CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206307Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 206-307	**Reviewer:** Banu S. Zolnik, Ph.D.	
Division:	Division of Transplant and Ophthalmic Products		
Applicant:	Alcon Research, Ltd.	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	Xtoro (under review)	**Acting Biopharmaceutics Supervisor:** Paul Seo, Ph.D.	
Generic Name:	Finafloxacin otic suspension, 0.3%	**Date Assigned:**	4/30/2014
Indication	for the treatment of acute otitis externa in pediatric (age (b) (4) (b) (4) and older), adult and elderly patients	**Date of Review:**	9/19/2014
Formulation/ Strength	Otic suspension, 0.3%	**Route of Administration**	Otic

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	Date of informal/Formal Consult	Primary Review due in DARRTS
Original dated 4/25/2014 Seq. 0004 dated 06/27/ 2014 Seq. 0005 dated 07/ 31/2014 Seq. 0012 dated 09/ 19/2014	NA	September 25, 2014

Type of Submission:	Original 505 (b)(1) Application
Review Key Points:	▪ Dissolution method and acceptance criteria ▪ The evaluation of the biowaiver request

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Submission:
NDA 206307 is a 505 (b)(1) NDA submission for Finafloxacin Otic Suspension, 0.3% for the treatment of acute otitis externa in pediatric (age (b) (4) and older), adult and elderly patients.

Review:
The Biopharmaceutics review is focused on the evaluation and acceptability of;
1) the dissolution method and acceptance criterion
2) the information supporting the biowaiver request

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

The Applicant agreed to the following milestones for the PMC:

- May 2015 - Dissolution Method Development Final Report Submission
- August 2015 - Acceptance Criteria Proposal Submission
- November 2015 - Final Report Submission

See PMC in Appendix 1.

2) Biowaiver request:

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

RECOMMENDATION:

The ONDQA-Biopharmaceutics team had reviewed NDA 206-307 and its amendments (Seq. 0004 Seq. 0005, Seq.0012) submitted on June 27, July 31, 2014 and September 19, 2014.

From the Biopharmaceutics perspective, NDA 206307 for finafloxacin otic suspension is recommended for **APPROVAL with a Post Marketing Commitment*.**

* PMC is included in Appendix 1.

Banu S. Zolnik, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: P. Seo

BIOPHARMACEUTICS ASSESSMENT

1. BACKGROUND

Submission

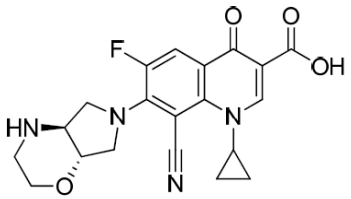
This 505 (b)(1) NDA submission for Finafloxacin Otic Suspension, 0.3% for the treatment of acute otitis externa in pediatric (age [redacted] (b) (4) and older), adult and elderly patients.

Finafloxacin (aka AL-60371) is a new molecular entity, a fourth generation topical fluoroquinolone class of broad spectrum antibiotic. The Applicant submitted two pivotal multicenter, randomized, double-masked, parallel-group, vehicle–controlled clinical studies **(C-10-018 and C-10-019)** in support for the approval of the proposed drug product.

Review

The Biopharmaceutics review is focused on the evaluation and acceptability of 1) the dissolution method and acceptance criterion, and 2) the information supporting the biowaiver request.

Drug Substance



Finafloxacin is a white to yellow powder or crystals. Solubility profile of finafloxacin in various solvents and aqueous solutions with different pH is shown below.

Table 3.2.S.1.3–1 Solubility of Finafloxacin ~~A~~L-60371 Drug Substance

Solvent	Solubility of AL-60371
Water	0.125 mg/mL
Acetate Buffer, pH 4.4	2.075 mg/mL
Phosphate Buffer, pH 7.3	1.389 mg/mL
DMSO	6.560 mg/mL
Ethanol	0.120 mg/mL
Acetontrile	1.263 mg/mL
Ethyl Acetate	0.198 mg/mL

Drug Product

The proposed drug product is formulated in a sterile suspension formulation. The components of the proposed drug product are presented below.

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

Component	Concentration % w/v	Function	Compendial Status
Finafloxacin (AL-60371)	0.3[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.

DISSOLUTION METHOD AND ACCEPTANCE CRITERION

The Applicant did not provide any information for the dissolution method in their submission. The following comments were conveyed to the Applicant in IR letter dated 6/10/2014.

1. *Since your proposed drug product is a suspension, the dissolution test should be added to the specifications of the drug product. Therefore, develop an in vitro dissolution test that is optimal for your proposed otic suspension product.*
2. *Provide the dissolution method development report with the following information/data:*
   a) *Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. It is noted that in general, lower rotation speeds are used for the dissolution of suspensions (25 rpm). If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified.*
   b) *Provide the complete dissolution profile data (individual, mean, SD, profiles) generated during the method development. The dissolution data*

should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim);

c) *A list of all relevant manufacturing variables and material attributes affecting the dissolution of your proposed product;*

d) *Data supporting the discriminating capability of the proposed dissolution method for meaningful manufacturing changes implemented to your proposed product. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e., ± 10-20% change to the specification-ranges of these variables) for the most relevant manufacturing variables (e.g. drug substance particle size etc.).*

3. *Note that the discriminating ability is not only determined by the dissolution method settings but also by the selected specification-sampling time point and specification value. For the selection of the dissolution acceptance criterion of your product, the following points should be considered:*

- *The complete dissolution profile data (e.g., 15, 20, 30, 45, 60, etc. minutes) from the pivotal clinical and PK batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criteria of your product.*
- *Specifications should be based on average in vitro dissolution data (n=12).*
- *The specification-time point should be selected when Q = (b) (4)% dissolution occurs.*

