7)
<i>Staphylococcus warneri</i>	21	(76.2)	9	(77.8)	16	(100.0)	7	(100.0)
<i>Streptococcus Group C</i>	3	(66.7)	2	(50)	2	(100.0)	2	(80.0)
<i>Streptococcus agalactiae</i>	6	(33.3)	3	(66.7)	5	(100.0)	3	(66.7)
<i>Streptococcus mitis</i>	9	(88.9)	12	(55.6)	7	(100.0)	11	(100.0)
<i>Streptococcus sanguinis</i>	4	(50.0)	8	(37.5)	3	(100.0)	4	(100.0)
<i>Streptococcus species</i>	8	(87.5)	7	(16.1)	7	(100.0)	5	(100.0)
<i>Streptococcus viridans group</i>	--	--	--	--	2	(100.0)	--	--
<b>Gram-Negative</b>								
<i>Turicella otitidis</i>	119	(72.3)	131	(13.5)	77	(72.7)	92	(60.9)
<i>Achromobacter zylooxidans</i>	5	(80.0)	4	(55)	5	(100.0)	4	(100.0)
<i>Acinetobacter genospecies 3</i>	--	--	--	--	2	(100.0)	1	(0.0)
<i>Acinetobacter baumannii</i>	4	(100.0)	1	(100)	4	(100.0)	1	(100.0)
<i>Aeromonas sobria</i>	--	--	--	--	1	(100.0)	--	--
<i>Aeromonas veronii</i>	--	--	--	--	--	--	--	--
<i>Alcaligenes faecalis</i>	--	--	--	--	--	--	--	--
<i>Citrobacter freundii</i>	2	(50.0)	4	(0)	2	(100.0)	2	(100.0)
<i>Citrobacter koseri</i>	--	--	--	--	1	(100.0)	3	(33.3)
<i>Enterobacter aerogenes</i>	4	(50.0)	2	(0)	4	(100.0)	2	(100.0)
<i>Enterobacter cloacae</i>	4	(100.0)	7	(57.1)	4	(100.0)	4	(75.0)
<i>Enterobacter hormaechei</i>	--	--	--	--	2	(100.0)	--	--
<i>Enterobacter sakazakii</i>	--	--	--	--	1	(100.0)	--	--
<i>Enterobacter species</i>	7	(71.4)	10	(21.4)	5	(100.0)	8	(75.0)
<i>Escherichia coli</i>	9	(66.7)	8	(41.7)	5	(100.0)	8	(75.0)
<i>Haemophilus influenzae</i>	--	--	--	--	1	(100.0)	--	--
<i>Klebsiella oxytoca</i>	1	(100.0)	4	(75)	1	(100.0)	4	(75.0)
<i>Klebsiella pneumoniae</i>	7	(57.1)	11	(39)	6	(100.0)	8	(75.0)
<i>Moraxella catarrhalis</i>	--	--	--	--	1	(100.0)	--	--
<i>Proteus mirabilis</i>	11	(72.7)	7	(15.6)	10	(100.0)	6	(66.7)
<i>Pseudomonas aeruginosa</i>	230	(70.9)	219	(36.2)	210	(90.5)	195	(60.0)
<i>Pseudomonas alcaligenes</i>	--	--	--	--	1	(100.0)	--	--
<i>Pseudomonas otitidis</i>	4	(100.0)	5	(100)	2	(100.0)	4	(75.0)
<i>Pseudomonas stutzeri</i>	--	--	--	--	1	(100.0)	--	--
<i>Serratia marcescens</i>	4	(75.0)	5	(35)	4	(100.0)	5	(100.0)
<i>Stenotrophomonas maltophilia</i>	16	(75.0)	4	(25)	13	(92.3)	4	(100.0)

N = number of subjects that had the specific organism; %Clinical Cure = percent cured with given baseline pathogen; % Microbiological outcome = percent eradicated or presumed eradication with given baseline pathogen. Shaded cells organisms (b) (4) where no information was provided in datasets or by applicant in submission documents SDN-013 and SDN-015

Source: Clinical Cure (Applicant's Data provided in SDN-013)  
 Microbiological Outcome (C-10-018 and C-10-019 datasets)

The microbiological response by aetiological pathogen present at baseline and by patient response across the treatment groups is shown in Table 40.

