

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

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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

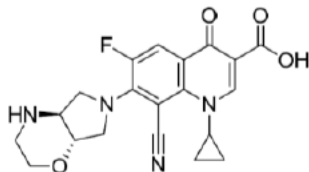
cc: Division File: NDA 206307; HFD-520 (CSO/ Puglisi); HFD-520 (MO/Boyd); HFD-520 (Chambers); HFD-880 (Lazor)

2. QUESTION BASED REVIEW

Because of the limited systemic exposure to finafloxacin following otological 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: C₂₉H₁₉FN₄O₄
 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 solubility 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)	(b)(4)	(b)(4)	NF
Sodium Chloride	(b)(4)	(b)(4)	USP
Magnesium Chloride (b)(4)	(b)(4)	(b)(4)	USP
Benzalkonium Chloride	(b)(4)	Preservative	NF
Sodium Hydroxide And / or Hydrochloric Acid	(b)(4)	Adjust pH	NF
Purified Water	(b)(4)	(b)(4)	USP

Note: FID = Formulation Identification Number

^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?*

Fluoroxacin 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. Fluoroxacin 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 Fluoroxacin Otic Suspension, 0.3%.
- Two additional Phase 1 PK studies.

Table 2.2.1-1: Completed Clinical Studies for Fluoroxacin 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%	14	4 drops, twice daily for 8 days (bilateral)
				Vehicle	7	4 drops, twice daily for 8 days (bilateral)
				Period 2: AL-60371A Oral Tablet (200 mg)	20	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%	347	4 drops, twice daily for 7 days
				Vehicle	346	
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%	274	4 drops, twice daily for 7 days
				Vehicle	275	

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 K₂EDTA 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 °C; in processed human K₂EDTA 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.

(b) (4)

12.23 Pharmacokinetics

Finafloxacin plasma concentrations (b) (4) 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 (b) (4) 2 of 14 subjects (b) (4); 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: [REDACTED] (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
- [REDACTED] (b) (4)

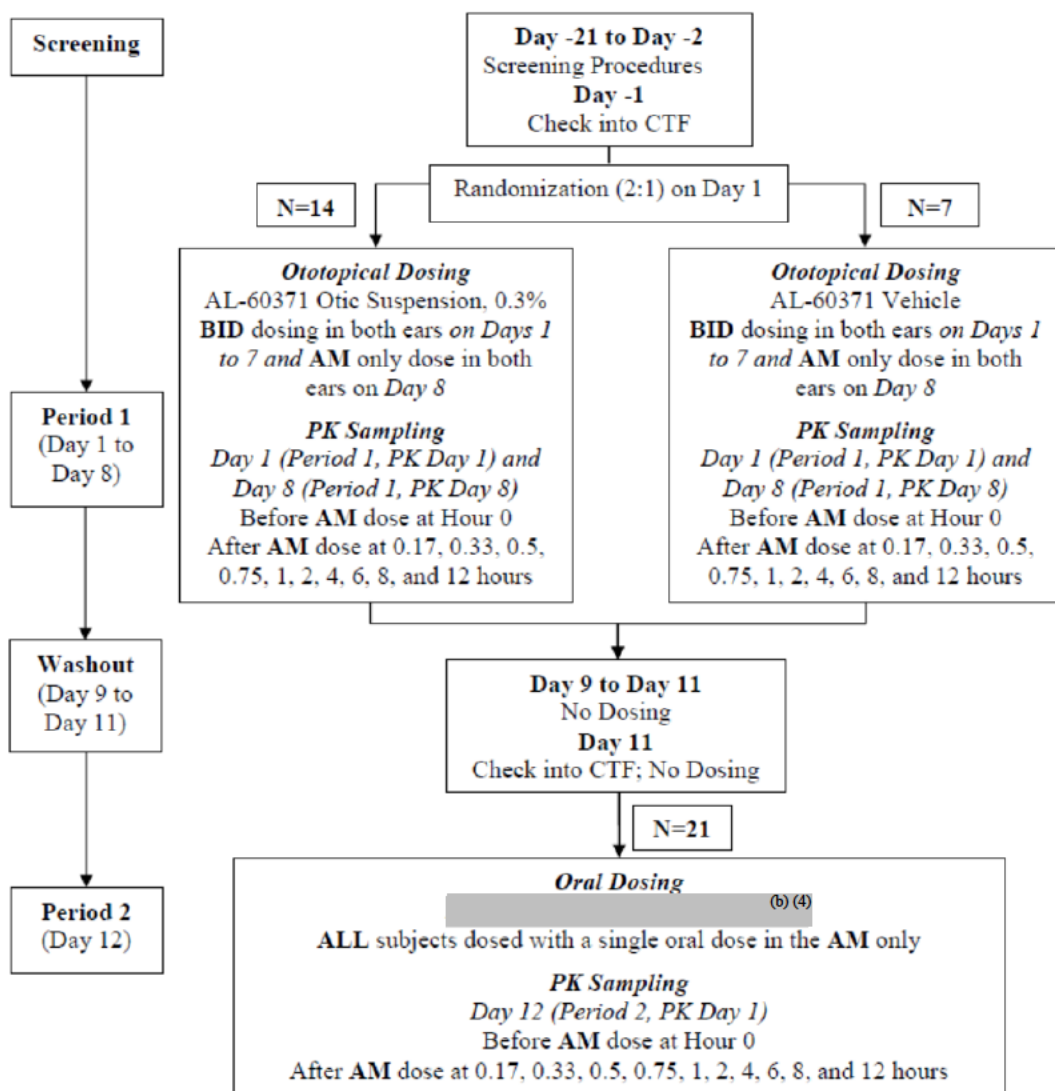
STUDY DESIGN:

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 K₂EDTA 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 K₂EDTA at -20 °C or colder.