Reviewer's Assessment of Applicant's June 27, 2014 Response: UNSATISFACTORY

The Applicant did not provide the requested information regarding the development of a dissolution method for the finafloxacin otic suspensions. However, it is the ONDQA-Biopharmaceutics current policy that all suspension formulations should have dissolution as one of the tests controlling the quality of the product. Therefore, the Applicant should develop a dissolution method for their drug product and the below comments were sent to the Applicant in an IR letter dated July 18, 2014

- *Although we acknowledge that your proposed drug product is locally acting, we do not agree with your conclusion provided in Amendment Serial 004 dated 6/27/2014, stating that a dissolution test is not needed for your drug product. We recommend that you develop an in vitro dissolution method, which testing conditions (i.e., equipment, volume, speed, medium etc.) are relevant for your proposed otic suspension product. We also recommend that you include the dissolution test in the specifications evaluating the quality of your drug product.*

Reviewer's Assessment of Applicant's July 31, 2014 (Seq. 0005) and September 19, 2014 (Seq.0012) Responses: SATISFACTORY

The Applicant agreed to develop a dissolution test and tentatively the following dissolution testing conditions are proposed: Apparatus 2, 25 rpm, medium: Formulation vehicle.

During the mid-cycle meeting with the Applicant, the Applicant agreed to develop a dissolution testing method as part of the Post-Marketing Commitment. The Applicant also agreed to the following milestones:

- May 2015 - Dissolution Method Development Final Report Submission
- August 2015 - Acceptance Criteria Proposal Submission
- November 2015 - Final Report Submission

Appendix 1 includes the post-marketing commitment. The PMC details will be stated in the Action Letter.

3) Biowaiver Request:

As per 21 CFR § 320.22 (b)(1), for certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident and therefore FDA may waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets a criteria such as to be an **otic solution**, and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

It is noted that for this specific otic drug product, there is no available an approved listed drug product; however, considering that the proposed drug product is an otic suspension, intended only for local therapeutic effect and its lack of systemic absorption was demonstrated in the submitted PK studies, Biopharmaceutics is of the opinion that for good cause, the requirement for the submission of evidence of in vivo bioavailability or bioequivalence can be waived and this deferral is compatible with the protection of the public health.

RISK ASSESSMENT TABLE

From Initial Quality Assessment			Review Assessment		
Product attribute / CQA	Factors that can impact the CQA	Risk Ranking*	Risk Mitigation Approach	Risk Evaluation [Acceptable/ Unacceptable]	Lifecycle Considerations/ Comments**
Dissolution	The Applicant did not evaluate the factors which may impact dissolution as a quality attribute (QA)	Not evaluated (NE)	The Applicant agreed to develop a dissolution method	Unacceptable	Post-marketing commitment to Develop dissolution method

* Risk ranking applies to product attribute/CQA (L, M, H)

APPENDIX 1

Post Marketing Commitment (To be finalized in the Action Letter)

NDA 206-307 PMC Development: Product Quality (CMC-Biopharmaceutics)

This template should be completed by ONDQA's Biopharmaceutics or CMC reviewer. For *each* type of CMC or Biopharmaceutics PMC in the Action Package (See #4 for a list of PMC types).

NDA Product Name:	NDA 206-307 Finafloxacin Otic Suspension
PMC # XXX Description:	The dissolution method development report with the complete data should be submitted within 6 months from NDA's action date. The report should include the following information: a. Solubility and pH data for the drug substance in the proposed dissolution medium; b. Detailed description of the dissolution test being proposed for the evaluation of the proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). The dissolution profile should be complete (i.e., 10, 15, 20, 30, 45, & 60 minutes) and cover at least (b) (4) % of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. The use of USP Apparatus 2 with mini-vessels (50-200 ml volume) should be considered for the dissolution testing of this otic suspension drug product. c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for the proposed drug product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim); and d. Include the complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

PMC Schedule Milestones:		
	Final Protocol Submission:	NA
	Study/Trial Completion:	NA
	Final Report Submission:	05/2015
	Other: NA	NA

PMC # XXXX Description:	A proposal for the dissolution acceptance criterion and the complete supportive data should be submitted within 12 months from NDA's action date. The selection of the proposed acceptance criterion should be based on the dissolution profile data (i.e., 10, 15, 20, 30, 45, and 60 minutes; N=12) from a minimum of 12 commercial batches and the stability data for registration batches. It is noted that the selection of the specification time point should be where Q = (b) (4) % dissolution occurs.

PMC Schedule Milestones:		
	Final Protocol Submission:	NA
	Study/Trial Completion:	NA
	Proposal Submission:	08/2015
	NA Final Report Submission	11/2015

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- ☐ Need for drug (unmet need/life-threatening condition)
- ☐ Long-term data needed (e.g., stability data)
- ☐ Only feasible to conduct post-approval
- ☐ Improvements to methods
- ☐ Theoretical concern
- ☐ Manufacturing process analysis
- ☒ Other (Dissolution acceptance criteria)

Resolution of interim dissolution acceptance criteria are generally handled as PMCs and not PMRs

2. Describe the particular review issue and the goal of the study.

The objective of the PMC is to ensure that the appropriate dissolution method and acceptance criterion have been established for this drug product.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMC study.