- Against *Staphylococcus aureus*, microbiological eradication was achieved 72 patients (87.8%) in the finafloxacin otic 0.3% suspension treatment group and 44 patients (60.3%) in the vehicle treatment group. The eradication rate varied based on fluoroquinolone sensitivity in finafloxacin otic suspension 0.3% treated subjects; 61 patients (91.0%) that had a fluoroquinolone sensitive *S. aureus* isolate eradicated their isolate whereas 11 patients (73.3%) that had a fluoroquinolone resistant *S. aureus* isolate achieved eradication.
- Against *Pseudomonas aeruginosa*, microbiological eradication was achieved in 190 patients (90.5%) in the finafloxacin otic 0.3% suspension treatment group and 117 patients (60.0%) in the vehicle treated group. In the finafloxacin otic suspension 0.3% treated group, 173 patients (90.6%) that had a fluoroquinolone sensitive *P. aeruginosa* isolate and 17 patients (89.5%) that had a fluoroquinolone-resistant *P. aeruginosa* isolate eradicated their isolate at Day 11(TOC).

Table 40: Microbiological Response for combined AOE Studies C-10-018 and C-10-019 by baseline pathogen and by patient response (PP-ITT population)

Baseline Pathogen	Finafloxacin Otic suspension 0.3%		Vehicle Control	
	Eradicated <sup>1</sup> N (%) <sup>3</sup>	Not Eradicated <sup>2</sup> N (%)	Eradicated <sup>1</sup> N (%)	Not Eradicated <sup>2</sup> N (%)
<i>Staphylococcus aureus</i>	72 (87.8)	10 (12.2)	44 (60.3)	29 (39.7)
Fluoroquinolone sensitive <sup>4</sup>	61 (91.0)	6 (9.0)	39 (60.9)	25 (39.1)
Fluoroquinolone resistant	11 (73.3)	4 (26.7)	5 (55.6)	4 (44.4)
<i>Pseudomonas aeruginosa</i>	190 (90.5)	20 (9.5)	117 (60.0)	78 (40.0)
Fluoroquinolone sensitive	173 (90.6)	18 (9.4)	104 (60.5)	68 (39.5)
Fluoroquinolone resistant	17 (89.5)	2 (10.5)	13 (56.5)	10 (43.5)

[1] Documented Eradication, Presumed Eradication

[2] Documented Persistence, Presumed Persistence

[3] Percentages are based upon Eradication + Non-Eradication = N = number of patients with given baseline pathogens

[4] Fluoroquinolone resistance was defined as having a ciprofloxacin and/or ofloxacin MIC  $\geq$  4 $\mu$ g/mL for *Staphylococcus aureus* or *Pseudomonas aeruginosa*

Source: Clinical Study Datasets C-10-018 and C-10-019

## Efficacy Summary Statement

There is substantial evidence of effectiveness consisting of adequate and well controlled studies (Studies C-10-018 and C-10-019) which demonstrate that finafloxacin otic suspension is superior to its vehicle in the treatment of acute otitis externa when dosed four drops twice daily for seven days or, when using an otowick, giving an initial dose of 8 drops, followed by 4 drops twice daily for seven days.

The primary efficacy endpoint, the proportion of patients with clinical cures at the Day 11 Visit, was found to be clinically relevant and statistically significant in both studies. Finafloxacin demonstrated superiority to vehicle in clinical cure rate, microbiological success and the median time to cessation of ear pain.

Finafloxacin otic suspension is recommended to be indicated for the treatment of acute otitis externa (AOE) caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

## 8. Safety

From the original Medical Officer Review dated 10/2/14:

### Studies/Clinical Trials Used to Evaluate Safety

**Table 7.1.1-1**  
**Summary of Completed Clinical Studies for AL-60371 Otic Suspension, 0.3%**

Study Identifier / Study Type	Study Design	Study Population	Dosing Regimen and Duration	Treatment (N)	Safety Assessments
<b>Safety and Efficacy Study (Confirmatory)</b>  C-10-018	Prospective, multicenter, double-masked, vehicle-controlled, parallel-group, randomized	Patients 11 months to 84 years with a diagnosis of AOE with a combined numerical score of $\geq 4$ in at least 1 affected ear at the Day 1 exam for tenderness, erythema, and edema	4 drops in the affected ear(s) twice daily for 7 days	<ul style="list-style-type: none"> <li>• Finafloxacin 0.3% (N=344)</li> <li>• Vehicle (N=342)</li> </ul>	<ul style="list-style-type: none"> <li>• Extent of exposure</li> <li>• Adverse events</li> </ul>
<b>Safety and Efficacy Study (Confirmatory)</b>  C-10-019	Prospective, multicenter, double-masked, vehicle-controlled, parallel-group, randomized	Patients age 2 to 82 years with a diagnosis of AOE with a combined numerical score of $\geq 4$ in at least 1 affected ear at the Day 1 exam for tenderness, erythema, and edema	4 drops in the affected ear(s) twice daily for 7 days	<ul style="list-style-type: none"> <li>• Finafloxacin 0.3% (N=274)</li> <li>• Vehicle (N=274)</li> </ul>	<ul style="list-style-type: none"> <li>• Extent of exposure</li> <li>• Adverse events</li> </ul>
<b>PK Study</b>  C-10-007	Single-center, multiple-dose, randomized, vehicle-controlled, fixed sequence study.	Healthy male and female subjects of any race/ethnicity, age 6 to 78 years	Period 1: 4 drops in both ears BID; 7 days of BID dosing followed by 1 day of dosing in both ears in the morning only 8 days)  Period 2: 1 tablet (200 mg) po per day (single dose)	Period 1: Finafloxacin 0.3% (N=14) Vehicle (N=7)  Period 2: AL-60371A 200 mg tablet (N=20)	<ul style="list-style-type: none"> <li>• Extent of exposure</li> <li>• Adverse events</li> <li>• Vital signs (P, BP)</li> <li>• External ear examination</li> <li>• EKG</li> <li>• Clinical laboratory tests</li> </ul>

