CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-799

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUN 17 1997

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	20-799
Submission date:	12-18-96
Product:	ofloxacin otic solution (0.3%)
Trade name:	FLOXIN® Otic
Sponsor:	Daiichi Pharmaceutical Co., LTD 14-10 Nihonbashi 3-Chome Chuo-ku, Tokyo 103 Japan
Type of submission:	Original application
OCPB Reviewer:	Jenny Zheng, Ph.D.
Date received for reviewing:	1-7-97

SYNOPSIS:

The sponsor, Daiichi Pharmaceutical Co., submitted NDA 20-799 to seek for the approval of FLOXIN® Otic. The product contains ofloxacin 0.3% and is indicated for use in the treatment of otitis external (OE), chronic suppurative otitis media (CSOM) and acute otitis media (AOM) in adults and adolescent.

Three bioavailability and pharmacokinetic studies were conducted to define the systemic absorption of ofloxacin from an otic solution applied to the middle and inner ear through a perforated ear drum or a tympanostomy tube, to confirm the exposure of the inner ear to ofloxacin and to measure the concentration of ofloxacin in the otorrhea. One supportive study was also included in the submission.

Although the studies were well designed, the information/data in human pharmacokinetics section of the submission was not sufficient to evaluate the pharmacokinetic parameters such as bioavailability due to the minimal systemic absorption and the inconsistent dose delivery. After dosing the otic solution, concentrations of ofloxacin in serum were not measurable in many of the samples taken, and, in those samples in which ofloxacin was measurable, the concentrations were very low (ng/mL), which are on the order of one thousandth of what would be observed after an oral therapeutic dose.

Fluorescence was detected in pharynx of about 50% of patients who received the Otic solution, which indicated the exposure of middle ear to the ofloxacin. The presence of the fluorescence in the pharynx depended on how the solution was applied to the patients. No fluorescence was detected in any of the patients in one of the groups in Study 8280A-PRT004, which could result from the improper technique applied by the investigator. It implies that the drug might not reach the target site if the drug was administered incorrectly.

Ofloxacin was also measured in the mucous membrane collected from the patients who underwent middle ear surgery following topical drug administration. Although the variability of ofloxacin concentration in mucous membrane was high, ofloxacin was detected in 11 of 16 patients and the concentration can be as high as μg/g. Ofloxacin concentration in otorrhea was also measured in the patients. However, the elimination of ofloxacin was probably not biologic, and clearance was most likely related to simple loss from the site through the eustachian tube and/or to the exterior through the external auditory canal. On the other hand, the samples of otorrhea were collected from the external auditory canal so that it is uncertain whether the ofloxacin actually reached middle ear and the site of infection. Therefore, the information provided by otorrhea data are limited.

RECOMMENDATION:

The program to study the systemic absorption following the topical administration of ofloxacin otic solution was adequate. The human biopharmaceutics/pharmacokinetics section of the NDA is acceptable. The general comments and the proposed changes to labeling should be conveyed to the sponsor.

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Note: Appendix II contains the detailed data such as serum concentrations. This information is being retained in the Division of Pharmaceutical Evaluation III, and can be obtained upon request.

BACKGROUND:

Ofloxacin, a fluoroquinolone class antibiotic, has *in vitro* activity against a broad range of gram-positive and gram-negative aerobic and anaerobic bacteria including all the pathogens usually associated with infections of the external and middle ear. The injectable solution, tablets and ophthalmic solution were developed in the early 90s and were commercially available in the market. Ofloxacin is being developed as an otic

solution at 0.3% for treatment of otitis external (OE), chronic suppurative otitis media (CSOM) and acute otitis media (AOM) in adults and adolescents. Doses are 0.5 mL b.i.d. for 10 days, 0.5 mL b.i.d. for 14 day and 0.25 mL b.i.d. for 10 days for OE patients, CSOM patients, and AOM patients, respectively.

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

I. ***Bioavailability:***

Bioavailability could not be estimated due to the minimal systemic absorption and the inconsistent dose delivery following topical administration of the otic solution.