- ☒ Dissolution testing (dissolution acceptance criteria)
- ☐ Assay
- ☐ Sterility
- ☐ Potency
- ☐ Product delivery
- ☐ Drug substance characterization
- ☐ Intermediates characterization
- ☐ Impurity characterization
- ☐ Reformulation
- ☐ Manufacturing process issues
- ☐ Other

Describe the agreed-upon study:

4. To be completed by ONDQA/OBP Manager:

☒ Does the study meet criteria for PMCs?
☒ Are the objectives clear from the description of the PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

BANU S ZOLNIK
09/25/2014

ANGELICA DORANTES
09/25/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	206,307
Submission Date(s):	April 25, 2014
Proposed Brand Name	TBD
Generic Name	Finafloxacin
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip M. Colangelo, Pharm.D., Ph.D.
OCP Division	DCP4
OND Division	DTOP
Applicant	Alcon Research, Ltd.
Relevant IND(s)	IND 110,576
Submission Type; Code	NME; Priority
Formulation; Strength(s)	Otic Suspension 0.3%
Indication	Treatment of acute bacterial otitis externa in both adults and children

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

Finafloxacin (AL-60371) Otic Suspension 0.3% is a new chemical entity, fourth generation, topical fluoroquinolone, which has enhanced activity in acidic environments (pH 5.5 - 6.2) relative to physiological pH. Fluoroquinolones comprise a number of drugs with broad-spectrum activity including the primary pathogens associated with acute otitis externa (AOE). The objective for the development of Finafloxacin Otic Suspension, 0.3%, is to provide a safe, efficacious, stable, and adequately preserved product for the topical treatment of AOE in pediatric, adult and elderly patients.

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

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

Additionally, in accordance to 21CFR§320.22(b)(1), the applicant requested a waiver from the requirements for submission of in vivo bioavailability or bioequivalence data.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in the NDA is acceptable and the reviewer recommends approval of Finafloxacin (AL-60371) Otic Suspension 0.3%.

The reviewer's proposed label changes in Appendix 4.1 should be forwarded to the sponsor.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

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

Yongheng Zhang, Ph.D.
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

Concurrence:

Philip Colangelo, Pharm.D., Ph. D.
Team Leader
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

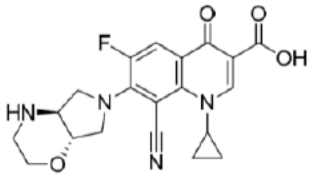
cc: Division File: NDA 206307; HFD-520 (CSO/ Puglisi); HFD-520 (MO/Boyd); HFD-520 (Chambers); HFD-880 (Lazor)

2. QUESTION BASED REVIEW

Because of the limited systemic exposure to finafloxacin following ototopical administration of finafloxacin, only relevant questions are addressed in this section.

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?



Molecular formula:	$C_{20}H_{19}FN_4O_4$
Molar Mass:	398.4 g/Mol
Chirality:	AL-60371 is chiral and has the *S*-configuration at both optically-active centers (see structural formula).

Finafloxacin is a white to yellow powder or crystals with water solubilty of 0.125 mg/mL. Finafloxacin Otic Suspension (i.e. Finafloxacin Suspension) is a sterile, stable, preserved suspension containing 0.3% w/v finafloxacin (**Table 2.1.1-1**). It will be packaged in white low density polyethylene (LDPE) (b) (4) dispenser bottles fitted with (b) (4) (b) (4) white (b) (4) closures.

Table 2.1.1-1: Composition of Finafloxacin Otic Suspension (FID 119420)

Component	Concentration % w/v	Function	Compendial Status
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.

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Finafloxacin Otic Suspension is a fourth generation, topical fluoroquinolone, with enhanced activity against bacteria in an acidic environment (pH 5.5 - 6.2) relative to physiological pH. Finafloxacin Otic Suspension, 0.3% has characteristics of this class including the mechanism of action (inhibition of both DNA gyrase and topoisomerase IV), but has enhanced Grampositive activity relative to second generation fluoroquinolones. It is indicated for the treatment of acute otitis externa (AOE), with or without an otowick, in pediatric (age (b) (4) and older), adult and elderly patients.

2.1.3. What are the proposed dosage(s) and route(s) of administration?

Instill four drops into the affected ear twice daily for seven days. For patients requiring use of an otowick, the initial dose can be doubled (to 8 drops), followed by 4 drops instilled into the affected ear twice daily for seven days.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical studies and clinical pharmacology used to support dosing or claims?

The Applicant submitted the following clinical study reports to support the NDA:

- Two Phase 3 clinical studies to confirm the safety and efficacy of Finafloxacin Otic Suspension, 0.3%.
- Two additional Phase 1 PK studies.

Table 2.2.1-1: Completed Clinical Studies for Finafloxacin Otic Suspension, 0.3%

Study Phase	Design	Population	Endpoints	Treatment Groups	Number of Patients	Dosing Regimen/ Duration
Safety / Clinical Pharmacology Studies						
C-10-007 Phase 1	Randomized, multiple-dose, fixed sequence pharmacokinetic study	Healthy male or female subjects 18 years of age or older	Plasma concentrations of AL-60371 will be described after single or multiple ototopical doses. Relative bioavailability of AL-60371 will be assessed after single dose for ototopical administration compared to oral administration.	Period 1 AL-60371 Otic Suspension, 0.3% Vehicle Period 2: AL-60371A Oral Tablet (200 mg)	14 7 20	4 drops, twice daily for 8 days (bilateral) 4 drops, twice daily for 8 days (bilateral) Single oral dose
C-10-022 Phase 1	Open-label, single visit study	Patients 6 years of age or older diagnosed with AOE	Plasma concentrations of AL-60371 will be described after a single ototopical dose of AL-60371 Otic Suspension 0.3%.	AL-60371 Otic Suspension, 0.3%	12 12 12	Single dose bilateral: 4 drops without otowick 4 drops with otowick 8 drops with otowick
Safety and Efficacy Studies in Patients with acute otitis externa (AOE)						
C-10-018 Phase 3	Multicenter, double-masked, parallel- group, vehicle-controlled, randomized	Subjects 6 months of age or older with a clinical diagnosis of AOE of less than 4 weeks duration	1° - Clinical cure at Day 11 (TOC) 2° - Microbiological success at Day 11 (TOC); Time to cessation of ear pain as reported by patient diary	AL-60371 Otic Suspension 0.3% Vehicle	347 346	4 drops, twice daily for 7 days
C-10-019 Phase 3	Multicenter, double-masked, parallel group, vehicle-controlled, randomized	Subjects 6 months of age or older with a clinical diagnosis of AOE of less than 4 weeks duration	1° - Clinical cure at Day 11 (TOC) 2° - Microbiological success at Day 11 (TOC); Time to cessation of ear pain as reported by patient diary	AL-60371 Otic Suspension 0.3% Vehicle	274 275	4 drops, twice daily for 7 days

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The primary and secondary endpoints for both Phase 3 studies were:

- Clinical cure at Day 11 (Test of cure, TOC)
- Microbiological success at Day 11 (TOC)
- Time to cessation of ear pain

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, an HPLC tandem mass spectrometry (HPLC/MS/MS) method was developed and validated for the determination of finafloxacin in human K_2EDTA plasma (*Refer to Section 2.6*).

