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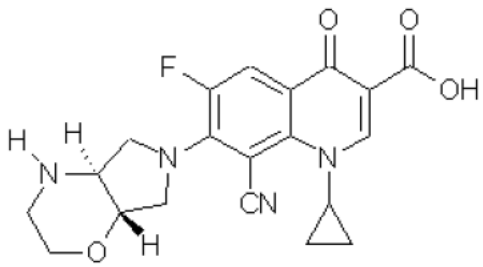
APPLICATION NUMBER:

206307Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206-307
Priority or Standard	Priority
Submit Date(s)	April 25, 2014
Received Date(s)	April 25, 2014
PDUFA Goal Date	December 25, 2014
Division / Office	DTOP/OAP
Reviewer Name(s)	Rhea A. Lloyd, MD
Review Completion Date	October 1, 2014
Established Name	Finafloxacin otic suspension, 0.3%
(Proposed) Trade Name	
Therapeutic Class	fluoroquinolone
Applicant	Alcon Research, Ltd. 6201 South Freeway Fort Worth, TX 76134-2099 817-293-0450
Formulation(s)	
Dosing Regimen	Instill 4 drops in the affected ear(s) twice daily for 7 days
Indication(s)	Treatment of acute otitis externa.
Intended Population(s)	Patients, 1 year of age or older with a clinical diagnosis of acute otitis externa (b) (4)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended from a clinical perspective that NDA 206-307, TRADENAME (finafloxacin otic suspension) 0.3% be approved for the treatment of acute otitis externa with labeling revisions listed in this review.

The dosing recommendation is for 7 days as is standard for topical otic anti-infective products.

There is substantial evidence of effectiveness consisting of adequate and well controlled studies which demonstrate that finafloxacin otic suspension is superior to its vehicle in the treatment of acute otitis externa when dosed four drops (b) (4) or, when using an (b) (4)

1.2 Risk Benefit Assessment

Findings from Studies C-10-018 and C-10-019 provided adequate evidence of safety and efficacy for finafloxacin otic suspension in the twice daily dosing regimen for the treatment of acute otitis externa. 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.

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

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

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

1.4 Recommendations for Postmarket Requirements and Commitments

There are no recommended Postmarketing Requirements or Phase 4 Commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Finafloxacin is a new chemical entity described as a fourth generation fluoroquinolone with activity against bacteria in relatively acidic environments (pH 5.5 - 6.2). Similar to other fluoroquinolones, finafloxacin's mechanism of action is inhibition of DNA gyrase and topoisomerase IV.

Finafloxacin otic suspension is formulated for otic administration. It is a white to off-white, aqueous suspension that is a sterile, preserved, multidose product indicated for otic infections.

Established Name:	finafloxacin otic suspension, 0.3%
Proposed Trade Name:	
Chemical Class:	new chemical entity
Pharmacological Class:	fluoroquinolone
Indication:	treatment of acute otitis externa

Dosing Regimen:	Instill 4 drops twice daily in the affected ear(s) for 7 days.
Age Groups:	Patients 1 year of age or older

Table 2.1-1 Composition of Finafloxacin Otic Suspension (FID 119420)

Component	Concentration % w/v	Function	Reference to Quality Standards
Finafloxacin (AL-60371)	0.3 [a]	Active	NOC [b]
Tyloxapol	(b) (4)	(b) (4)	USP
Hydroxyethyl Cellulose (b) (4)			NF
Sodium Chloride			USP
Magnesium Chloride (b) (4)			USP
Benzalkonium Chloride		Preservative	NF
Sodium hydroxide and/or hydrochloric acid		Adjust pH	NF NF
Purified Water		(b) (4)	USP

Note: FID = Formulation Identification Number
a Adjust for purity; **b** NOC = Non-compendial; **c** Added as a (b) (4)% solution, based on assay

2.2 Tables of Currently Available Treatments for Proposed Indications

There are many 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 fluoroquinolone otic drug products available containing ciprofloxacin, ciprofloxacin and hydrocortisone and ofloxacin.

2.3 Availability of Proposed Active Ingredient in the United States

Finafloxacin is a new chemical entity that has not been approved in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no specific issues which need to be addressed.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Finafloxacin otic suspension has been studied under IND 110576 which was opened in September 2011 with the submission of a protocol for Phase 1 studies.

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. Regarding the clinical development, the Agency suggested that standardized otowick use and the submission of drug-device studies be incorporated in the clinical studies if the otowick was to be included in labeling. 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 6 months 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.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There is no evidence that the studies reviewed in this supplement were not conducted in accordance with acceptable clinical ethical standards. The results of the clinical inspections were pending at the time of this review.

3.2 Compliance with Good Clinical Practices

The studies performed under IND 110,576 (C-10-018 and C-10-019) were conducted in accordance with the International Conference of Harmonization E6 Guidelines for Good Clinical Practices (GCPs), the Declaration of Helsinki.

Before initiation of the studies, the original protocol, all protocol amendments, the informed consent documents and all supportive information were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study. The study began after receiving written approval from each EC/IRB.

3.3 Financial Disclosures

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.

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

See Section 9.4 of this review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Finafloxacin Otic Suspension is a multi-dose product with 0.005% benzalkonium chloride added for antimicrobial preservation. The formulation, an isotonic topical suspension, also contains hydroxyethyl cellulose (b) (4), tyloxapol (b) (4), magnesium chloride as (b) (4), sodium chloride (b) (4), and purified water (b) (4). The formulation is adjusted to a pH of 6.0 with sodium hydroxide and/or hydrochloric acid.

Alcon developed Finafloxacin Otic Suspension (FID 119420) as a sterile, broad-spectrum antibacterial, preserved therapeutic product for the treatment of otic bacterial infections in patients with acute otitis externa (AOE). The clinical trial formulation contains 0.3% of the active drug substance. A suspension dosage form was selected since finafloxacin exhibits a low solubility (0.3 mg/mL) in purified water at the intrinsic pH of (b) (4).

Table 4.1-1 Regulatory Acceptance Specifications for Finafloxacin Otic Suspension

Test	Specification
Finafloxacin (AL-60371) ID (HPLC) [a]	Positive
Finafloxacin (AL-60371) ID (TLC) [a]	Positive
Finafloxacin (AL-60371) Assay (HPLC)	90-110% of Label
Finafloxacin (AL-60371) Impurities (HPLC): [b] (b) (4) Any single unspecified impurity Total impurities	 NMT (b) (4)% of active NMT % of active NMT % of active NMT % of active
Benzalkonium Chloride ID (HPLC) [a]	Positive
Benzalkonium Chloride Assay (HPLC) [a]	80-120% of label
Sodium Chloride	USP
Appearance, Suspension: Color (Visual) Uniformity (Visual or HPLC)	 White to Off-White Uniform Suspension
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 (b) (4)
Particle Size by (b) (4): (b) (4)	 NLT (b) (4) (b) (4) NMT (b) (4)
Sterility	Pass USP

a Release test only; **b** Report any single impurity (b) (4)% of label;

4.2 Clinical Microbiology

Refer to the Clinical Microbiology review for details.

4.3 Preclinical Pharmacology/Toxicology

Refer to the Pharmacology Toxicology review for details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Finafloxacin's mechanism of action is inhibition of DNA gyrase and topoisomerase IV similar to that of other fluoroquinolones.

4.4.2 Pharmacodynamics

Finafloxacin is a fluoroquinolone that demonstrates improved antibacterial activity under acidic conditions (pH 5.8).

4.4.3 Pharmacokinetics

The systemic pharmacokinetics of AL-60371 after otic administration of AL-60371 otic suspension, 0.3% was evaluated in healthy subjects in Study C-10-007 and in patients with acute otitis externa (AOE) in Study C-10-022. (b) (4)

In Study C-10-007, healthy subjects received 4 drops in each ear twice daily for 7.5 days. Quantifiable AL-60371 concentrations (> 0.05 ng/mL) were observed in plasma samples from only 2 of the 14 subjects at 3 time points and the AL-60371 concentrations in these samples were slightly above the quantitation limit.

In Study C-10-022, AOE patients were randomized to two treatment groups. Both groups received 4 drops of finafloxacin, however, one utilized the otowick and the other did not. An additional nonrandomized treatment group received 8 drops of finafloxacin with the otowick. Each group included 12 patients. Quantifiable AL-60371 concentrations (> 0.05ng/mL) were observed in the plasma samples from 2 of the 36 patients. In the first of the 2 patients (male, 4 drops with otowick), quantifiable levels of 0.12 ng/mL, 0.100 ng/mL and 0.0735 ng/mL were measured at 0.5, 1.0 and 2 hours, respectively. In the second subject (female, 8 drops with otowick), quantifiable levels of 0.141 ng/mL and 0.234 ng/mL were observed at 1 and 2 hours, respectively.

Systemic pharmacokinetics (C_{max}, T_{max}, AUC, $t_{1/2}$) were determined in healthy subjects as part of Alcon Clinical Study C-10-007. Subjects were administered a single 200 mg oral tablet dose of AL-60371. Peak AL-60371 plasma concentrations were observed between 20 minutes and 4 hours, with a median T_{max} of 45 minutes. The mean C_{max} and AUC $_{0\text{-}12hr}$ values were 2509 ± 945 ng/mL and 6715 ± 2354 ng*hr/mL, respectively. After Cmax, plasma concentrations declined with a median half-life of 2.68 hours.