Study Identifier / Study Type	Study Design	Study Population	Dosing Regimen and Duration	Treatment (N)	Safety Assessments
PK Study C-10-022	Multicenter, open-label, single-dose PK study, parallel-group randomized to without and with otowick (4 drops/ear); a non-randomized group with otowick 8 drops per ear.	Acute otitis externa patients, 6 years of age and older with and without otowick	• 4 drops or 8 drops in each ear / day (a single dose)	<ul style="list-style-type: none"> <li>• Finaxofloxacin 0.3%, 4 drops with otowick (N=12)</li> <li>• Finaxofloxacin 0.3% 4 drops without otowick (N=12)</li> <li>• Finaxofloxacin 0.3% 8 drops with otowick (N=12)</li> </ul>	<ul style="list-style-type: none"> <li>• Extent of exposure</li> <li>• Adverse events</li> </ul>

**Table 7.2.1-1 Overview of Exposure to Study Drug by Protocol All Studies**

Protocol Number	Safety Population	Topical Otic Dosing		Oral Dosing		
		Finaxofloxacin (AL-60371)		Vehicle	AL-60371A <sup>c</sup>	
		N=688		N=623	N=20	
		BID	Single Dose <sup>b</sup>	BID	Single Dose	
<b>Efficacy and Safety Studies</b>						
C-10-018	686	344	---	342	---	
C-10-019	548	274	---	274	---	
<i>Subtotal</i>	1234	618	---	616	---	
<b>Pharmacokinetic Studies</b>						
C-10-007	21 <sup>a</sup>	14	---	7	20	
C-10-022	36	---	36	---	---	
<i>Subtotal</i>	57	14	36	7	20	
<b>Total</b>	<b>1291</b>	<b>632</b>	<b>36</b>	<b>623</b>	<b>20</b>	
Source Table 2.7.4.1-1						

AL-60371 = finaxofloxacin, free base

AL-60371A = finaxofloxacin, hydrochloride salt

a After the otic dose period (Period 1), 20 subjects in protocol C-10-007 were also exposed to AL-60371A 200 mg tablet during the oral dose period (Period 2). One subject with exposure to Vehicle discontinued from the study prior to the oral dose period.

b Single dose = 3 groups combined (4 drops per ear with otowick group, 4 drops per ear without otowick group and 8 drops per ear with otowick group). Finaxofloxacin otic suspension, 0.3%; Finaxofloxacin otic suspension vehicle.

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c AL-60371A = AL-60371A 200 mg tablet

No deaths were reported during the clinical studies involving finafloxacin otic suspension including Study C-10-018 and Study C-10-019.

**Table 6.1.3-1**  
**C-10-18 Subject Disposition**  
**All Randomized Subjects**

<b>Subject Disposition</b>	<b>Finafloxacin (N=347)</b>	<b>Vehicle (N=346)</b>
Safety Population	344	342
ITT Population	344	342
Culture positive subset (MITT)	311	302
Pathogen positive subset (PMITT)	145	138
Per-Protocol Population	314	324
Culture positive subset (MPP)	281	287
Pathogen positive subset (PMPP)	126	127
Completed Study	297 (85.6%)	250 (72.3%)
Discontinued Study	50 (14.4%)	96 (27.7%)
<i>Reasons for Discontinuation</i>		
Adverse Event	6 (1.7%)	15 (4.3%)
Lost to Follow-up	3 (0.9%)	4 (1.2%)
Subject Decision Unrelated to an AE	4 (1.2%)	3 (0.9%)
Treatment Failure	33 (9.5%)	66 (19.1%)
BL Culture + for Group A Strep	0	1 (0.3%)
BL Culture + for Yeast / Fungi	0	1 (0.3%)
Other	2 (0.6%)	2 (0.6%)
Randomized in Error	2 (0.6%)	4 (1.2%)
Note: There were 7 patients who did not receive study medication. 6 of these patients did not attend any visit after visit 1. Patient 1647 exited at Visit 2 but did not dose with study medication. Source: Adapted from Table 10.1-1 and Table 10.1-2.		