2.2.4. Exposure-response

2.2.4.1. Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The rationale for the final dose selection of 0.3 % dose strength/4 drops per eye/BID was based on the following studies:

- Results from nonclinical studies show that formulations of finafloxacin containing 0.10%, 0.15% or 0.3% of AL 60371, with at least 0.05% soluble concentration, eradicated *P. aeruginosa* from the external ear canal in a guinea pig model of acute otitis externa. Based upon nonclinical efficacy and toxicology results, a maximum tolerated dose of 0.3% of finafloxacin was chosen for the clinical trials.
- The selection of 4 drops in each ear is consistent with the posology of similar otic products. Doses in excess of 4 to 5 drops tend to "flow out" of the ear canal due to the presence of cerumen, and/or otorrhea and swelling of the canal. Conversely, doses of fewer than 4 to 5 drops may result in only 1 to 2 drops actually entering the ear canal due to movement or "missed" drops.
- The frequency and duration of the proposed treatment regimen is the standard of care for antibiotic treatment of ear infections. Extensive literature references exist citing various ciprofloxacin and ofloxacin dosing regimens, generally BID or QD for 7 days. Once daily dosing may lead to increasing the potential severity of AOE and extending the duration of a patient's symptoms as a consequence of a "missed" dose. More than twice daily dosing (eg, TID or QID) likely does not offer significant benefit and may contribute to patient noncompliance with the dosing regimen.

2.2.4.2. Does this drug prolong the QT or QTc interval?

No thorough QT study was conducted. ECG readings were performed for all subjects in the PK study, C-10-007. No subjects experienced a clinically relevant change in ECG findings, and no adverse events related to ECG findings were reported. Three subjects had a change in ECG (normal to abnormal) not considered clinically relevant.

2.2.5. What are the PK characteristics of the drug?

Systemic exposure to finafloxacin was evaluated following single ototopical dose (4 drops per ear without otowick; 4 or 8 drops per ear with otowick) in AOE patients and multiple ototopical doses (4 drops per ear; BID for 7 days) in healthy subjects. Quantifiable (i.e. LLOQ of 0.05 ng/mL) finafloxacin concentrations were only observed in plasma samples (up to 0.0812 ng/mL) from 2 of 14 healthy subjects at a total of 3 time points. Similarly, quantifiable finafloxacin concentrations were only observed in plasma samples (up to 0.234 ng/mL) from 2 of 36 AOE patients. No PK parameters could be determined.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Finafloxacin (AL-60371) was identified and measured in human plasma.

2.6.2. Which metabolites have been selected for analysis and why?

No metabolites were selected for analysis.

2.6.3. What bioanalytical methods are used to assess concentrations?

An HPLC tandem mass spectrometry (HPLC/MS/MS) method was developed and validated for the determination of finafloxacin in human K2EDTA plasma (TDOC-0013755) by (b) (4)

2.6.3.1. What is the range of the standard curve? What curve fitting techniques are used?

The working range of the method was 0.0500 – 25.0 ng/mL. The limit of quantitation (LOQ) was 0.0500 ng/mL. Weighted linear regression was used for curve fitting.

2.6.3.2. What are the accuracy, precision, and selectivity at these limits?

The assay accuracy and precision were determined from the assay standards and QCs. The accuracy and precision values are satisfactory. Assay selectivity was confirmed by analyzing ten individual human plasma samples and none yielded interfering peaks when concentrations were above LLOQ.

2.6.3.3. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

The stability of finafloxacin was demonstrated in plasma for up to five freeze/thaw cycles; in plasma for 4 to 24 hours after thawing; in plasma for up to 24 hours at room temperature; in plasma for 433 days at -20 and -70 ºC; in processed human K_2EDTA plasma samples at room temperature; at room temperature for 96 hours prior to reinjection for the analyte and IS in injection solvent placed in the autosampler.

2.6.3.4. What is the QC sample plan?

QCs were prepared in plasma at concentrations of 0.05, 0.15, 10.0, 20, 75 (5-fold dilution), and 1500 (100-fold dilution) ng/mL of finafloxacin.

3. LABELING RECOMMENDATIONS

See Appendix 4.1.

4. APPENDICES

4.1. Proposed Package Insert with Clinical Pharmacology Edits as of 2014

Edits are noted as strikethrough and in red.

[redacted]

12.~~2~~3 Pharmacokinetics

Finafloxacin plasma concentrations [redacted] were evaluated following single or repeated ototopical doses of TRADENAME (finafloxacin otic suspension~~)~~, 0.3%). In healthy subjects administered 4 drops in each ear twice daily for seven days, quantifiable finafloxacin concentrations were observed in [redacted] 2 of 14 subjects [redacted]; and these concentrations were just above the quantitation limit (0.05 ng/mL). Similarly, in AOE patients administered a single dose of 4 or 8 drops in each ear, quantifiable finafloxacin concentrations of up to 0.234 ng/mL were observed in plasma samples from 2 of 36 AOE patients.