DATA ANALYSIS

Non-compartmental methods of analysis were planned to be utilized in estimating the PK parameters (C_{max}, T_{max}, AUC, and t_{1/2}) 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 (C_{max}, T_{max}, AUC, t_{1/2}) 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						
<i>Hispanic, Latino, or Spanish</i>						
White	1	(5.0)	0	(0.0)	1	(16.7)
<i>Not Hispanic, Latino, or Spanish</i>						
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-60371 concentrations.

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:

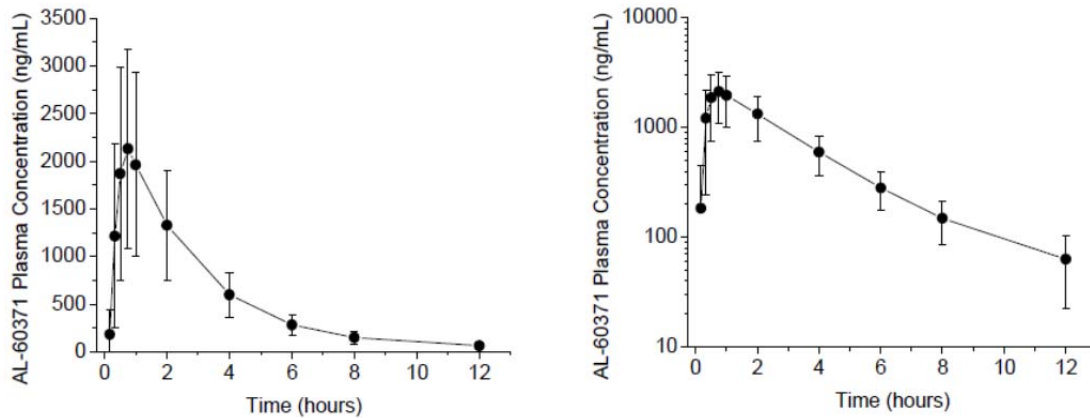
- Subject 1018: Day 1, at 1 and 4 hours postdose - 0.0534 and 0.0603 ng/mL, respectively.
- Subject 1011: Day 8, at 12 hours post-dose - 0.0812 ng/mL.

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 C_{max}, T_{max}, AUC and t_{1/2} values.

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_{0-12hr} pharmacokinetic values were 2509 + 945 ng/mL and 6715 + 2354 ng*hr/mL, respectively. After C_{max}, 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

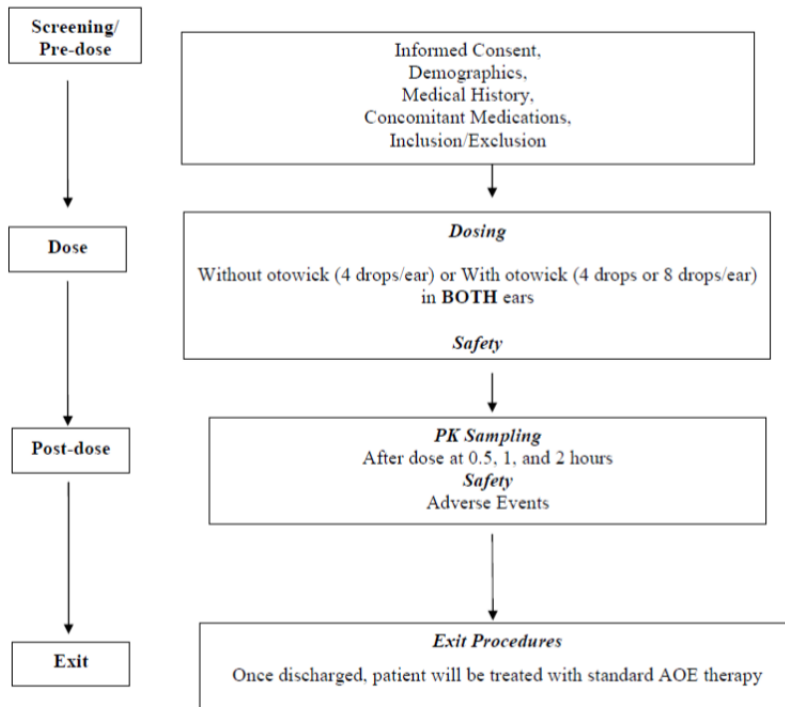
- AL-60371 Otic Suspension, 0.3%; Batch Number: 11-501299-1, FID 116616

STUDY DESIGN:

This is a multicenter, open-label, single dose pharmacokinetic study, parallel-group randomized to without and with ototwick (4 drops per ear), and a nonrandomized group with ototwick 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 K₂EDTA 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 K₂EDTA at -20 °C or colder.

DATA ANALYSIS

Non-compartmental methods of analysis were planned to be utilized in estimating the PK parameters (C_{max}, T_{max}, AUC, and t_{1/2}) 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								
<i>Hispanic, Latino, or Spanish</i>								
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