Approximately 46% of patients in the culture positive subset did not have pretherapy isolates of *S. aureus* or *P. aeruginosa* and were thus excluded from the Pathogen Positive subset of the ITT population. The most frequent reason for discontinuation was treatment failure which was experienced by 19.1% of the Vehicle group and 9.5% of the Finafloxacin group

**Table 6.2.3-1**  
**C-10-19 Subject Disposition**  
**All Randomized Subjects**

<b>Subject Disposition</b>	<b>Finafloxacin (N=274)</b>	<b>Vehicle (N=275)</b>
Safety Population	274	274
ITT Population	274	274
Culture positive subset (MITT)	239	241
Pathogen positive subset (PMITT)	147	130
Per-Protocol Population	250	244

<b>Subject Disposition</b>	<b>Finafloxacin (N=274)</b>	<b>Vehicle (N=275)</b>
Culture positive subset (MPP)	217	217
Pathogen positive subset (PMPP)	134	118
Completed Study	237 (86.5%)	179 (65.1%)
Discontinued Study	37 (13.5%)	95 (34.5%)
<i>Reasons for Discontinuation</i>		
Adverse Event	12 (4.4%)	7 (2.5%)
Lost to Follow-up	1 (0.4%)	3 (1.1%)
Subject Decision Unrelated to an AE	3 (1.1%)	1 (0.4%)
Treatment Failure	21 (7.7%)	83 (30.2%)
BL Culture + for Group A Strep	0	0
BL Culture + for Yeast / Fungi	0	0
Other	0	1 (0.4%)
Randomized in Error	0	1 (0.4%)
Note: Patient 1238 was randomized in error and did not receive study medication. Source: Adapted from Table 10.1-1 and Table 10.1-2.		

Approximately 50% of patients in the culture positive subset of the ITT population did not have pretherapy isolates of *S. aureus* or *P. aeruginosa* and were thus excluded from the pathogen positive subset of the ITT population. Fewer patients were included in the pathogen positive subsets of the ITT and PP populations in the Vehicle group than the Finafloxacin group. The most frequent reason for discontinuation was treatment failure which was experienced by 30.2% of the Vehicle group and 7.7% of the Finafloxacin group.

**Table 7.4.1-1**  
**Overall Frequency and Incidence of Adverse Events Occurring at Rates  $\geq$  1.0%**  
**Studies C-10-018 and C-10-019: Pooled Safety Populations**

<b>Coded Adverse Event <sup>a</sup></b>	<b>Finafloxacin (N=618)</b>	<b>Vehicle (N=616)</b>
Ear discomfort	2 (0.3%)	9 (1.5%)
Ear pain	3 (0.5%)	9 (1.5%)
Ear pruritus	8 (1.3%)	6 (1.0%)
Headache	11 (1.8%)	18 (2.9%)
Otitis media	8 (1.3%)	14 (2.3%)
Otitis externa	11 (1.8%)	9 (1.5%)
Nausea	7 (1.1%)	1 (0.2%)

Source: Table 2.7.4.2-1  
 a MedDRA version 15.0

Adverse events reported by greater than or equal to 1% of patients and more frequently in the finafloxacin group were ‘ear pruritus’, ‘otitis externa’, and ‘nausea’.

A single adverse event was reported in Study C-10-022 in the 8 Drops with Otowick treatment group. The adverse event was coded ear hemorrhage. This adverse event resolved without treatment within 2 hours.

## **Safety Summary Statement**

Findings from Studies C-10-018 and C-10-019 provided adequate evidence of safety for finafloxacin otic suspension in the twice daily dosing regimen for the treatment of acute otitis externa. Overall, XTORO (finafloxacin otic suspension) 0.3% was safe and well tolerated in Studies C-10-018 and C-10-019. Reactions most frequently reported with finafloxacin otic suspension were ear pruritus and nausea.

The application supports the safety of XTORO (finafloxacin otic suspension) 0.3% for the treatment of acute otitis externa. The safety profile of finafloxacin is similar to currently approved antimicrobial otic products.

## **9. Advisory Committee Meeting**

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

## **10. Pediatrics**

The safety and efficacy of XTORO in treating acute otitis externa in pediatric patients one year or older have been demonstrated in adequate and well controlled clinical trials (Studies C-10-018 and C-10-019).