4.2. Individual Study Review

4.2.1. Study C-10-007

Study Number: C-10-007
A fixed-sequence pharmacokinetic, relative bioavailability and safety study of AL-60371 otic suspension, 0.3% in healthy subjects

Sample Analysis Dates: 19 October 2011 to 04 November 2011
Study Director: Jay Smith, MD, PhD, Alcon.
Analytical site: (b) (4)

OBJECTIVES:

(1) To assess the systemic pharmacokinetics of AL-60371 in healthy subjects following single dose or multiple ototopical doses (BID for 7 days) of AL-60371 Otic Suspension, 0.3% in both ears.

(2) To assess the relative bioavailability of AL-60371 after ototopical administration compared to oral administration AND to assess the safety of AL-60371 Otic Suspension, 0.3% in healthy subjects following twice daily ototopical dosing for 7 days.

FORMULATION & ADMINISTRATION

- AL-60371 Otic Suspension, 0.3%; Batch Number: 11-501299-1, FID 116616
- (b) (4)

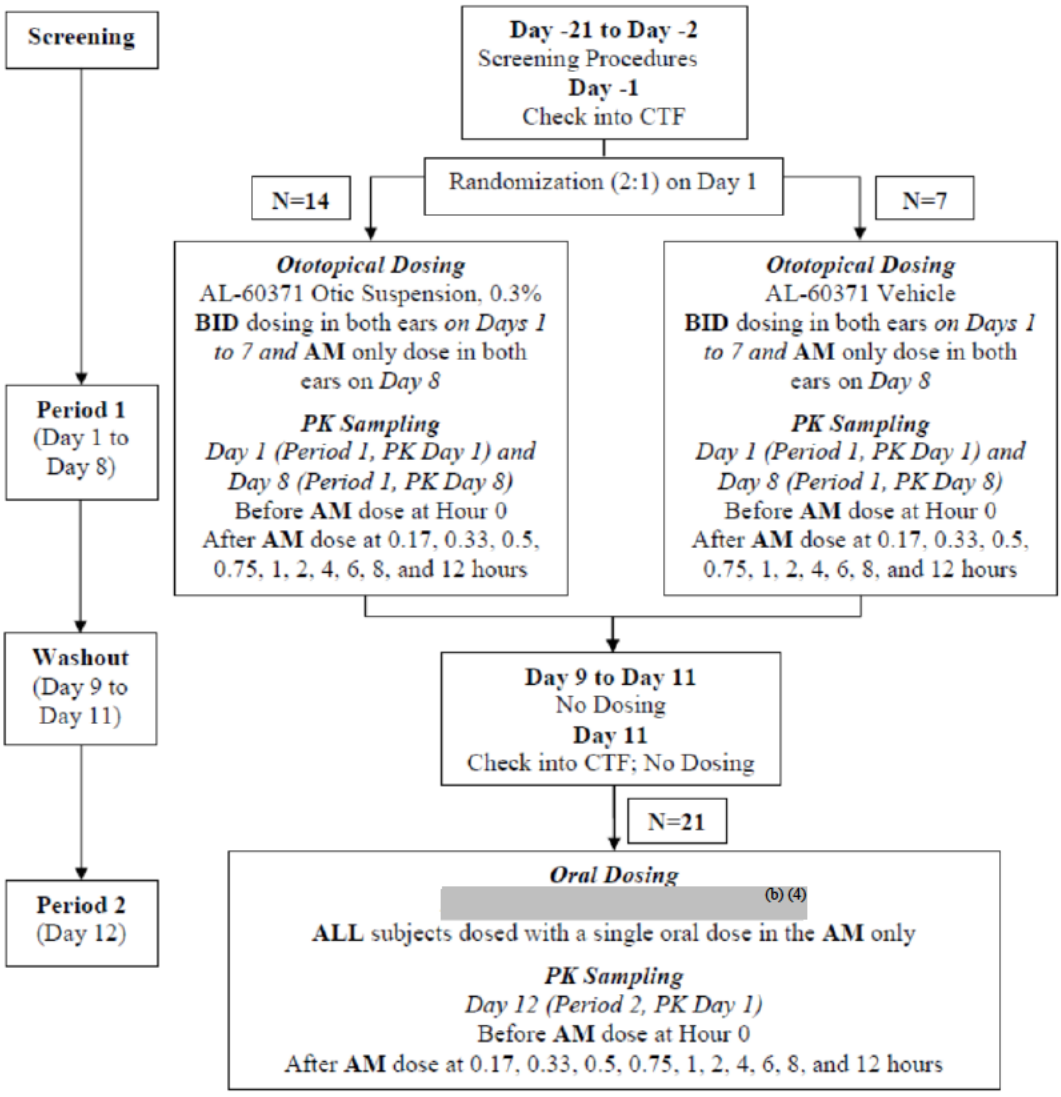
STUDY DESIGN:

This is a single center, multiple-dose, randomized, vehicle-controlled, fixed-sequence study. A fixed dosing frequency paradigm was used to evaluate the PK of AL-60371 (**Figure 1**).

The PK sampling was conducted on Days 1, 8, and 12 at the following time points:

- Day 1 (Period 1, PK Day 1): Predose and 10 min, 20 min, 0.5, 0.75, 1, 2, 4, 6, 8, and 12 hours post the morning dose. (*Note: the 12 hour AM post-dose PK samples were deemed unevaluable for PK analysis for all subjects due to the PM dose on Day 1 was erroneously administered before the 12 hour AM post-dose PK sample was collected*).
- Day 8 (Period 1, PK Day 8): Trough (Hour 0) and 10 min, 20 min, 0.5, 0.75, 1, 2, 4, 6, 8, and 12 hours after the morning dose.
- Day 12 (Period 2, PK Day 1): Predose (Hour 0) and 10 min, 20 min, 0.5, 0.75, 1, 2, 4, 6, 8, and 12 hours post the oral dose.