(b) (4)

Because of the very low levels of systemic exposure following otic doses of AL-60371 otic suspension, 0.3%, drug-drug interactions are not likely.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Summary of Completed Clinical Studies for AL-60371 Otic Suspension, 0.3%

Study Identifier / Study Type	Study Objective	Study Design	Treatment Group	Dosing Regimen/ Duration	Endpoints
Safety / Clinical Pharmacology Studies					
Study C-10-007 IND 110576 Phase 1	Evaluate the pharmacokinetics of AL-60371 after otic dosing.	Randomized, multiple-dose, fixed sequence PK study in healthy male and female subjects 18 years of age or older.	Period 1: AL-60371 otic suspension 0.3% (N=14) Vehicle (N=7) Period 2: AL-60371A oral tablet (200 mg) (N=20)	4 drops, BID for 8 days (bilateral) Single oral dose	Plasma concentrations of AL-60371 will be described after single or multiple otic doses. Relative bioavailability of AL-60371 will be assessed after single dose for otic administration compared to oral administration.
Study C-10-022 IND 110576 Phase 1	Evaluate the pharmacokinetics of AL-60371 with and without otowick use	Open-label, single visit study in patients 6 years of age or older diagnosed with AOE.	AL-60371 otic suspension 0.3% • N=12 • N=12 • N=12	Single dose bilateral: • 4 drops w/o otowick • 4 drops w/ otowick • 8 drops w/otowick	Plasma concentrations of AL-60371 will be described after a single otic dose of AL-60371 otic suspension, 0.3%

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	*1° Efficacy Endpoint:* Clinical cure at Day 11 (TOC) *2° Efficacy Endpoint:* 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	*1° Efficacy Endpoint:* Clinical cure at Day 11 (TOC) *2° Efficacy Endpoint:* Microbiological success at Day 11 (TOC); Time to cessation of ear pain as reported by patient diary

Reviewer's Comments:
Studies C-10-018 and C-10-019 were the subject of a Special Protocol agreement with the Agency dated May 29, 2012. These studies incorporated pediatric dosing consistent with the Pediatric Written Request which was issued by the Agency on February 22, 2013.

5.2 Review Strategy

The submitted clinical study reports, clinical protocols and relevant literature reports were reviewed. Modules 1 and 5 of the submission were reviewed in depth.

5.3 Discussion of Individual Studies/Clinical Trials

Studies C-10-018 and C-10-019: Safety and Efficacy Evaluation of Topical AL-60371 Otic Suspension, 0.3% in the Treatment of Acute Otitis Externa

Reviewer's Comment:
The protocol for the two identical Phase 3 studies submitted in this application were the subject of a Special Protocol Agreement with the Agency, letter dated May 29, 2012. The studies were identical in design and conducted in parallel.

Study Objectives
To demonstrate the superiority of Finafloxacin Otic Suspension, 0.3% (Finafloxacin) relative to Finafloxacin Vehicle (Vehicle) based on clinical cures at test-of-cure (TOC) for the treatment of acute otitis externa (AOE). (Finafloxacin was referred to as AL-60371 in the protocol and analysis plans for the studies.)

Methodology
The studies were prospective, multicenter, randomized, double-masked, vehicle-controlled, parallel-group in design. Enrolled patients were randomized in a 1:1 ratio to receive finafloxacin or vehicle administered as 4 drops in the affected ear(s) twice daily for 7 days. A microbiological specimen from the enrolled ear(s) that contains at least 1 of the following organisms considered etiological agents of acute otitis externa (AOE): *Pseudomonas aeruginosa* and/or *Staphylococcus aureus* was considered to be pathogen positive.

Patients were evaluated for safety and efficacy during the four post-baseline visits: an on-therapy visit (Visit 2, Day 3), an end-of-therapy visit (Visit 3, Day 8), and a Test-of-Cure visit (Visit 4, Day 11). Patients completed a telephone diary twice daily in which they recorded assessments of ear pain, pain medication use, and impact of ear pain on their sleep and other daily activities. In addition, patients completed an AOE treatment satisfaction questionnaire (AOE-TSQ) at the end-of-therapy visit (i.e., Day 8).

For each study, enrollment of 500 patients (250 per treatment group) was planned in order to obtain 280 patients in the pathogen positive intent-to-treat (ITT) analysis subset.

Study Schedule

	Visit 1 Screening/ Baseline	Visit 2 On-Therapy	Visit 3 EOT	Visit 4 TOC/Early Exit
Procedure/ Assessment	**Day 1**	**Day 3 + 2 days**	**Day 8 + 2 days**	**Day 11 + 2 days**
Patient screening	X			
Informed consent	X			
Demographics	X			
Medical history	X			
Concomitant medications	X	X	X	X
Inclusion/Exclusion	X			
Urine pregnancy test [a]	X			X
Clinical assessment	X	X	X	X
Ear cleansing [b]	X	X	X	X
Ear culture	X			X
Otowick insertion [c]	X	X		
Register in IVRS/IWRS	X			
Patient daily diary [d]	X	X	X	X
Dispense study medication/ acetaminophen	X	X[b]		
Demonstrate dosing technique	X	X[b]		
First dose in office	X			
Study coordinator phone call to patient [e]	X	X		
Treatment Satisfaction Questionnaire [f]			X	X[g]
Adverse events [h]	X	X	X	X
Collect study medication			X	X[i]
Exit from IVRS/IWRS				X

EOT = end-of-therapy; IVRS/IWRS = Interactive Voice/Web Response System; TOC = test-of-cure
[a] Performed for women of childbearing potential, before randomization and at exit.
[b] As needed.
[c] Investigators inserted an otowick if the ear canal was compromised by 50% or greater (ie, moderate or severe edema).
[d] Diaries were completed by the patient or parent/legal guardian twice daily throughout the entire study in an electronic diary.
[e] The study coordinator contacted the patient by telephone on Days 2 through 7 (except on the day of Visit 2) to ensure dosing and diary compliance and to evaluate patient progress.
[f] Treatment Satisfaction Questionnaire was completed only by patients > 8 years of age.
[g] Completed only if patient exited prior to Visit 3 (or missed Visit 3).
[h] Monitored for adverse events as described in the study protocol.
[i] Only if the study drug was not collected at Visit 3.

Study Population
Inclusion Criteria
Patients were eligible for enrollment in the study if they met the following criteria:

1. At least 6 months of age.
2. Had a clinical diagnosis of AOE based on clinical observation and of presumed bacterial origin in at least 1 ear.
3. Had a combined numerical score of ≥ 4 in at least 1 affected ear at the Day 1 exam for tenderness, erythema, and edema.
    a. For a patient with a bilateral infection, only 1 ear must have met this criterion (e.g., patient may have been enrolled with a numerical score of 4 in 1 ear and a numerical score of 1 in the other ear; both ears were assessed, cultured, and treated with Study Medication).
4. Agreed to read and sign the informed consent. When required by the Independent Ethics Committee (IEC/Institutional Review Board (IRB), children must have agreed to sign an approved assent form.
5. Agreed to refrain from water immersion of the ears during the conduct of the entire study without the use of appropriate dry ear precautions as described in Protocol Section 10.3.5 and the Manual of Procedures (MOP).
6. Agreed to comply with the requirements of the study. Patient (or parent/guardian) must have agreed to administer the study medication as directed, complete required study visits, and comply with the protocol.
7. Females who were not pregnant, not lactating and were not planning a pregnancy. All females of childbearing potential (those who are not premenstrual, not postmenopausal or not surgically sterile) may have participated only if they had a negative urine pregnancy test prior to randomization, and if they agreed to use adequate birth control methods to prevent pregnancy throughout the study. Adequate birth control methods included topical, hormonal-oral, implantable or injectable contraceptives; mechanical-spermicide in conjunction with a barrier such as condom or diaphragm; intrauterine device (IUD); or surgical sterilization of partner (must be ≥ 6 months post vasectomy). For non-sexually active females, abstinence was regarded as an adequate method of birth control; however, if the patient became sexually active during the study, she must have agreed to use adequate birth control methods as defined above for the remainder of the study.

Exclusion Criteria
Patients demonstrating any medical condition (systemic or otic) that may, in the opinion of the Investigator, have precluded the safe administration of test article or safe participation in the study were not enrolled. The following specific conditions excluded patients from participation in the study.

1. Duration of signs or symptoms of AOE greater than 28 days in the affected ear(s) as reported by patient or parent/guardian.
2. Presence of a tympanostomy tube or perforated tympanic membrane in the affected ear(s). Patients with a history of tympanic membrane perforation were not be enrolled unless the absence of a current perforation was confirmed at Visit 1 prior to enrollment.

3. Clinically diagnosed otic disease other than AOE (e.g., malignant otitis externa) in the affected ear(s).
4. Known or suspected ear infection of yeast, fungal or mycobacterial origin in the affected ear(s).
5. History of/or active herpes simplex, vaccinia, or varicella infections or overt viral infection of the pinna (e.g., Herpes Zoster oticus) or tympanic membrane (e.g., myringitis bullosa) in the affected ear(s). Patients with active herpetic infections in locations other than the ear were also excluded.
6. History of/or active congenital abnormalities of the external auditory canal (e.g. aplasia, atresia, stenosis, or duplication) or obstructive bony exostoses in the affected ear(s).
7. Active mastoiditis or other suppurative ear disorders (e.g., cholesteatoma associated) in the affected ear(s).
8. History of/or active malignant tumors of the external auditory canal in the affected ear(s).
9. Prior otologic surgery within 6 months of study entry in the affected ear(s).
10. Active seborrheic dermatitis or other skin conditions of the external auditory canal in the affected ear(s).
11. Current or prior history of an immunosuppressive disorder (e.g., HIV-positive or current immunosuppressive therapy or cancer chemotherapy) or known acute or chronic renal disorders or active hepatitis.
12. Diabetic patients (controlled or uncontrolled).
13. Any systemic disease or disorder, complicating factor or structural abnormality that would negatively affect the conduct or outcome of the study (e.g., cleft palate (including repairs), Down Syndrome, and cranial-facial reconstruction).
14. Any current known or suspected infection requiring systemic antimicrobial therapy.
15. Use of prohibited medications or inadequate washout of any medication listed within the protocol.
16. Concomitant use of topical or oral analgesics (i.e., nonsteroidal anti-inflammatory (NSAID) and aspirin products) which may have anti-inflammatory effects. Patients on stable, prophylactic low dose aspirin therapy (≤ 81 mg per day) at the time of enrollment may have been enrolled and may have continued the low dose aspirin during the study. Use of acetaminophen was permitted during the trial.
17. Known or suspected allergy or hypersensitivity to quinolones or other ingredients present in the medications used in the study.
18. Patients who used hearing aids and were unwilling to discontinue their use during the study period.
19. Patients who used ear plugs, head phones or ear buds and were unwilling to discontinue their use during the study period.
20. Therapy with another investigational study medication or device within the 30 days prior to Visit 1.
21. Previous enrollment in any Alcon sponsored investigational drug trial for AL-60371 Otic Suspension.
22. More than 1 patient from the same family or household could not be enrolled into this study (or other AL-60371 study) at the same time.
23. Family or household members of site or Sponsor (or Designee) personnel directly involved in this study (or other AL-60371 study) could not be enrolled.

24. Anticipated change in the use of any medication during the study that may have affected the conduct or outcome of the study. Patients must have been stabilized on these medications for at least 30 days prior to the Visit 1 and continued on the same regimen throughout the study.
25. Additionally, the Medical Monitor may have declared any patient ineligible for enrollment for a sound medical reason.