A Pediatric Written Request was issued for finafloxacin in the treatment of acute otitis externa on 2/22/13. The written request specified that pediatric patients aged 1 to 13 years be enrolled.

This application was presented at the Pediatric Exclusivity Board on 8/26/14; the application was found to be in compliance with the written request, and exclusivity was granted.

This application was presented at the Pediatric Regulatory Committee (PeRC) on 11/5/14. PeRC agreed with the partial waiver from assessments for the pediatric age group birth to 1 year. Necessary studies would be impossible or highly impracticable because there are too few children with disease/condition to study.

## 11. Other Relevant Regulatory Issues

### OSI

A Office of Scientific Investigations (OSI) audit was requested.

Per the DSI review finalized 10/7/14:

The identical pivotal studies C-10-018 and C-10-019 entitled, "Safety and Efficacy Evaluation of Topical AL-60371 Otic Suspension, 0.3% in the Treatment of Acute Otitis Externa", were inspected in support of this application. Drs. Calcagno's and Schwartz's clinical sites were selected for inspection because they were among the highest enrolling sites.

### II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Frank A. Calcagno CYN3ergy Research 24850 Southeast Stark Street, Suite #180 Gresham, OR 97030	C-10-018/ 5019/ 39	6-13 Aug 2014	NAI
Richard H. Schwartz, M.D. Advanced Pediatrics 100 East Street South East, Suite #301 Vienna, VA 22180	C-10-019/ 2234/ 43	18-19 Aug 2014	NAI

#### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

Neither Dr. Calcagno nor Dr. Schwartz was issued a Form FDA 483, and the final classification of these inspections was No Action Indicated (NAI). The data generated by these clinical sites appear adequate in support of the respective indication.

### FINANCIAL DISCLOSURE

Alcon has determined there were no financial interests or arrangements to disclose from investigators in clinical studies C-10-018, C-10-019 and C-10-022. There are financial interests or arrangements to disclose from the investigator, Dr. (b) (6), who participated in clinical trial (b) (6). Dr. (b) (6) is not employed by the applicant.

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Investigators and Payment Description	Total Monies by Investigator
(b) (6) MD, PhD and Sub-Investigators Consulting fees	\$32,244.30
<b>Total</b> (b) (6)	\$32,244.30

Alcon took the following steps to minimize potential bias of clinical study results by any of the investigators:

- The study was randomized, controlled and double-masked in Period 1.
- The biostatistical and clinical pharmacology staffs were masked to treatment assignments.
- The Principal Investigator and all sub-Investigators were prohibited from administering study drugs to patients.
- The safety variables were assessed by masked observers.
- The treatment code was not broken by the investigators or the Applicant.

12. **DMEPA**

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review dated 11/5/14 finding the proprietary name, XTORO, to be conditionally acceptable.

This review constituted a re-assessment of the proposed proprietary name, Xtoro, written in response to the resubmission of this proprietary name by the applicant. DMEPA found the proposed name, Xtoro, unacceptable in OSE Review 2014-17319 dated July 24, 2014, due to the potential confusion with two other products that were also under review (b) (4)

DMEPA also provided recommendations on the packaging configuration and the package insert labeling in a review finalized 9/15/14.

**OPDP**

The Office of Prescription Drug Promotion (OPDP) reviewed the substantially complete draft product labeling for XTORO (finaxofloxacin otic suspension) 0.3% and offered the following comments in their review finalized 10/10/14. Note that this review contains all of the comments placed on the SharePoint version of the package insert by all reviewers. Many of the comments are no longer applicable because the draft label has been edited.

**Comment [KH1]:** This [ (b) (4) ] can be deleted, if both dosage form and route of administration are part of nonproprietary name, they do not need to be repeated.

**DTOP Comments:** *Per the October 2013 Labeling Review Tool, this recommendation is incorrect. There are otic and ophthalmic products which are not topical despite their established names; for clarity the route of administration should be part of the Product Title in the Highlights.*

**Comment [KH2]:** Note to PharmTox: According to eLIST the established pharmacologic class is “quinolone antimicrobial”.

**DTOP Comments:** *The final draft label refers to the product as a quinolone antimicrobial.*

**Comment [CGC3]:** OPDP Comment: We note that these [Table of Contents] titles do not coincide with what is presented in the full prescribing information. We recommend revising for consistency with the full PI.

**DTOP Comments:** *The final draft label has modified these subsections.*

**Comment [CGC4]:** OPDP Comment: We note that other quinolone otic products (Ciprodex) include information relating to hypersensitivity in the Contraindications and/or Warnings section of their PI's. Should similar risk information be included in this PI? OPDP defers to DTOP on the inclusion of this information.