Figure 1: Study schematic



ASSAY METHODOLOGY:

The method and bioanalysis of AL-60371 are acceptable (Validation report TDOC0013755; Bioanalytical report TDOC0015085). AL-60371 plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA plasma by (b) (4)

The lower limit of quantification for AL-60371 was 0.0500 ng/mL and the upper limit of quantification was 25.0 ng/mL. There were no precision or accuracy issues identified for AL-60371 based on the bioanalytical report. The precision and accuracy were evaluated using plasma AL-60371 QC samples at five concentration levels: 0.0500 ng/mL, 0.150 ng/mL, 10 ng/mL, 20 ng/mL, 75.0 ng/mL (5-fold dilution), and 1500 ng/mL (100-fold dilution).

Analyte interference evaluation showed that ten different individual lots of human blank plasma had no interference on the quantification of AL-60371.

Fifty samples were selected for incurred sample reanalysis, and the results were acceptable.

All samples were analyzed within the time demonstrated long-term storage stability in human plasma containing K_2EDTA at -20 °C or colder.

DATA ANALYSIS

Non-compartmental methods of analysis were planned to be utilized in estimating the PK parameters (Cmax, Tmax, AUC, and t½) from the plasma concentrations of AL-60371 after single ototopical/oral dose and multiple ototopical doses. In addition, the % relative bioavailability of AL-60371 was planned to be estimated. Due to insufficient ototopical plasma concentration data, it was not possible to characterize systemic PK parameters or assess the relative bioavailability of AL 60371 by the ototopical route. Oral dose PK parameters were determined.

Formal hypothesis testing was not planned for this study. In lieu of formal testing, descriptive statistics (number [N], mean, coefficient of variation, median, minimum, and maximum values) were planned to summarize PK parameters (Cmax, Tmax, AUC, t½) following single and multiple ototopical twice daily doses of AL-60371 Otic Suspension, 0.3%. Similar descriptive statistics were planned to be utilized in summarizing the oral dose PK parameters. Due to insufficient ototopical plasma concentration data, descriptive statistics of the ototopical PK parameters could not be determined. Descriptive statistics of the oral dose PK parameters were determined.

RESULTS:

Ototopical dose
Fourteen (14) subjects were randomized to be administered ototopical doses of AL-60371 Otic Suspension, 0.3% in both ears twice daily for 7 days, plus 4 drops in both ears on the morning of Day 8. Seven (7) subjects were randomized to be administered ototopical doses of AL-60371 Otic Suspension Vehicle at the same frequency (**Table 1**).

Table 1: Demographic Statistics by Treatment Group

	Total (N = 20)		AL-60371 (N=14)		Vehicle (N=6)	
	N	(%)	N	(%)	N	(%)
Total	**20**		**14**		**6**	
Age (Years)						
Adults (18-64 yrs)	20	(100.0)	14	(100.0)	6	(100.0)
Sex						
Male	10	(50.0)	7	(50.0)	3	(50.0)
Female	10	(50.0)	7	(50.0)	3	(50.0)
Ethnicity						
Hispanic, Latino, or Spanish	1	(5.0)	0	(0.0)	1	(16.7)
Not Hispanic, Latino, or Spanish	19	(95.0)	14	(100.0)	5	(83.3)
Race						
Asian	1	(5.0)	0	(0.0)	1	(16.7)
Black or African American	1	(5.0)	1	(7.1)	0	(0.0)
White	18	(90.0)	13	(92.9)	5	(83.3)
Ethnicity and Race						
Hispanic, Latino, or Spanish						
White	1	(5.0)	0	(0.0)	1	(16.7)
Not Hispanic, Latino, or Spanish						
Asian	1	(5.0)	0	(0.0)	1	(16.7)
Black or African American	1	(5.0)	1	(7.1)	0	(0.0)
White	17	(85.0)	13	(92.9)	4	(66.7)

AL-60371 = AL-60371 Otic Suspension, 0.3%
Vehicle = AL-60371 Otic Suspension Vehicle

There were 14 evaluable subjects in the active treatment group and 6 evaluable subjects in the Vehicle treatment group. Plasma samples from the Vehicle treatment group were not analyzed for AL-60371concentrations.

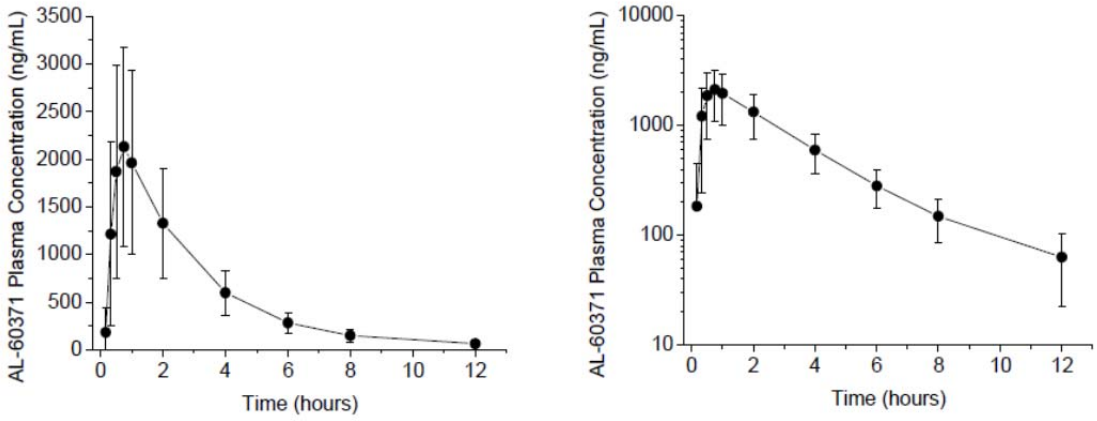
AL-60371 concentrations were quantifiable (> 0.05 ng/mL) in three plasma samples from 2 of the 14 subjects at 3 time points. Plasma concentrations of AL-60371 were not quantifiable (< 0.05 ng/mL) in all other samples collected:

- Subject 1018: Day 1, at 1 and 4 hours postdose - 0.0534 and 0.0603 ng/mL, respectively.
- Subject 1011: Day 8, at 12 hours post-dose - 0.0812 ng/mL.