Removal of Patients from Therapy or Assessment
Discontinuation from the study was defined as exiting the study after Visit 1 (Day 1) but prior to Visit 4 (Day 11), regardless of reason. For patients who discontinued from the study, all attempts were made to complete the early exit procedures.

Patients were discontinued from the study at any time if, in the opinion of the Investigator or the Alcon medical monitor, their continued participation posed a health risk. Additionally, at any time during the study, and for any reason, patients may have withdrawn their consent to continue participation. In general, patients were discontinued from the study for any of the following reasons:

- Lost to follow-up
- Treatment failure
- Study ear was culture positive at baseline for Group A Streptococci (GAS), or pure culture of fungi or yeast
- AE
- Patient decision unrelated to an AE
- Other

If the patients discontinued the study between visits, the Investigator attempted to contact the patient and requested their return for the early exit procedures. Patients who discontinued the study and who were unable or unwilling to return for the early exit procedures were instructed, whenever possible, to discontinue use of the study drug and to return the unused study drug to the Investigator.

Treatment Failures
Patients who showed no clinically relevant response to the study drug or who experienced worsening in the signs and/or symptoms of AOE (i.e., erythema, edema and/or tenderness) after at least 2 full days (i.e., 4 doses) of treatment may have been considered "treatment failures".

At Visit 2, the Investigator may have chosen to continue the patient in the study and review the patient's progress at the next scheduled visit. At Visit 3, however, if the patient continued to have signs and/or symptoms that required further treatment, the patient was considered a treatment failure and discontinued from the study; if the residual signs and symptoms did not require alternative therapy, the patient may have continued in the study and returned for Visit 4. At Visit 4, if the patient had residual signs and symptoms (even if the signs and/or symptoms resolved at Visit 3), the patient was classified in the statistical analysis as a treatment failure (i.e., outcome of "no" for clinical cure). However, because the patient completed Visit 4, the exit eCRF reflected that the patient completed the study.

Upon study discontinuation due to treatment failure, which could have occurred at any time during the study, a complete clinical examination including the collection of otic culture specimen(s) was required and any factors leading to the failure (e.g., water exposure to the enrolled ear(s)) were recorded in the comment section of the exit eCRF. Any alternative therapy prescribed for the treatment failure was noted as a comment on the source and eCRF. Worsening of the signs and/or symptoms that lead to or were associated with discontinuation from the study due to treatment failure should not have been reported as AEs.

Identity of Investigational Products
Both study drugs were supplied in identical opaque bottles with an attached label that included the kit and protocol numbers. The study drugs were labeled and shipped to the investigational sites by Alcon.

Study Drug	Lot Numbers	Formulation Identification Numbers
Finafloxacin	11-501299-1	119420
Vehicle	11-501282-1	118744

Criteria for Evaluation
Primary Efficacy Endpoint

- Proportion of patients with clinical cures at the Day 11 (Test of Cure) Visit
    - A clinical cure was attained if the sum of the numerical scores of the 3 signs and symptoms of AOE (tenderness, erythema, and edema) was 0 at Day 11 (TOC).

Secondary Efficacy Endpoints

- Proportion of patients with microbiological successes at the Day 11 (TOC) visit
    - Microbiological success was attained if all pre-therapy bacteria were absent from the exit otic specimen. The presence of fungi and/or yeast was not considered in the determination of microbiological success.
- Median time (in days) to cessation of ear pain as reported by the patient or parent/legal guardian via the telephone diary
    - Cessation of ear pain was defined as occurring on the first time point that ear pain was absent (morning or evening) and did not reoccur in any subsequent diary entries. Day 1 was the starting point for this time-to-event analysis.

Supportive Efficacy Endpoints

- Proportion of patients with overall clinical cures at Day 11 (the TOC visit)
  An overall clinical cure was attained if a patient was both a clinical cure and a microbiological success at the Day 11 (TOC) visit.
- Proportion of patients with sustained clinical cures at Days 3 and 8
  A sustained clinical cure was attained if the sum of the numerical scores of the 3 signs and symptoms of AOE was 0 at the visit of interest (Day 3 or Day 8) and remained 0 throughout the study.
- Proportion of patients with sustained cures for each of the individual signs and symptoms of AOE at Days 3 and 8

A sustained cure was attained if the numerical score for an individual sign or symptom was 0 at the visit of interest (Day 3 or Day 8) and remained 0 throughout the study.

- Proportion of patients with cures for each of the individual signs and symptoms of AOE at Day 11 (the TOC visit)
  A cure was attained at Day 11 if the numerical score for an individual sign or symptom was 0 at that visit.
- Median time (in days) to not taking pain medication as reported by the patient or parent / legal guardian via concomitant medication entries.
  Time to not taking pain medication for ear pain was defined as occurring on the first day that pain medication was not taken for ear pain with no additional use during the study (as reported by the patient or parent / legal guardian as part of the concomitant medications).

Statistical Methods
Determination of Sample Size
A 56% pathogen-positive rate observed at baseline was assumed based on previous Alcon AOE studies. Therefore, the sample size and power were based upon the enrollment of at least 500 patients (approximately 250 per treatment arm) in order to obtain at least 280 evaluable patients in the ITT analysis set who were pathogen positive at baseline (approximately 140 per treatment arm). These patient numbers, in combination with those from other studies, are expected to fulfill the requirement of patient exposure to Finafloxacin.

Based on previous Alcon data, the estimated clinical cure rate at the Day 11 visit in the Finafloxacin treatment group is 74%. With at least 280 patients in the ITT analysis set who are pathogen positive at baseline (approximately 140 per treatment arm), the study has approximately 90% power to detect a treatment difference of 20 percentage points in the clinical cure rate at the Day 11 visit (Finafloxacin compared with Vehicle).

Evaluability
Intent to Treat Population
The primary analysis set for all primary, secondary and supportive analyses was the pathogen positive subset of the ITT population. The pathogen positive subset of the ITT population was to include all patients who receive Study Medication and had cultures positive for *Pseudomonas aeruginosa* or *Staphylococcus aureus* at baseline in the study ear.

The overall ITT population and the subset of ITT patients who are culture positive at baseline will also be evaluated for the primary endpoint of clinical cures at Day 11 (TOC). Additionally, the culture positive subset of the ITT population will be evaluated for microbiological success and overall cures at Day 11 (TOC). The overall ITT population will also be evaluated for the time to cessation of ear pain and the time to not taking pain medication for ear pain.

Per Protocol Population
The PP population (as well as the pathogen positive and culture positive subsets) will be evaluated for the primary efficacy endpoint. Additionally, the culture positive and pathogen positive subsets of the PP population will be evaluated for microbiological success and overall cures at Day 11 (TOC).

Safety Population
All patients who are administered test article or potentially use test article will be evaluable for safety analyses.

Table 1
Definitions to Establish Culture Positive and Pathogen Positive Subsets of Patients

Term	Definition
Culture positive	A microbiological specimen from the enrolled ear(s) that contains 1 or more bacterial organism(s).
Pathogen	The following 2 organisms considered etiological agents of AOE will be considered pathogens: *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
Pathogen positive	A microbiological specimen from the enrolled ear(s) that contains at least 1 pathogen (as defined within this table).

Reviewer's Comment:
The primary analysis utilized the Pathogen Positive subset of the ITT population. However, the clinical review will focus on the Culture Positive subset of the ITT population, in order to consider all bacteria cultured.

Study Ear Definition

Hierarchical Order for Defining Study Ear	Enrolled Ear(s)	Culture Positive[a] Ear(s)	Pathogen Positive[b] Ear(s)	Study Ear Definition
1	Both[c]	Both	Both	The evaluable ear with the higher value for the sum of the numerical scores of tenderness, erythema and edema at baseline. If both ears were rated equally, the right ear was defined as the study ear.
2	Both[c]	Both	One	The pathogen positive ear
3	Both[c]	One	One	The pathogen positive ear
4	Both[c]	Both	Neither	The evaluable ear with the higher value for the sum of the numerical scores of tenderness, erythema and edema at baseline. If both ears were rated equally, the right ear was defined as the study ear.
5	Both[c]	One	Neither	The culture positive ear
6	Both[c]	Neither	Neither	The evaluable ear with the higher value for the sum of the numerical scores of tenderness, erythema and edema at baseline. If both ears were rated equally, the right ear was defined as the study ear.
7	One	One	One	The enrolled ear
8	One	One	Neither	The enrolled ear
9	One	Neither	Neither	The enrolled ear

[a] Culture Positive: a microbiological specimen from the enrolled ear(s) that contained 1 or more bacterial organism(s); this included all bacteria recovered at baseline
[b] Pathogen Positive: a microbiological specimen that contained at least 1 of the following organisms (considered etiological agents of AOE) in the enrolled ear(s) at baseline: *Pseudomonas aeruginosa* and/or *Staphylococcus aureus*
[c] Only the enrolled ear(s) that also met the baseline requirement for signs and symptoms were considered in the determination of study ear
Note: Patients with a baseline culture that was positive for GAS, pure culture yeast or fungi were exited from the study and were not considered in the subsets of culture -positive patients.

Primary Efficacy Analysis
The number and percent of patients who achieved clinical cure at Day 11 in the Finafloxacin and Vehicle groups were compared using a stratified Cochran-Mantel-Haenszel (CMH) test adjusted for the stratification variable of baseline otowick use.

Secondary Efficacy Analysis
The number and percent of patients who achieved microbiological success at Day 11 (TOC) was summarized overall and by treatment group. The microbiological success rates at Day 11 in the Finafloxacin and Vehicle groups were compared using a stratified CMH test adjusted for the stratification variable of baseline otowick use.

The median time to cessation of ear pain was summarized overall and by treatment group. The Cox proportional hazard model, including covariates for baseline otowick use and pain medication use, was employed to assess differences between the Finafloxacin and Vehicle groups in the time to cessation of ear pain. Survival curves were also generated.

Supportive Efficacy Analysis
For the overall, sustained, and Day 11 cure rates, a stratified CMH test was used to evaluate the treatment effects adjusted for the stratification variable of baseline otowick use.

The median time to no pain medication use was summarized overall and by treatment group. A Cox proportional hazard model with otowick use as a baseline covariate was used to assess differences between the Finafloxacin and Vehicle groups in the time to not taking pain medication for ear pain (i.e., the time to permanently discontinuing the use of pain medication among patients who used medication for ear pain at baseline). Survival curves were also generated.