**DTOP Comments:** *The final draft label references hypersensitivity in Section 5.2.*

**Comment [KH5]:** Should hypersensitivity be considered as W&P, to be consistent with other quinolone otic products? Is there reason to believe that this won't have similar hypersensitivity reactions as other topical quinolones?

**DTOP Comments:** *The final draft label references hypersensitivity in Section 5.2.*

**Comment [CGC6]:** OPDP Comment: We concur with comment [KH7] below requesting the inclusion of additional information about the two phase 3 clinical trials. Additional details include: patient demographics, doses received (including duration), trial design, etc. Also, if applicable, we recommend disclosing the percentage of patients that discontinued the drug due to adverse reactions. We also recommend disclosing what adverse reaction resulted in the most discontinuations.

**Comment [KH7]:** Consider including more information about the baseline demographics of exposed population, trial designs, etc. according to Section III(B)(1) of the [Adverse Reaction guidance](#).

**DTOP Comments:** *Regarding comments 6 and 7, we do not agree that the requested information provides useful information for the prescribing physician. These are not placebo controlled, trials; they are vehicle controlled trials in which the vehicle contains a preservative with an antimicrobial effect.*

**Comment [KH8]:** Consider: Per 21 CFR 201.57 (c)(7)(ii)(A) Clinical Trials Experience: The rate of occurrence of an adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless such data cannot be determined or presentation of comparator rates would be misleading.

**DTOP Comments:** *These trials did not use a placebo; they utilized a vehicle control arm which contains the same constituent as the drug product with the exception of the active ingredient, flaxoxacin.*

**Comment [AJM9]:** Internal note: changed from [REDACTED] (b)(4)” to “at least 1300”. The 1300 goes with the rabbit (both the neural tube effects and the limb anomalies). The [REDACTED] (b)(4) goes with the rat (neural tube [REDACTED] (b)(4) only). The sentence should lead with the more important effect, and also should lead with the lower exposure margin.

**DTOP Comments:** *The final draft label has been revised.*

**Comment [CGC10]:** OPDP Comment: We note that 6.1% and 2.5% of finafloxacin patients in Studies C-10-018 and C-10-019, respectively were  $\geq 65$  years of age. OPDP would like to confirm that this constitutes an adequate number of geriatric patients to detect a difference in safety or effectiveness when compared to younger patients. If not, we recommend revising to, “Clinical studies of finafloxacin did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects,” or similar.

**DTOP Comments:** *There are an adequate number of geriatric subjects to detect a difference in safety and effectiveness.*

**Comment [KH11]:** This should be consistent with how we define in HL.

**DTOP Comments:** *The final draft label refers to the product as a [REDACTED] (b)(4).*

**Comment [SS12]:** Suggested re-wording of this section to include a more general statement about the action of fluoroquinolones. This is consistent with what is in other fluoroquinolone labels.

**DTOP Comments:** *The final draft label has been revised.*

**Comment [CGC13]:** OPDP Comment: Would it be appropriate to include a header here, since this information doesn’t relate to “Cross Resistance.” For example, other anti-infective labels have included headers such as, “Activity in vitro and in vivo,” “Antibacterial Activity,” and “Spectrum of Activity.” Should a similar header be included here? OPDP defers to DTOP.

**DTOP Comments:** *The final draft label has been revised.*

**Comment [AJM14]:** Draft note for Alcon: [REDACTED] (b)(4)  
[REDACTED] The study results should be omitted from the label.

**DTOP Comments:** *The final draft label has been revised.*

**Comment [AJM15]:** Draft note to Alcon: This section [REDACTED] (b)(4) is not relevant for the proposed indication.

**DTOP Comments:** *The final draft label has been revised.*

**Comment [CGC16]:** OPDP Comment: If possible, we recommend including additional information regarding these clinical studies. Additional details include: patient demographics, pertinent inclusion/exclusion criteria, etc. Please refer to the January 2006 Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.

*DTOP Comments:* Consistent with our responses for comments 6 and 7, we do not agree that the requested information provides useful information for the prescribing physician. These are not placebo controlled, trials; they are vehicle controlled trials in which the vehicle contains a preservative with an antimicrobial effect.