Oral dose
Quantifiable concentrations of AL-60371 were observed in plasma samples from 19 subjects at all time points providing sufficient data for determinations of individual subject and mean Cmax, Tmax, AUC and t1/2 values.

Peak AL-60371 plasma concentrations were observed between 20 minutes and 4 hours, with a median Tmax of 45 minutes. The mean Cmax and AUC0-12hr pharmacokinetic 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.

Figure 2: Mean Plasma Concentrations of AL-60371 after a Single 200 mg Oral Tablet



SPONSORS CONCLUSIONS:

Systemic exposure following either single or repeated ototopical doses of AL-60371 Otic Suspension, 0.3% is extremely low with levels in nearly all samples collected being below the quantitation limit of a sensitive mass spectrometry assay with a lower limit of 0.05 ng/mL. Due to insufficient plasma concentration data, it is not possible to characterize systemic pharmacokinetic parameters in healthy subjects or assess the relative bioavailability of AL-60371 by the ototopical route.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Study C-10-007 adequately assessed the systemic exposure to AL-60371 following single or multiple ototopical doses (four drops per ear; BID for 7 days) of AL-60371 Otic Suspension, 0.3% in healthy subjects. The sponsor's conclusions are valid.

4.2.2. Study C-10-022

Study Number: C-10-022
An Open-Label, Pharmacokinetic Study of AL-60371 Otic Suspension, 0.3% in Acute Otitis Externa Patients

Sample Analysis Dates: 14 October 2011 to 15 November 2011
Study Director: Peter Roland, MD, Alcon.
Analytical site: (b) (4)

OBJECTIVES:

To evaluate systemic PK of AL-60371 in patients with acute otitis external after a single ototopical administration of AL-60371 Otic Suspension, 0.3%.

FORMULATION & ADMINISTRATION

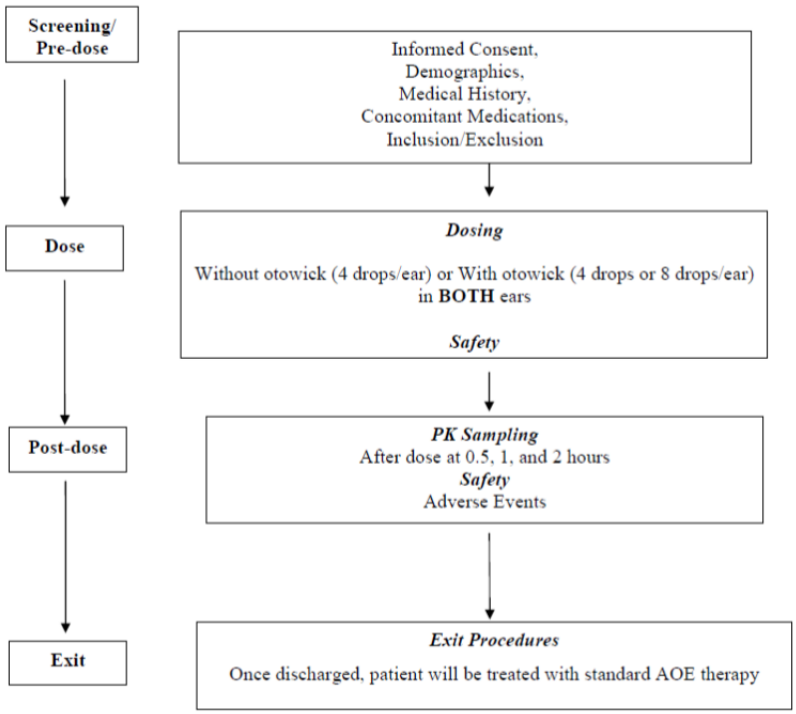
- AL-60371 Otic Suspension, 0.3%; Batch Number: 11-501299-1, FID 116616

STUDY DESIGN:

This is a multicenter, open-label, single dose pharmacokinetic study, parallel-group randomized to without and with otowick (4 drops per ear), and a nonrandomized group with otowick 8 drops per ear (**Figure 1**).

PK sampling: 0.5, 1, and 2 hours post-dose.

Figure 1: Study schematic



ASSAY METHODOLOGY:

The method and bioanalysis of AL-60371 are acceptable (Validation report TDOC0013755; Bioanalytical report TDOC0015236). AL-60371 plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA plasma by (b) (4)

The lower limit of quantification for AL-60371 was 0.0500 ng/mL and the upper limit of quantification was 25.0 ng/mL. There were no precision or accuracy issues identified for AL-60371 based on the bioanalytical report. The precision and accuracy were evaluated using plasma AL-60371 QC samples at five concentration levels: 0.0500 ng/mL, 0.150 ng/mL, 10 ng/mL, 20 ng/mL, 75.0 ng/mL (5-fold dilution), and 1500 ng/mL (100-fold dilution).

Analyte interference evaluation showed that ten different individual lots of control human blank plasma had no interference on the quantification of AL-60371.

No incurred sample reanalysis was conducted because there were insufficient samples meeting inclusion criteria (i.e. > LLOQ) to provide useful information.

All samples were analyzed within the time demonstrated long-term storage stability in human plasma containing K_2EDTA at -20 °C or colder.

DATA ANALYSIS

Non-compartmental methods of analysis were planned to be utilized in estimating the PK parameters (Cmax, Tmax, AUC, and t½) from the plasma concentrations of AL-60371 after single ototopical dose.

Formal hypothesis testing was not planned for this study.