Daily Diaries and AOE Treatment Satisfaction Questionnaires
A 2-sample t-test was used to investigate differences between treatment groups for each of the diary questions. Results for patients 12 years of age or younger and 13 years of age or older were evaluated separately and combined using the overall ITT data set.

Summary tables were generated overall and by treatment for the number and percent of responses in each category within the AOE-TSQ and Pediatric AOE-TSQ. Inferential analyses were performed as appropriate (CMH rank score test or chi-square test) to compare differences between responses in the Finafloxacin and Vehicle groups. Results of the AOE-TSQ and the Pediatric AOE-TSQ were summarized separately and were also combined using the overall ITT analysis set.

Safety Parameters
All reported AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and were presented for each treatment group by severity (mild, moderate, or severe) and relationship to the study drug.

Extent of exposure was calculated as days on therapy, which was defined as the difference in days between the date of last administration of study drug and the date on which study drug was first administered, plus 1.

6 Review of Efficacy

Efficacy Summary

6.1 Indication for Study C-10-018

For the treatment of acute otitis externa (AOE) in pediatric, adult and elderly patients

6.1.1 Methods

The description of the clinical trial design is contained in Section 5.3. Clinical study reports, clinical protocols and literature references were submitted related to the clinical trial in support of the New Drug Application.

6.1.2 Demographics

Table 6.1.2-1
Demographic Characteristics
Culture Positive Subset – ITT Population

Variables		Finafloxacin (N=311)	Vehicle (N=302)	Total (N=613)
Age (years)	Mean (SD)	31.2 (20.2)	31.9 (21.6)	31.5 (20.9)
	12 mo. – 13 years [a, b]	90 (28.9%)	100 (33.1%)	190 (30.1%)
	28 days – 23 months [a, b]	3 (1.0%)	2 (0.7%)	5 (0.8%)
	2 – 11 years	55 (17.7%)	70 (23.2%)	125 (20.4%)
	12 – 17 years	57 (18.3%)	40 (13.2%)	97 (15.8%)
	18 – 64 years	177 (56.9%)	165 (54.6%)	342 (55.8%)
	≥ 65 years	19 (6.1%)	25 (8.3%)	44 (7.2%)
Sex: n (%)	Male	135 (43.4%)	139 (46.0%)	274 (44.7%)
	Female	176 (56.6%)	163 (54.0%)	339 (55.3%)
Race: n (%)	White	270 (86.8%)	249 (82.5%)	519 (84.7%)
	Black or African American	17 (5.5%)	17 (5.6%)	34 (5.5%)
	Asian	2 (0.6%)	10 (3.3%)	12 (2.0%)
	Native Hawaiian	0	0	0
	American Indian	4 (1.3%)	1 (0.3%)	5 (0.8%)
	Other	4 (1.3%)	6 (2.0%)	10 (1.6%)
	Multi-racial	14 (4.5%)	19 (6.3%)	33 (5.4%)
Ethnicity: n (%)	Hispanic, Latino or Spanish	106 (34.1%)	105 (34.8%)	211 (34.4%)
	Not Hispanic, Latino or Spanish	205 (65.9%)	197 (65.2%)	402 (65.6%)
Source: Table 14.1.1-7				

a This is the age bracket specified in the Pediatric Written Request for Finafloxacin.
b Patients under 6 months of age were not enrolled. The youngest patient evaluable for Finafloxacin Otic Suspension 0.3% was 11 months old and for Finafloxacin Vehicle was 9 months old.
b Patients in the ITT population

Reviewer's Comment:
Patient demographics were well-balanced across the treatment groups at baseline.

Table 6.1.2-2
Baseline Characteristics of the Study Ear Culture Positive Subset – ITT Population

Baseline Characteristics		Finafloxacin (N=311)	Vehicle (N=302)	Total (N=613)
Tenderness	None	3 (1.0%)	3 (1.0%)	6 (1.0%)
	Mild	57 (18.3%)	51 (16.9%)	108 (17.6%)
	Moderate	196 (63.0%)	187 (61.9%)	383 (62.5%)
	Severe	55 (17.7%)	61 (20.2%)	116 (18.9%)
Erythema	None	1 (0.3%)	2 (0.7%)	3 (0.5%)
	Mild	79 (25.4%)	78 (25.8%)	157 (25.6%)
	Moderate	189 (60.8%)	190 (62.9%)	379 (61.8%)
	Severe	42 (13.5%)	32 (10.6%)	74 (12.1%)
Edema	None	11 (3.5%)	4 (1.3%)	15 (2.4%)
	Mild	186 (59.8%)	202 (66.9%)	388 (63.3%)
	Moderate	85 (27.3%)	71 (23.5%)	156 (25.4%)
	Severe	29 (9.3%)	25 (8.3%)	54 (8.8%)
Ear Cleansing	Suction	11 (12.9%)	7 (8.0%)	18 (10.5%)
	Dry Mop	53 (62.4%)	59 (67.8%)	112 (65.1%)
	Lavage	17 (20.0%)	15 (17.2%)	32 (18.6%)
	Suction and Dry Mop	4 (4.7%)	6 (6.9%)	10 (5.8%)
	Suction and Lavage	0	0	0
	Dry Mop and Lavage	0	0	0
	Suction, Dry Mop, and Lavage	0	0	0
	Total Assessed	85 (100.0%)	87 (100.0%)	172 (100.0%)
	Not Required	226	215	441
	Not Assessed	0	0	0
Otowick Use	No Wick	221 (71.1%)	216 (71.5%)	437 (71.3%)
	Inserted at BL visit	90 (28.9%)	86 (28.5%)	176 (28.7%)
BL Otowick Use Status	No BL Otowick Use	223 (71.7%)	215 (71.2%)	438 (71.5%)
	BL Otowick Use	88 (28.3%)	87 (28.8%)	175 (28.5%)
Duration of Current Episode	Up to 7 Days	234 (75.2%)	228 (75.5%)	462 (75.4%)
	8 to 14 Days	55 (17.7%)	50 (16.6%)	105 (17.1%)

Baseline Characteristics		Finafloxacin (N=311)	Vehicle (N=302)	Total (N=613)
	15 to 21 Days	16 (5.1%)	20 (6.6%)	36 (5.9%)
	22 to 28 Days	6 (1.9%)	4 (1.3%)	10 (1.6%)
	> 28 Days	0	0	0
	Mean (SD)	6.1 (5.5)	6.0 (5.3)	6.1 (5.4)
Source: Tables 14.1.2-15, 14.1.2-16, 14.1.2-17				

Reviewer's Comment:
Baseline characteristics of the study ear were well-balanced across the treatment groups.

Table 6.1.2-3
All Pre-Therapy Isolates by Treatment Group
Culture Positive Subset – ITT Population

Pre-therapy Isolates [a]	Finafloxacin	Vehicle
Total Isolates All Categories	767	754
Gram Positive Bacteria	**581 (75.8%)**	**548 (72.7%)**
Corynebacteriaceae		
Corynebacterium amycolatum	10	7
Corynebacterium auris	6	5
Corynebacterium species	24	37
Turicella otitidis	71	65
Enterococcaceae		
Enterococcus faecalis	22	18
Micrococcaceae		
Micrococcus species	5	1
Staphylococcaceae		
Staphylococcus aureus	67	52
Staphylococcus auricularis	85	73
Staphylococcus capitis	58	73
Staphylococcus caprae	21	14
Staphylococcus epidermidis	112	113
Staphylococcus haemolyticus	8	8
Staphylococcus hominis	4	11
Staphylococcus lugnunensis	4	6
Staphylococcus species	11	16
Staphylococcus warneri	14	4
Streptococcaceae		
Streptococcus agalactiae	6	2
Streptococcus species	5	1
Gram Negative Bacteria	**168 (21.9%)**	**182 (24.1%)**
Enterobacteriaceae		
Escherichia coli	6	8
Klebsiella pneumoniae	6	9
Proteus mirabilis	8	5
Pseudomonadaceae		
Pseudomonas aeruginosa	102	123
Xanthomonodaceae		
Stenotrophomonas maltophilia	8	1

Pre-therapy Isolates [a]	Finafloxacin	Vehicle
Yeast		
Candida parapsilosis	8	11
Source: Table 14.2-60		

a Listing of bacterial organisms present in ≥ 5 isolates pre-therapy in either treatment group.

6.1.3 Subject Disposition

Table 6.1.3-1
Subject Disposition
All Randomized Subjects

Subject Disposition	Finafloxacin (N=347)	Vehicle (N=346)
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%)
Reasons for Discontinuation		
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.

Reviewer's Comment:
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.

Protocol Deviations
Forty-eight patients were excluded from the PP analysis set. The reasons for exclusion of these patients were associated with the following deviations:

- Otowick use at baseline – 35 patients
  An otowick was not inserted when clinical criteria were met, an otowick was inserted when clinical criteria were not met, or the patient was randomized into the incorrect wick/no wick strata
- Exclusion criteria – 7 patients
- Inclusion criteria – 3 patients
- Dosing of study drug for 9 days – 3 patients

Specific visits or ears were excluded from the PP analyses for the following deviations:

- Use of a concomitant medication – 2 patients
- Protocol violation (baseline otowick use) – 4 patients
- Visit out of window – 46 patients

6.1.4 Analysis of Primary Endpoint(s)

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 included 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 [a]	p value [b]
Pathogen Positive Subset - PMITT					
Day 11 n/N (%)	**104/145 (71.7%)**	**46/138 (33.3%)**	**38.4**	**(27.6, 49.1)**	**<0.0001**

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

Reviewer's Comment:
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.

Sensitivity Analysis

This sensitivity analyses presented below include the ITT population (all randomized patients) and PP population (all randomized patients without major protocol deviations) as well as the culture positive subsets of both populations which included patients who received study medication and had cultures positive for one or more bacterial organisms at baseline in the study ear.