**Comment [CGC17]:** OPDP Comment: How does this population subset differ from the pathogen positive subset? Does this mean 1 or more of any type of bacterial organisms or is this limited to the two indicated microorganisms (i.e. *P. aeruginosa* and *S. aureus*). If this statement refers to additional bacteria that is not indicated for Finaxofloxacin, OPDP is concerned that this statement could be used to broaden the approved indication for the drug (i.e. suggest that Finaxofloxacin has demonstrated efficacy in ear infections caused by multiple bacterial organisms). OPDP would like to confirm that these studies were adequately designed to detect efficacy in this patient population subset. If the studies are not considered substantial evidence to support claims suggesting efficacy in AOE infections caused by multiple bacterial organisms (including those not indicated), we recommend deleting. OPDP defers to DTOP. (b) (4)

We note that other data in the Clinical Studies section discloses the number of patients in each treatment arm and/or population subset.

*DTOP Comments:* Disagree. Microbiological success required that all pretherapy bacteria were absent from the exit otic specimen obtained at Day 11. It is a critical secondary endpoint in otitis externa trials and bacterial conjunctivitis trials

**Comment [KH18]:** Allergic information is not in the FPI – do we want to include this in FPI?

*DTOP Comments:* The final draft label references hypersensitivity in Section 5.2.

#### **BIOSTATISTICS**

Per the Biostatistics consultative review finalized 9/24/14:

Studies C-10-018 and C-10-019 were two identically designed phase 3 studies. Both were multicenter, randomized, double-masked, vehicle-controlled, parallel-group studies to evaluate the safety and efficacy of Finaxofloxacin otic suspension, 0.3% versus Vehicle in the treatment of AOE. For both studies, patients aged 6 months and older, with a clinical diagnosis of AOE were enrolled. The primary efficacy endpoint was the percentage of patients with clinical cures at the test-of-cure (TOC) visit (Day 11 + 2); a subject was considered as clinical cure if the subject's sum score of ear tenderness, erythema, and edema was zero (i.e., none). There were two secondary efficacy endpoints for both studies: the percentage of patients with microbiological success at the TOC visit defined as all pre-

therapy bacteria being absent in the exit specimen; and time to cessation of ear pain, defined as the first time point that ear pain was absent (morning or evening) and did not return for any/all subsequent diary entries. Cessation of ear pain was reported by the patient or parent/legal guardian via a telephone diary at 1/2 day interval.

The protocol-defined primary analysis set for the evaluation of the primary, secondary efficacy endpoints was the pathogen positive subset of intent-to-treat (ITT) population (referred as ITT pathogen positive subset throughout this review), which included all subjects who received study treatment and had a microbiological specimen in the study ear that contained at least one of the following two organisms (considered by the applicant as etiological agents of AOE) at baseline: *Pseudomonas aeruginosa* and/or *Staphylococcus aureus*.

A total of 686 subjects were randomized and treated at 67 centers across U.S., Canada, and Puerto Rico in Study C-10-018; 613 (89.4%) were included in the ITT culture positive subset; 283 (41.2%) were included in the ITT pathogen positive subset. In Study C-10-019, 548 subjects were randomized and treated at 46 centers across U.S., Canada, and Puerto Rico; 480 (87.6%) were included in the ITT culture positive subset; 277 (50.5%) were included in the ITT pathogen positive subset.

**Table 1: Summary of the Primary and Secondary Efficacy Results (ITT pathogen positive subset and ITT culture positive subset)**

Clinical Cure at TOC						
	Study C-10-018			Study C-10-019		
	Finafloxacin	Vehicle	Finafloxacin vs. Vehicle Difference (95% CI) <sup>a</sup>	Finafloxacin	Vehicle	Finafloxacin vs. Vehicle Difference (95% CI) <sup>a</sup>
Pathogen + Subset	104/145 (71.7%)	46/138 (33.3%)	38.4% (27.6%, 49.1%)	101/147 (68.7%)	52/130 (40.0%)	28.7% (17.4%, 40.0%)
Culture + Subset	226/311 (72.7%)	154/302 (51.0%)	21.7% (14.2%, 29.2%)	170/239 (71.1%)	112/241 (46.5%)	24.7% (16.1%, 33.2%)
Microbiological Success at TOC						
	Study C-10-018			Study C-10-019		
	Finafloxacin	Vehicle	Finafloxacin vs. Vehicle Difference (95% CI) <sup>a</sup>	Finafloxacin	Vehicle	Finafloxacin vs. Vehicle Difference (95% CI) <sup>a</sup>
Pathogen + Subset	97/145 (66.9%)	18/138 (13.0%)	53.9% (44.4%, 63.4%)	97/147 (66.0%)	15/130 (11.5%)	54.4% (45.0%, 63.9%)
Culture + Subset	189/311 (60.8%)	50/302 (16.6%)	44.2% (37.4%, 51.1%)	155/239 (64.9%)	41/241 (17.0%)	47.8% (40.2%, 55.5%)
Median Time (day) to Cessation of Ear Pain						
	Study C-10-018			Study C-10-019		
	Finafloxacin	Vehicle	Finafloxacin vs. Vehicle Difference (95% CI) <sup>b</sup>	Finafloxacin	Vehicle	Finafloxacin vs. Vehicle Difference (95% CI) <sup>b</sup>
Pathogen + Subset	4.0	7.0	-3.0 (-5.0, -0.8)	3.0	6.5	-3.6 (-5.0, -2.0)
Culture + Subset	4.0	5.0	-1.0 (-2.0, 0.0)	3.0	5.5	-2.3 (-3.0, -1.0)