RESULTS:

A total of 36 patients with AOE were administered ototopical doses of AL-60371 Otic Suspension, 0.3%. No patients were discontinued and none were excluded from PK evaluation. Twelve patients without otowicks received 4 drops per ear. Twelve patients with otowicks received 4 drops per ear and 12 with otowicks received 8 drops per ear.

Table 1: Demographic Statistics by Treatment Group

	Total (N = 36)		4 Drops without Otowick (N=12)		4 Drops with Otowick (N=12)		8 Drops with Otowick (N=12)	
	N	%	N	%	N	%	N	%
Total	36		12		12		12	
Age (Years)								
6 to 11 years	6	(16.7)	1	(8.3)	3	(25.0)	2	(16.7)
12 to 17 years	2	(5.6)	1	(8.3)	1	(8.3)	0	(0.0)
18 to 64 years	25	(69.4)	9	(75.0)	8	(66.7)	8	(66.7)
65 years or older	3	(8.3)	1	(8.3)	0	(0.0)	2	(16.7)
Sex								
Male	16	(44.4)	4	(33.3)	7	(58.3)	5	(41.7)
Female	20	(55.6)	8	(66.7)	5	(41.7)	7	(58.3)
Ethnicity								
Hispanic, Latino, or Spanish	36	(100.0)	12	(100.0)	12	(100.0)	12	(100.0)
Race								
Black or African American	4	(11.1)	2	(16.7)	0	(0.0)	2	(16.7)
Multi-racial	9	(25.0)	3	(25.0)	2	(16.7)	4	(33.3)
White	23	(63.9)	7	(58.3)	10	(83.3)	6	(50.0)
Ethnicity and Race								
Hispanic, Latino, or Spanish								
Black or African American	4	(11.1)	2	(16.7)	0	(0.0)	2	(16.7)
Multi-Racial	9	(25.0)	3	(25.0)	2	(16.7)	4	(33.3)
White	23	(63.9)	7	(58.3)	10	(83.3)	6	(50.0)

4 Drops Without Otowick = 4 drops of AL-60371 Otic Suspension, 0.3% in each ear without otowick
4 Drops With Otowick = 4 drops of AL-60371 Otic Suspension, 0.3% in each ear with otowick
8 Drops With Otowick = 8 drops of AL-60371 Otic Suspension, 0.3% in each ear with otowick

Quantifiable AL-60371 concentrations (> 0.05 ng/mL) were observed in plasma samples from 2 of the 36 patients. Plasma concentrations of AL-60371 were not quantifiable (< 0.05 ng/mL) in all other samples collected. As a result, there were insufficient data to determine PK parameters:

- Subject 3006 (male, 4 drops without otowick) had quantifiable levels in his 0.5 (0.12 ng/mL), 1 (0.100 ng/mL) and 2 hour (0.0735 ng/mL) plasma samples
- Patient 2109 (female, 8 drops with otowick) had quantifiable levels in her 1(0.141 ng/mL) and 2 hour (0.234 ng/mL) plasma samples.

SPONSORS CONCLUSIONS:

Systemic exposure following ototopical doses of AL-60371 Otic Suspension, 0.3% is extremely low with levels in nearly all samples collected being below the quantitation limit of a sensitive mass spectrometry assay with a lower quantitation limit of 0.05 ng/mL. Due to insufficient plasma concentration data, it is not possible to characterize the systemic pharmacokinetic parameters of AL-60371.

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Study C-10-022 adequately assessed the systemic exposure to AL-60371 following single dose of AL-60371 Otic Suspension, 0.3% in AOE patients. The sponsor's conclusions are valid.

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/s/

YONGHENG ZHANG
08/19/2014

PHILIP M COLANGELO
08/19/2014

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA:	206307
Drug Name:	Finafloxacin Otic Suspension
Applicant:	Alcon Research, Ltd.
Indication:	Treatment of acute otitis externa (AOE)
Submission Date:	April 25, 2014
Filing Date:	June 24, 2014
PDUFA Date:	February 25, 2015
OCP Primary Reviewer:	Yongheng Zhang Ph. D.
OCP Team Leader:	Philip Colangelo Pharm. D., Ph.D.

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			N/A	See Note Below
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	Yes			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	Yes			PK information obtained in clinical studies C-10-007 (healthy subjects; multiple doses) and C-10-022 (AOE patients; single dose)
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			N/A	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	Yes			Study Report PKDM1492 provided
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	Yes			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	Yes			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-	Yes			

	summary)?				
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	Yes			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	Yes			

Fileability: **Is the Clinical Pharmacology section of the application fileable?** **(if 'NO', please comment as to why it is not fileable)**	YES			

Note:

The formulation (Formulation Identification number: FID 116616) used in both PK studies (C-10-007 and C-10-022) and toxicology studies is different from that (FID 119420) used in the Phase 3 trials (C-10-018 and C-10-019). FID 119420 is the to-be-marketed formulation.

The compositions for both formulations are as follows:

Table 2.3.P.5–8 Toxicology Batch Composition for the Solution Formulation (FID 116616)

Component	Concentration % w/v	Function
Finafloxacin Hydrochloride (AL-60371A)	0.33[a]	Active
Magnesium Chloride (b) (4) (b) (4)	(b) (4	(b) (4)
Benzalkonium Chloride (b) (4)		Preservative (b) (4)
Sodium Hydroxide And / or Hydrochloric Acid		Adjust pH (b) (4)
Purified Water		(b) (4)

Table 2.3.P.1–1 Composition of Finafloxacin Otic Suspension (FID 119420)

Component	Concentration % w/v	Function	Compendial Status
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.

From a clinical pharmacology perspective, the composition differences between the two formulations are not expected to influence the limited systemic exposure following otic administration of finafloxacin otic suspension.

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/s/

YONGHENG ZHANG
06/02/2014

PHILIP M COLANGELO
06/02/2014