Table 6.1.4-2
Primary Efficacy - Clinical Cures at Day 11 (TOC)

	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b]
ITT Population					
Day 11 n/N (%)	**245/418 (71.2%)**	**173/418 (50.6%)**	**20.6**	**(13.5, 27.8)**	**<0.0001**
PP Population					
Day 11 n/N (%)	**215/371 (71.9%)**	**156/371 (50.0%)**	**21.9**	**(14.4, 29.4)**	**<0.0001**

Source Tables 14.2-16, 14.2-28
a 95% confidence interval based on a non-stratified analysis; b Test = stratified CMH

Reviewer's Comment:

Finafloxacin was also superior to vehicle in the proportion of patients who achieved clinical cure at Day 11 (TOC visit) in the ITT and PP populations. The treatment group differences were statistically significant in both comparisons and similar to that seen in the pathogen- and culture-positive subpopulations.

In actual clinical use, finafloxacin will most often be prescribed for patients with the constellation of signs and symptoms of acute otitis externa without first obtaining a culture. Analysis of the ITT population provides efficacy information for this clinical setting. Thus, finafloxacin should be efficacious when prescribed in the absence of a prior culture.

Table 6.1.4-3
Primary Efficacy - Clinical Cures at Day 11 (TOC)
Culture Positive Subset

	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b]
Culture Positive Subset - MITT					
Day 11 n/N (%)	**226/380 (72.7%)**	**154/380 (51.0%)**	**21.7**	**(14.2, 29.2)**	**<0.0001**
Culture Positive Subset - MPP					
Day 11 n/N (%)	**197/338 (73.2%)**	**141/338 (50.7%)**	**22.5**	**(14.6, 30.4)**	**<0.0001**

Source CSR Tables 14.2-22, 14.2-30
a 95% confidence interval based on a non-stratified analysis; b Test = stratified CMH

Reviewer's Comment:
Finafloxacin was also superior to vehicle in the proportion of patients who achieved clinical cure at Day 11 (TOC visit) in the culture positive subsets of the ITT and PP populations. The treatment group differences were statistically significant in both comparisons and similar to that seen in the pathogen positive subset of the ITT population.

6.1.5 Analysis of Secondary Endpoints(s)

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 [a]	p value [b, c]
Pathogen Positive Subset - PMITT					
Day 11 n/N (%)	**97/145 (66.9%)**	**18/138 (13.0%)**	**53.9**	**(44.4, 63.4)**	**<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.

Reviewer's Comment:
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.

Sensitivity Analysis
This sensitivity analysis utilized the culture positive subset of the ITT and PP populations which included all patients who received study medication and had cultures positive for one or more bacterial organisms at baseline in the study ear.

Table 6.1.5-2
Secondary Efficacy - Microbiological Success at Day 11 (TOC)
Culture Positive Subset

	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b]
Culture Positive Subset - MITT					
Day 11 n/N (%)	**189/239 (60.8%)**	**50/239 (16.6%)**	**44.2**	**(37.4, 51.1)**	**<0.0001**
Culture Positive Subset - MPP					
Day 11 n/N (%)	**160/206 (59.5%)**	**46/206 (16.5%)**	**42.9**	**(35.6, 50.2)**	**<0.0001**

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

Reviewer's Comment:
Though the vehicle group cure rate was larger by approximately 10 points in the pathogen positive ITT, the finafloxacin group was also superior to the vehicle group in the proportion of patients who achieved microbiological success at Day 11 (TOC visit) in the culture positive subsets of the ITT and PP populations. The treatment group differences were statistically significant in both comparisons.

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 [b]
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

Reviewer's Comment:
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.

6.1.6 Other Endpoints

One supportive efficacy endpoint was overall clinical cures at Day 11. An overall clinical cure was attained if the patient achieved both clinical cure and microbiological success at Day 11.

Table 6.1.6-1
Supportive Efficacy – Overall Clinical Cures at Day 11 (TOC)
ITT Population – Pathogen Positive Subset

	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b, c]
Pathogen Positive Subset - PMITT					
Day 11 n/N (%)	**81/145 (55.9%)**	**12/138 (8.7%)**	**47.2**	**(37.8, 56.5)**	**<0.0001**

a 95% confidence interval based on a non-stratified analysis; **b** p-value based on a stratified CMH.

Reviewer's Comment:
The proportion of patients who achieved an overall clinical cure 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.

Sensitivity Analysis
This sensitivity analysis utilized the culture positive subset of the ITT and PP populations which included all patients who received study medication and had cultures positive for one or more bacterial organisms at baseline in the study ear.

Table 6.1.6-2
Secondary Efficacy – Overall Cures at Day 11 (TOC)
Culture Positive Subset

	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b]
Culture Positive Subset - MITT					
Day 11 n/N (%)	**161/200 (51.8%)**	**39/200 (12.9%)**	**38.9**	**(32.1, 45.6)**	**<0.0001**
Culture Positive Subset - MPP					
Day 11 n/N (%)	**135/172 (50.2%)**	**37/172 (13.3%)**	**36.9**	**(29.7, 44.1)**	**<0.0001**

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

Reviewer's Comment:
Though the treatment group differences (point estimates) were approximately 10 points smaller, finafloxacin was also superior to vehicle in the proportion of patients who achieved overall cures at Day 11 (TOC visit) in the Culture Positive subsets of the ITT and PP populations. The treatment group differences were statistically significant in both comparisons.

6.1.7 Subpopulations

Table 6.1.7-1
Efficacy by Baseline Otowick Use and Treatment
ITT Population – Culture Positive Subset

	Finafloxacin	Vehicle	Delta	95% CI
Clinical Cures at Day 11 (TOC)				
BL Otowick Use	56/88 (63.6%)	38/87 (43.7%)	20.0	(5.5, 34.4)
No BL Otowick Use	170/223 (76.2%)	116/215 (54.0%)	22.3	(13.6, 31.0)
Microbiological Success at Day 11 (TOC)				
BL Otowick Use	54/88 (61.4%)	20/87 (23.0%)	38.4	(24.9, 51.9)
No BL Otowick Use	135/223 (60.5%)	30/215 (14.0%)	46.6	(38.7, 54.5)

Source: Table 14.2-23, 14.2-25 and 14.2-27

Reviewer's Comment:

The finafloxacin group was consistently superior to the vehicle group regardless of baseline otowick use. The patients who had no baseline otowick use were numerically superior in the Clinical Cure at Day 11 (TOC) and Overall Cure at Day 11 (TOC). Patients with baseline otowick use had a slightly higher proportion of patients with microbiological success compared to those with no baseline otowick use.

Pediatric Efficacy

A Pediatric Written Request was issued for finafloxacin in the treatment of acute otitis externa on February 22, 2013. The written request specified that pediatric patients aged 1 to 13 years be enrolled. Efficacy data for this pediatric subpopulation is reviewed here.

Table 6.1.7-2
Clinical Cures at Day 11 (TOC)

Age	Finafloxacin	Vehicle	Delta
Pathogen Positive Subset - ITT			
< 1 year	0	0	---
1 – 13 years	37 / 47 (78.7%)	10 / 47 (21.3%)	57.4
> 13 years	67 / 98 (68.4%)	36 / 91 (39.6%)	28.8
Age	**Finafloxacin**	**Vehicle**	**Delta**
Culture Positive Subset - ITT			
< 1 year	1 / 1 (100.0%)	1 / 1 (100.0%)	---
1 – 13 years	69 / 83 (83.1%)	38 / 88 (43.2%)	40.0
> 13 years	156 / 227 (68.7%)	115 / 213 (54.0%)	14.7

Source: NDA 206307 SDN007 submitted August 11, 2014; Efficacy Information Amendment.

Table 6.1.7-3
Microbiological Success at Day 11 (TOC)

Age	Finafloxacin	Vehicle	Delta
Pathogen Positive Subset - ITT			
< 1 year	0	0	---
1 – 13 years	32 / 47 (68.1%)	1 / 47 (2.1%)	66.0
> 13 years	65 / 98 (66.3%)	17 / 91 (18.7%)	47.6
Culture Positive Subset - ITT			
< 1 year	1 / 1 (100.0%)	1 / 1 (100.0%)	---
1 – 13 years	56 / 83 (67.5%)	10 / 88 (11.4%)	56.1
> 13 years	132 / 227 (58.1%)	39 / 213 (18.3%)	39.8

Source: NDA 206307 SDN007 submitted August 11, 2014; Efficacy Information Amendment.

Reviewer's Comment:
In pediatric patients aged 1-13 years, finafloxacin was numerically superior to vehicle in the proportion of patients who achieved clinical cure, microbiological success and overall cure at Day 11 (TOC visit) in both the pathogen positive and culture positive subsets of the ITT population.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No evidence of tolerance or withdrawal effects has been detected in this trial or in previous trials with finafloxacin otic suspension.

6.1.10 Additional Efficacy Issues/Analyses

Refer to Section 6.2.10 for a pooled analysis of Clinical Cures at Day 11, the Test-of-Cure visit by baseline pathogen in the study ear.

6.2 Indication for Study C-10-019

For the treatment of acute otitis externa (AOE) in pediatric, adult and elderly patients

6.2.1 Methods

The description of the clinical trial design is contained in Section 5.3. Clinical study reports, clinical protocols and literature references were submitted related to the clinical trial in support of the New Drug Application.

6.2.2 Demographics

Table 6.2.2-1
Demographic Characteristics
Culture Positive Subset - ITT Population

Variables		Finafloxacin (N=239)	Vehicle (N=241)	Total (N=480)
Age (years)	Mean (SD)	19.0 (15.6)	19.7 (15.7)	19.3 (15.6)
	12 mo. – 13 years [a, b]	158 (66.1%)	147 (60.1%)	305 (63.5%)
	2 – 11 years	106 (44.4%)	102 (42.3%)	208 (43.3%)
	12 – 17 years	52 (21.8%)	55 (22.8%)	107 (22.3%)
	18 – 64 years	75 (31.4%)	80 (33.2%)	155 (32.3%)
	≥ 65 years	6 (2.5%)	3 (1.2%)	9 (1.9%)
Sex: n (%)	Male	108 (45.2%)	89 (36.9%)	197 (41.0%)
	Female	131 (54.8%)	152 (63.1%)	283 (59.0%)
Race: n (%)	White	205 (85.8%)	195 (80.9%)	400 (83.3%)
	Black or African American	22 (9.2%)	32 (13.3%)	54 (11.3%)
	Asian	2 (0.8%)	3 (1.2%)	5 (1.0%)
	Native Hawaiian	1 (0.4%)	1 (0.4%)	2 (0.4%)
	American Indian	5 (2.1%)	1 (0.4%)	6 (1.3%)
	Other	2 (0.8%)	5 (2.1%)	7 (1.5%)
	Multi-racial	2 (0.8%)	4 (1.7%)	6 (1.3%)
Ethnicity: n (%)	Hispanic, Latino or Spanish	66 (27.6%)	60 (24.9%)	126 (26.3%)
	Not Hispanic, Latino or Spanish	173 (72.4%)	181 (75.1%)	354 (73.8%)
Source: Table 14.1.1-7				

a Patients under 6 months of age were not enrolled. The youngest patient evaluable for Finafloxacin Otic Suspension 0.3% was 2 years old and for Finafloxacin Vehicle was 11 months old. This is the age bracket specified in the Pediatric Written Request for Finafloxacin.
b Patients in the ITT population

Reviewer's Comment:
Patient demographics were well balanced across the treatment groups at baseline.