<sup>a</sup> 95% CI calculated based on normal approximation to binomial data.

<sup>b</sup> Difference and 95% confidence interval estimated using bootstrap procedure with 10,000 bootstrap samples, non-stratified analysis.

Source: Tables 11.4.1.3-2, 11.4.1.2-1, 14.2-24, 14.2-93, and 14.2-94 of Study C-10-018 report; and Tables 11.4.1.3-2, 11.4.1.2-1, 14.2-24, 14.2-89, and 14.2-90 of Study C-10-019 report.

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Finafloxacin otic suspension 0.3% demonstrated superiority to Vehicle in terms of:

- The percentage of patients who achieved a clinical cure at the TOC visit;
- The percentage of patients who achieved microbiological success at the TOC visit;
- And the median time to cessation of ear pain as reported by patients (or parents/guardians) in half (1/2) day increments.

The statistical reviewer recommends the approval of Finafloxacin otic suspension 0.3% for the treatment of AOE.

### **13. Labeling**

NDA 206307, XTORO (finafloxacin otic suspension) 0.3% is recommended for approval for the treatment of acute otitis externa (AOE) caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus* with the labeling found in the Appendix of this review submitted December 2, 2014 (package insert and carton and container labeling) and December 9, 2014 (patient package insert).

### **14. Recommendations/Risk Benefit Assessment**

#### **RECOMMENDED REGULATORY ACTION:**

NDA 206307, XTORO (finafloxacin otic suspension) 0.3% is recommended for approval for the treatment of acute otitis externa (AOE) caused by susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

There is substantial evidence of effectiveness consisting of adequate and well controlled studies (Studies C-10-018 and C-10-019) which demonstrate that finafloxacin otic suspension is superior to its vehicle in the treatment of acute otitis externa when dosed four drops twice daily for seven days or, when using an otowick, giving an initial dose of 8 drops, followed by 4 drops twice daily for seven days.

The primary efficacy endpoint, the proportion of patients with clinical cures at the Day 11 Visit, was found to be clinically relevant and statistically significant in both studies. Finafloxacin demonstrated superiority to vehicle in clinical cure rate, microbiological success and the median time to cessation of ear pain.

#### **RISK BENEFIT ASSESSMENT:**

Findings from Studies C-10-018 and C-10-019 provided adequate evidence of safety for finafloxacin otic suspension in the twice daily dosing regimen for the treatment of acute otitis externa. Overall, XTORO (finafloxacin otic suspension) 0.3% was safe and well tolerated. Reactions most frequently reported with finafloxacin otic suspension were ear pruritus and nausea.

The safety profile of finafloxacin is similar to currently approved quinolone antimicrobial otic products.

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William M. Boyd, M.D.  
NDA 206307  
XTORO (finafloxacin otic suspension) 0.3%

Pharmacology/Toxicology, Biostatistics, Product Quality, Clinical, Clinical Pharmacology, Biopharmacology, and Clinical Microbiology have recommended approval for this application.

**RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:**

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

The following wording is recommended for the Postmarketing Commitment regarding the development of a dissolution testing method:

We remind you of your postmarketing commitments:

2828-1            Submit the dissolution method development report with the complete data.

The timetable you submitted on September 19, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission:    05/2015

2828-2            Submit a proposal for the dissolution acceptance criterion and the complete supportive data. The selection of the proposed acceptance criterion should be based on the dissolution profile data (i.e., 10, 15, 20, 30, 45, and 60 minutes; N=12) from a minimum of 12 commercial batches and the stability data for registration batches.

The timetable you submitted on September 19, 2014, states that you will conduct this study according to the following schedule:

Proposal Submission:            08/2015

Final Report Submission:       11/2015

## Appendix

The following package insert and carton and container labeling submitted by the applicant on 12/2/14 (package insert and carton and container labeling) and 12/9/14 (patient package insert) are acceptable:

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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WILLIAM M BOYD  
12/09/2014

WILEY A CHAMBERS  
12/10/2014