Table 6.2.2-2
Baseline Characteristics of the Study Ear
ITT Population – Culture Positive Subset

Baseline Characteristics		Finafloxacin (N=239)	Vehicle (N=241)	Total (N=480)
Tenderness	None	0	1 (0.4%)	1 (0.2%)
	Mild	41 (17.2%)	29 (12.0%)	70 (14.6%)
	Moderate	153 (64.0%)	188 (78.0%)	341 (71.0%)
	Severe	45 (18.8%)	23 (9.5%)	68 (14.2%)
Erythema	None	3 (1.3%)	2 (0.8%)	5 (1.0%)
	Mild	57 (23.8%)	74 (30.7%)	131 (27.3%)
	Moderate	166 (69.5%)	155 (64.3%)	321 (66.9%)
	Severe	13 (5.4%)	10 (4.1%)	23 (4.8%)
Edema	None	3 (1.3%)	2 (0.8%)	5 (1.0%)
	Mild	182 (76.2%)	183 (75.9%)	365 (76.0%)
	Moderate	46 (19.2%)	51 (21.2%)	97 (20.2%)
	Severe	8 (3.3%)	5 (2.1%)	13 (2.7%)
Ear Cleansing	Suction	9 (15.5%)	7 (14.9%)	16 (15.2%)
	Dry Mop	39 (67.2%)	30 (63.8%)	69 (65.7%)
	Lavage	10 (17.2%)	9 (19.1%)	19 (18.1%)
	Suction and Dry Mop	0	0	0
	Suction and Lavage	0	0	0
	Dry Mop and Lavage	0	1 (2.1%)	1 (1.0%)
	Suction, Dry Mop, and Lavage	0	0	0
	Total Assessed	58 (100.0%)	47 (100.0%)	105 (100.0%)
	Not Required	181	193	374
	Not Assessed	0	0	0
Otowick Use	No Wick	201 (84.1%)	203 (84.2%)	404 (84.2%)
	Inserted at BL visit	38 (15.9%)	38 (15.8%)	76 (15.8%)
BL Otowick Use Status	No BL Otowick Use	202 (84.2%)	202 (84.5%)	404 (84.2%)
	BL Otowick Use	37 (15.5%)	39 (16.2%)	76 (15.8%)
Duration of Current Episode	Up to 7 Days	206 (86.2%)	203 (84.2%)	409 (85.2%)
	8 to 14 Days	22 (9.2%)	25 (10.4%)	47 (9.8%)
	15 to 21 Days	9 (3.8%)	11 (4.6%)	20 (4.2%)
	22 to 28 Days	2 (0.8%)	2 (0.8%)	4 (0.8%)
	> 28 Days	0	0	0
	Mean (SD)	4.6 (4.1)	4.9 (4.7)	4.8 (4.4)
Source: Tables 14.1.2-15, 14.1.2-16, 14.1.2-17				

Reviewer's Comment:
Baseline characteristics of the study ear were well balanced across the treatment groups at baseline.

6.2.3 Subject Disposition

Table 6.2.3-1
Subject Disposition
All Randomized Subjects

Subject Disposition	Finafloxacin (N=274)	Vehicle (N=275)
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
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%)
Reasons for Discontinuation		
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.

Reviewer's Comment:
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.

Protocol Deviations

Fifty-four patients were excluded from the PP analysis set. The reasons for exclusion of these patients were associated with the following deviations:

- Otowick use at baseline – 42 patients
  An otowick was not inserted when clinical criteria were met, an otowick was inserted when clinical criteria were not met, or the patient was randomized into the incorrect wick/no wick strata
- Exclusion criteria – 3 patients
  More than 1 patient was enrolled from the same household (a deviation reported for 2 patients) or the patient was enrolled despite the medical monitor's declaration of ineligibility (a deviation reported for 1 patient)
- Study drug used for entire study (14 days) – 3 patients
- Concomitant use of antibiotics – 2 patients
- Concomitant use of steroids – 2 patients
- Incorrect study drug dispensed – 2 patients

Specific visits or ears were excluded from the PP analyses for the following deviations:

- Concomitant use of antibiotics – 2 patients
- Concomitant use of ibuprofen – 2 patients (1 at Day 8 and 1 at Day 11)
- Visit out of window – 5 patients (all at Day 8)
- Otowick use at baseline – 8 patient ears (5 right ears, 3 left ears)
  An otowick was not inserted when clinical criteria was met, an otowick was inserted when clinical criteria were not met, or the patient was randomized into the incorrect wick/no wick strata

6.2.4 Analysis of Primary Endpoint(s)

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 will include 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 [a]	p value [b]
Pathogen Positive Subset - PMITT					
Day 11 n/N (%)	**101/147 (68.7%)**	**52/130 (40.0%)**	**28.7**	**(17.4, 40.0)**	**<0.0001**

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

Reviewer's Comment:
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.

Sensitivity Analysis

This sensitivity analyses presented below include the ITT population (all randomized patients) and PP population (all randomized patients without major protocol deviations) as well as the culture positive subsets of both populations which included patients who received study medication and had cultures positive for one or more bacterial organisms at baseline in the study ear.

Table 6.2.4-2
Primary Efficacy - Clinical Cures at Day 11 (TOC)

	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b]
ITT Population					
Day 11 n/N (%)	**245/418 (71.2%)**	**173/418 (50.6%)**	**20.6**	**(13.5, 27.8)**	**<0.0001**
PP Population					
Day 11 n/N (%)	**215/371 (71.9%)**	**156/371 (50.0%)**	**21.9**	**(14.4, 29.4)**	**<0.0001**

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

Reviewer's Comment:

Finafloxacin was also superior to vehicle in the proportion of patients who achieved clinical cure at Day 11 (TOC visit) in the ITT and PP populations. The treatment group differences were statistically significant in both comparisons and similar to that seen in the pathogen- and culture-positive subpopulations. In actual clinical use, finafloxacin will most often be prescribed for patients with the constellation of signs and symptoms of acute otitis externa without first obtaining a culture. Analysis of the ITT population provides efficacy information for this clinical setting. Thus, finafloxacin should be efficacious when prescribed in the absence of a prior culture.

Table 6.2.4-3
Primary Efficacy - Clinical Cures at Day 11 (TOC)
Culture Positive Subset

	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b]
Culture Positive Subset - MITT					
Day 11 n/N (%)	**170/239 (71.1%)**	**112/241 (46.5%)**	**24.7**	**(16.2, 33.2)**	**<0.0001**
Culture Positive Subset - MPP					
Day 11 n/N (%)	**156/217 (71.9%)**	**103/259 (47.7%)**	**24.2**	**(15.3, 33.2)**	**<0.0001**

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

Reviewer's Comment:
Finafloxacin was also superior to vehicle in the proportion of patients who achieved clinical cure at Day 11 (TOC visit) in the culture positive subsets of the ITT and PP populations. The treatment group differences were statistically significant in both comparisons and similar to that seen in the pathogen positive subset of the ITT population.

6.2.5 Analysis of Secondary Endpoints(s)

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 [a]	p value [b, c]
Pathogen Positive Subset - PMITT					
Day 11 n/N (%)	**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.

Reviewer's Comment:
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.

Sensitivity Analysis

This sensitivity analysis utilized the culture positive subset of the ITT and PP populations which included all patients who received study medication and had cultures positive for one or more bacterial organisms at baseline in the study ear.

Table 6.2.5-2
Secondary Efficacy - Microbiological Success at Day 11 (TOC)
Culture Positive Subset

	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b]
Culture Positive Subset - MITT					
Day 11 n/N (%)	**155/239 (64.9%)**	**41/241 (17.0%)**	**47.8**	**(40.2, 55.5)**	**<0.0001**
Culture Positive Subset - MPP					
Day 11 n/N (%)	**143/217 (65.9%)**	**35/216 (16.2%)**	**49.7**	**(41.7, 57.7)**	**<0.0001**

a 95% confidence interval based on a non-stratified analysis; b Unadjusted p-value based on a stratified CMH

Reviewer's Comment:

Finafloxacin was also superior to vehicle in the proportion of patients who achieved microbiological success at Day 11 (TOC visit) in the culture positive subsets of the ITT and PP populations. The treatment group differences were statistically significant in both comparisons.

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 [a]
Median (SE)	**3.0 (0.2)**	**6.5 (0.3)**	**<0.0001**
Mean	4.0	7.0	
Min, Max	(1.0, 13.0)	(1.5, 12.5)	

a Adjusted, Cox proportional hazard model for treatment comparison.

Reviewer's Comment:

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.

6.2.6 Other Endpoints

A supportive efficacy endpoint was overall clinical cures at Day 11. An overall clinical cure was attained if the patient achieved both clinical cure and microbiological success at Day 11.

Table 6.2.6-1
Supportive Efficacy – Overall Clinical Cures at Day 11 (TOC)
ITT Population – Pathogen Positive Subset

	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b, c]
Pathogen Positive Subset - PMITT					
Day 11 n/N (%)	**78/147 (53.1%)**	**15/130 (11.5%)**	**41.5**	**(31.8, 51.3)**	**<0.0001**

a 95% confidence interval based on a non-stratified analysis; **b** p-value based on a stratified CMH.

Reviewer's Comment:
The proportion of patients who achieved an overall clinical cure 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.

Sensitivity Analysis
This sensitivity analysis utilized the culture positive subset of the ITT and PP populations which included all patients who received study medication and had cultures positive for one or more bacterial organisms at baseline in the study ear.

Table 6.1.6-2
Secondary Efficacy – Overall Cures at Day 11 (TOC)
Culture Positive Subset

	Finafloxacin	Vehicle	Delta	95% CI [a]	p value [b]
Culture Positive Subset - MITT					
Day 11 n/N (%)	**125/239 (52.3%)**	**31/241 (12.9%)**	**39.4**	**(31.8, 47.1)**	**<0.0001**
Culture Positive Subset - MPP					
Day 11 n/N (%)	**117/217 (53.9%)**	**25/216 (11.6%)**	**42.3**	**(34.5, 50.2)**	**<0.0001**

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

Reviewer's Comment:
Finafloxacin was also superior to vehicle in the proportion of patients who achieved overall cures at Day 11 (TOC visit) in the culture positive subsets of the ITT and PP populations. The treatment group differences were statistically significant in both comparisons and similar to that observed with the pathogen positive subset of the ITT population.

6.2.7 Subpopulations

Table 6.2.7-1
Efficacy by Baseline Otowick Use and Treatment
ITT Population – Culture Positive Subset

	Finafloxacin	Vehicle	Delta	95% CI
Clinical Cures at Day 11 (TOC)				
BL Otowick Use	25/37 (67.6%)	17/39 (43.6%)	24.0	(2.3, 45.7)
No BL Otowick Use	145/202 (71.8%)	95/202 (47.0%)	24.8	(15.5, 34.0)
Microbiological Success at Day 11 (TOC)				
BL Otowick Use	29/37 (78.4%)	6/39 (15.4%)	63.0	(45.6, 80.4)
No BL Otowick Use	126/202 (62.4%)	35/202 (17.3%)	45.0	(36.6, 53.5)

Source: Table 14.2-23, 14.2-25 and 14.2-27

Reviewer's Comment:
The Finafloxacin group was consistently numerically superior to the Vehicle group regardless of baseline otowick use.

Pediatric Efficacy

A Pediatric Written Request was issued for finafloxacin in the treatment of acute otitis externa on February 22, 2013. The written request specified that pediatric patients aged 1 to 13 years be enrolled. Efficacy data for this pediatric subpopulation is reviewed here.

Table 6.2.7-2
Clinical Cures at Day 11 (TOC)

Age	Finafloxacin	Vehicle	Delta
Pathogen Positive Subset - ITT			
< 1 year	0	0	---
1 – 13 years	66 / 99 (66.7%)	34 / 81 (42.0%)	24.7
> 13 years	35 / 48 (72.9%)	18 / 49 (36.7%)	36.2
Age	**Finafloxacin**	**Vehicle**	**Delta**
Culture Positive Subset - ITT			
< 1 year	0	1 / 1 (100.0%)	---
1 – 13 years	96 / 132 (72.7%)	54 / 127 (42.5%)	30.2
> 13 years	74 / 107 (69.2%)	57 / 113 (50.4%)	18.7

Source: NDA 206307 SDN007 submitted August 11, 2014; Efficacy Information Amendment.

Table 6.2.7-3
Microbiological Success at Day 11 (TOC)

Age	Finafloxacin	Vehicle	Delta
Pathogen Positive Subset - ITT			
< 1 year	0	0	---
1 – 13 years	63 / 99 (63.6%)	10 / 81 (12.3%)	51.3
> 13 years	34 / 48 (70.8%)	5 / 49 (10.2%)	60.6
Culture Positive Subset - ITT			
< 1 year	0	1 / 1 (100.0%)	---
1 – 13 years	86 / 132 (65.2%)	19 / 127 (15.0%)	50.2
> 13 years	69 / 107 (64.5%)	21 / 113 (18.6%)	45.9

Source: NDA 206307 SDN007 submitted August 11, 2014; Efficacy Information Amendment.

Reviewer's Comment:
Finafloxacin was numerically superior to vehicle in the proportion of patients who achieved clinical cure, microbiological success and overall cure at Day 11 (TOC visit) in both the Pathogen Positive and Culture Positive subsets of the ITT population.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

No evidence of tolerance or withdrawal effects has been detected in this trial or in previous trials with latanoprost ophthalmic solution.

6.2.10 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 (%)
Bacillus cereus	6	3 (50.0%)	3	2 (66.7%)
Corynebacterium amycolatum	12	6 (50.0%)	10	6 (60.0%)
Corynebacterium auris	16	13 (81.3%)	8	3 (37.5%)
Enterococcus casseliflavus	5	4 (80.0%)	0	---

Organism	Finafloxacin N=550		Vehicle N=543	
	Total N	Clinical Cures n (%)	Total N	Clinical Cures n (%)
Enterococcus faecalis	28	15 (53.6%)	20	10 (50.0%)
Micrococcus species	7	6 (85.7%)	2	0 (0.0%)
Staphylococcus aureus [a]	**82**	**56 (98.3%)**	**71**	**29 (40.8%)**
Staphylococcus auricularis	101	78 (77.2%)	92	63 (68.5%)
Staphylococcus capitis	60	43 (71.7%)	83	45 (54.2%)
Staphylococcus caprae	27	25 (92.6%)	36	22 (61.1%)
Staphylococcus epidermidis	157	108 (68.8%)	155	75 (48.4%)
Staphylococcus haemolyticus	13	8 (61.5%)	10	5 (50.0%)
Staphylococcus hominis	8	6 (75.0%)	14	8 (57.1%)
Staphylococcus lugdunensis	7	4 (57.1%0	10	3 (30.0%)
Staphylococcus pasteuri	5	5 (100.0%)	3	2 (66.7%)
Staphylococcus simulans	5	3 (60.0%)	6	3 (50.0%)
Staphylococcus warneri	21	16 (76.2%)	9	7 (77.8%)
Streptococcus agalactiae	6	2 (33.3%)	3	2 (66.7%)
Streptococcus mitis	9	8 (88.9%)	12	4 (33.3%)
Streptococcus species	8	7 (87.5%)	7	5 (71.4%)
Turicella otitidis	119	86 (72.3%)	131	77 (58.8%)
Achromobacter xylosoxidans	5	4 (80.0%)	4	1 (25.0%)
Escherichia coli	9	6 (66.7%)	8	2 (25.0%)
Klebsiella pneumonia	7	4 (57.1%)	11	2 (18.2%)
Proteus mirabilis	11	8 (72.7%)	7	4 (57.1%)
Pseudomonas aeruginosa [a]	**230**	**163 (70.9%)**	**219**	**76 (34.7%)**
Stenotrophomonas maltophilia	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 sponsor 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 ≥ 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 (%)
Corynebacterium auris	9	8 (88.9%)	4	2 (50.0%)
Staphylococcus capitis	45	33 (73.3%)	63	36 (57.1%)
Staphylococcus caprae	16	14 (87.5%)	21	15 (71.4%)
Staphylococcus epidermidis	91	66 (72.5%)	92	51 (55.4%)
Staphylococcus warneri	13	10 (76.9%)	8	6 (75.0%)
Turicella otitidis	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

Reviewer's Comment:

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%).*

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 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
Safety and Efficacy Study (Confirmatory) **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 ≥ 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	• Finafloxacin 0.3% (N=344) • Vehicle (N=342)	• Extent of exposure • Adverse events
Safety and Efficacy Study (Confirmatory) **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 ≥ 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	• Finafloxacin 0.3% (N=274) • Vehicle (N=274)	• Extent of exposure • Adverse events
PK Study **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)	• Extent of exposure • Adverse events • Vital signs (P, BP) • External ear examination • EKG • Clinical laboratory tests

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)	• Finafloxacin 0.3%, 4 drops with otowick (N=12) • Finafloxacin 0.3% 4 drops without otowick (N=12) • Finafloxacin 0.3% 8 drops with otowick (N=12)	• Extent of exposure • Adverse events

7.1.2 Categorization of Adverse Events

The routine clinical testing required to establish the safety of topical otic drops were adequately addressed in the design and conduct of this clinical trial.

All adverse events were coded using a MedDRA dictionary and received independent causality assessments from the Investigator and the Medical Monitor.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Because of the small number of reported adverse events in the clinical studies, events were pooled for Studies C-10-018 and C-10-019.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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

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

AL-60371 = finafloxacin, free base AL-60371A = finafloxacin, 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). Finafloxacin otic suspension, 0.3%; Finafloxacin otic suspension vehicle.
c AL-60371A = AL-60371A 200 mg tablet

Table 7.2.1-2
Extent of Exposure – Confirmatory Studies (C-10-018, C-10-019)
Safety Population

	Total N	1 Day N (%)	2-4 Days N (%)	5-6 Days N (%)	7-10 Days N (%)	> 10 Days N (%)
Total	1234	7 (0.6%)	129 (10.5%)	29 (2.4%)	1064 (86.2%)	5 (0.4%)
Finafloxacin	618	2 (0.3%)	41 (6.6%)	11 (1.8%)	559 (90.5%)	5 (0.8%)
Vehicle	616	5 (0.8%)	88 (14.3%)	18 (2.9%)	505 (82.0%)	0

Source: Table 2.7.4.1-5

Table 7.2.1-3
Extent of Exposure (for Dosing Label) – Confirmatory Studies (C-10-018, C-10-019)
Safety Population

	Total N	< 7 Days N (%)	≥ 7 Days N (%)
Total	1234	165 (13.4%)	1069 (86.6%)
Finafloxacin	618	54 (8.7%)	564 (91.3%)
Vehicle	616	111 (18.0%)	505 (82.0%)

Source: Table 2.7.4.1-6

Table 7.2.1-4
Mean Extent of Exposure to Study Medication (in Days)
Confirmatory Studies (C-10-018, C-10-019)
Safety Population

	Total (N=1234)	Finafloxacin (N=618)	Vehicle (N=616)
Mean	6.7	6.9	6.5
SD	1.4	1.3	1.6
Median	7.0	7.0	7.0
(Min, Max)	(1.0, 12.0)	(1.0, 12.0)	(1.0, 10.0)

Source: Table 2.7.4.1-7

Reviewer's Comment:
The extent of exposure was 7 days or greater for the 91% of patients in the finafloxacin group and 82% of patients in the vehicle group. .

7.2.2 Explorations for Dose Response

Finafloxacin 0.3% was administered in one dosage regimen. Four drops were instilled twice daily in the affected ears on Days 1 through 7 in each of the Phase 3 studies. No dose response information was obtained for the indication.

7.2.3 Special Animal and/or In Vitro Testing

No special toxicology studies were conducted with finafloxacin otic suspension 0.3%. Adequate nonclinical investigations of finafloxacin otic suspension were performed for and submitted in the original NDA 206-307 for Finafloxacin Otic Suspension 0.3%.

7.2.4 Routine Clinical Testing

The routine clinical testing required to evaluate the safety concerns of finafloxacin otic suspension 0.3% were adequately addressed in the design and conduct of this clinical trial.

7.2.5 Metabolic, Clearance, and Interaction Workup

Adequate nonclinical investigations of finafloxacin otic suspension were submitted in this NDA. Refer to the nonclinical reviews for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events reported during the development of finafloxacin otic suspension 0.3% are consistent with other topical quinolones. The assessment of these adverse events within the clinical trials was adequate.

7.3 Major Safety Results

7.3.1 Deaths

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

7.3.2 Nonfatal Serious Adverse Events

One patient in the Vehicle group experienced two serious adverse events, anxiety and gastroenteritis.

7.3.3 Dropouts and/or Discontinuations

Refer to Sections 6.1.3 and 6.2.3 for listings of patients discontinued from the study and for the reasons of discontinuation. The majority of study discontinuations were due treatment failure in both treatment groups.

7.3.4 Significant Adverse Events

Refer to Section 7.4.1 for Common Adverse Events. No other significant adverse events were identified.

7.3.5 Submission Specific Primary Safety Concerns

No specific primary safety concerns were identified for the submission.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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

Coded Adverse Event [a]	Finafloxacin (N=618)	Vehicle (N=616)
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

Reviewer's Comment:
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.

7.4.2 Laboratory Findings

Clinical laboratory evaluations were obtained in the PK Study, C-10-007. Laboratory test results for hematology, blood chemistry, and urinalysis parameters were evaluated. There were no significant findings with the exception of one subject who experienced a decrease in absolute neutrophil count at the Day 12/Exit Visit.

This subject, a 41 year old woman, experienced a decrease in absolute neutrophil count at the Day12/Exit Visit and the occurrence was reported as an adverse event (coded to Neutropenia). The subject received a single dose of AL-60371A Oral Tablet 200 mg at the same visit (Day12/Exit Visit) and was also exposed to AL-60371 Otic Suspension, 0.3% during the otic dosing period (Day 1 – Day 8) prior to the single oral dose. This neutropenia event resolved without treatment after 12 days and was assessed to be related to the use of study drug.

The subject's actual systemic exposure level of AL- 60371 during the otic dosing period was below the limit of quantitation (<0.05 ng/mL). Based on the lack of measurable systemic AL-60371 exposure during the otic dosing period, and no clinically relevant treatment group differences in neutrophil count mean changes from baseline to exit visit, the single case of neutropenia was considered to be an outlier by the applicant.

Clinical laboratory evaluations were not performed in either Study C-10-018 or Study C-10-019.

Reviewer's Comment:
A single subject experienced a decrease in absolute neutrophil count after receiving a single dose of AL-60371A 200 mg oral tablet in the pharmacokinetic study and being exposed to AL-60371 otic suspension, 0.3% during the otic dosing period prior to the single dose. The event of decrease in absolute neutrophil count resolved without treatment after 12 days.

7.4.3 Vital Signs

Cardiovascular parameters (pulse and blood pressure) were measured for all subjects in the study. No changes in pulse rate or blood pressure were assessed as clinically relevant.

Vital signs were not evaluated in either Study C-10-018 or Study C-10-019.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were performed for all subjects at baseline and an additional time point in Study C-10-007. No safety issues were identified when the ECGs were compared to baseline.

Electrocardiograms were not performed in either Study C-10-018 or Study C-10-019.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were conducted for this product.

7.4.6 Immunogenicity

Immunogenicity testing was not performed in either Study C-10-018 or Study C-10-019.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Finafloxacin otic suspension 0.3% was administered in one dose level (Four drops in the affected ear(s) twice daily for 7 days) in each of the phase 3 studies. No dose response information was obtained.

7.5.2 Time Dependency for Adverse Events

Finafloxacin does not have a delayed onset of action. Exploration of time to onset was not conducted.

7.5.3 Drug-Demographic Interactions

An evaluation of adverse events according to age category for infants and toddlers (28 day to 23 months), children (2 to 11 years), adolescent (12 to 17 years), adult (18 to 64 years) and elderly (65 years of age or older) populations in Studies C-10-018 and C-10-019. Based on a review of adverse events by these subgroups, the events are consistent with the overall safety population. When evaluated by gender and race, adverse events were also consistent with that seen in the overall safety population.

7.5.4 Drug-Disease Interactions

A review of adverse events by subpopulations categorized by concomitant diseases revealed no safety concerns.

7.5.5 Drug-Drug Interactions

Specific drug interaction studies have not been conducted with Finafloxacin Otic Suspension, 0.3%. Given the low systemic concentration of finafloxacin following topical otic administration of the product, drug interactions are unlikely to occur.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Finafloxacin is closely related to the approved fluoroquinolone, moxifloxacin which has been evaluated for carcinogenic potential. A study to assess the carcinogenic potential of moxifloxacin in selected target organs was submitted previously in Bayer HealthCare AG's AVELOX® Tablets NDA 21-085 and referenced in Alcon's VIGAMOX® NDA 21-598.

The need for 2-year carcinogenicity studies was discussed at the Type B meeting held in November 2011 with the Division of Transplant and Ophthalmology. The agency agreed at that time with the sponsor's position that carcinogenicity studies may not be required provided human clinical data shows sufficiently low systemic exposure. A carcinogenicity waiver has been submitted (IND amendment 0023, May 21, 2013).

7.6.2 Human Reproduction and Pregnancy Data

Pregnant women and nursing mothers were excluded from the clinical development program for finafloxacin. There have been no clinical studies in human reproduction or pregnancy performed.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety population included six patients (3 in each treatment group) aged 28 days to 23 months. No adverse events were reported for these patients. The clinical development program did not produce any evidence that the otic administration of finafloxacin had any adverse effect on weight bearing joints or the pediatric population generally.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence for the potential for overdose or potential for abuse with finafloxacin. No reports of overdose were received during the clinical studies with finafloxacin otic suspension, 0.3%.

7.7 Additional Submissions / Safety Issues

The Safety Update was submitted on September 22, 2014. Per Alcon:

> No clinical studies evaluating Finafloxacin Otic Suspension, 0.3% are ongoing, have been initiated or completed since the NDA was submitted in April 2014 and Finafloxacin Otic Suspension, 0.3% is not marketed any country. There is no new Safety information available for Finafloxacin Otic Suspension, 0.3%.

Supportive Clinical Safety Information – Study C-13-026

Alcon submitted supportive clinical safety information from an Alcon sponsored trial (C-13-(b) (4). This study evaluated the safety and efficacy of an investigational otic suspension (b) (4) compared to Ciprodex otic suspension for the treatment of acute otitis media with tympanostomy tubes (AOMT) in pediatric subjects. This study was recently discontinued for business purposes. The safety information remains masked.

No deaths or serious adverse events were reported in Study C-13-026. Two subjects were discontinued from study participation due to adverse events after the trial was discontinued.

Table 7.7-1
Reported Adverse Events in Study C-13-026 by System Organ Class
Masked Treatment Groups

Preferred Term	Outcome	Participation Discontinued
Bronchiolitis	Not Recovered	No
Device occlusion	Not Recovered	No
Diarrhea	Recovered	No
Ear pain	Recovered	No
Ear tube removal	Not recovered	Yes
Excoriation	Recovered	No
Lymphadenopathy	Recovered	No
Otitis externa fungal	Recovered	No
Otitis media acute	Recovered	Yes
Otitis media acute	Recovered	No
Otitis media acute	Recovered	No
Otitis media acute	Recovered	No
Otitis media acute	Recovered	No
Otitis media chronic	Recovered	No
Pyrexia	Recovered	No
Pyrexia	Recovered	No
Rash pustular	Recovered	No
Rhinorrhea	Recovered	No
Upper respiratory tract infection	Recovered	No
Upper respiratory tract infection	Not recovered	No
Vomiting	Recovered	No

Reviewer's Comment: *The adverse events reported in Study C-13-026 are consistent with those observed in Studies C-10-018 and C-10-019. No new safety signals were observed.*

8 Postmarket Experience

Finafloxacin is not a marketed drug product. There are no Postmarketing data to report.

9 Appendices

9.1 Literature Review/References

An independent literature review did not produce any additional significant information regarding finafloxacin.

9.2 Advisory Committee Meeting

The application did not raise any issues which were thought to benefit from a discussion at an Advisory Committee meeting..

9.3 Labeling Recommendations

Following is the applicant's proposed labeling submitted in the April 30, 2014, submission.

The reviewer's additions are noted in underline and deletions by.

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

9.4 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 206-307

Submission Date(s): April 25, 2014

Applicant: Alcon Research Ltd.

Product: Finafloxacin otic suspension, 0.3%

Reviewer: Rhea A. Lloyd, MD

Date of Review: July 17, 2014

Covered Clinical Study (Name and/or Number):
C-10-007, C-10-018, C-10-019 and C-11-022.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: Study C-10-007: (b) (6) Study C-10-018: 65 investigators Study C-10-019: 53 investigators Study C-11-022: 3 investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: One Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator in sponsor of covered study: None		
Is an attachment provided with details of the disclosable financial	Yes ☒	No ☐ (Request details from applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Alcon has determined there were no financial interests or arrangements to disclose from investigators in studies C-10-018, C-10-019 and C-10-022.

There are financial interests or arrangements to disclose from the investigator, (b) (6) (b) (6), MD, PhD (b) (6)), who was the principal investigator for clinical trial (b) (6). Dr. (b) (6) is not employed by the applicant.

Investigators and Payment Description	***Total Monies by Investigator***
(b) (6) ***MD, PhD and Sub-Investigators***	
Consulting fees	*$32,244.30*
Total (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.*

1 See [web address].

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RHEA A LLOYD
10/02/2014

WILLIAM M BOYD
10/02/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:	Applicant:	Stamp Date:
206307	Alcon Research, Ltd.	April 25, 2014
Drug Name: Finafloxacin Otic Suspension, 0.3%	**NDA/BLA Type:**	

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:		X		

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: C-10-018 Indication: Treatment of acute otitis externa (AOE) Pivotal Study #2: C-10-019 Indication: Treatment of acute otitis externa (AOE)	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The studies submitted included pediatric patients in fulfillment of a Pediatric Written Request.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		X		See Statistical filing review for details.
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RHEA A LLOYD
06/03/2014

WILLIAM M BOYD
06/04/2014