II. ***Pharmacokinetics:***

The pharmacokinetics studies were performed in three studies. Ofloxin® otic solution was given to each patient through the external auditory canal at a single dose. In Study 8280A-PRT004 and 8280-PRT005, plasma was collected at different time points and the concentrations of ofloxacin in plasma were measured. The results showed that ofloxacin was not measurable in most of samples and the concentration was very low even in those samples in which ofloxacin was measurable. In addition to ofloxacin measurement in plasma, the presence of fluorescence in the pharynx was also observed and reported in the two studies. Similarly, the fluorescence was observed only in some of the patients.

In Study 8280A-PRT001, the patients underwent middle ear surgery. Not only was ofloxacin measured in plasma but in otorrhea and mucosa membrane. The results were summarized in Table 1. As shown in the results, the appearance of ofloxacin in both plasma or in the pharynx were not predictable. The ofloxacin levels in plasma were very low after topical administration of ofloxacin solution compared with that after oral administration of ofloxacin. Therefore, when Ofloxin® was given to the patient, the efficacy should be the major concern rather than the safety. A supportive study was included in the submission and the results were summarized in Table 2.

Table 1. Summaries of pharmacokinetics studies

Study Number	Disease	Subjects Number Treatment	Placebo	Dose	Sampling Time	Mean Pharmacokinetic Parameters (CV%) C_{max}	T_{max} hr	AUC_{0-t} ng•hr/mL
8280A-PRT004	with tympanostomy tubes without active otitis media	17	8	10 drops 0.5 ml 1.5 mg	Serum: 0.5, 1, 2, 4, 6 hr;	Serum: n=5 of 17 subjects 4.1 ng/mL (33.2); Fluorescence in pharynx: n=8 of 17	n=5 0.8 hr (33.8)	n=5 17.7 (39.8)
8280-PRT005	tympanostomy tubes and otorrhea with otitis media	5	2	10 drops 0.5 ml 1.5 mg	Serum: 0, 1, 2, 4, 6 hr	Serum: n=3 of 5 subjects 5.4 ng/mL (63.9); Fluorescence in pharynx: n=3 of 5	n=3 1.3 (44.6)	n=3 20.8 (63.5)
8280A-PRT001	With chronic suppurative otic media (CSOM)	Group A: 20 (4 children; and 2 subjects were excluded); Group B: 18 (two subjects were excluded)	0	Adults: 10 drops 0.5 ml 1.5 mg Children: 5 drops 0.25ml 0.75 mg	**Group A:** Serum: 0, 0.5 hr (adults), and last otorrhea sampling time. Otorrhea: 0, 0.5 hr and the two other points at either 2, 4, 6 and 8 hours. **Group B:** Serum: at any two or three of 0,1,1.5, 2 and 2.5 hr; Mucosa: 1 or 1.5, or 2 or 2.5hr.	**Group A:** Serum: n= 4 of 12 subjects range:1.4-10 ng/mL; otorrhea: n=18 of 18 subjects range (30 minutes): 388.8-2849.8 µg/g; **Group B:** Serum: n=8 of 16 subjects range: 1.1-4.1 ng/mL (any time points) Mucosa: n= 11 of 16 subjects Highly variable 1.2-602 µg/g at any sampling time.	NA	NA

Table 2. Pharmacokinetic Parameters Of Ofloxacin From An Otic Solution

	Test	Dosage	Sampling	Results
8280J-MET002	Test 1: Acute or chronic otitis media	10 drops of 0.5% (2.5mg/0.5 ml) Multiple dose	Serum: 30 or 60 or 75 or 90 minutes. Mucous membrane: 30 or 60 or 75 minutes.	Serum: n=11 range: 4-17 ng/mL Mucous membrane: n=4 range: 19.5-319.5 µg/g
	Test 2: Suppurative otitis media	10 drops of 0.3% (1.5 mg/0.5 ml) Multiple dose	Serum: 30 minutes	Serum: n=13 range: <2-13 ng/mL
	Test 3: Otitis media	5 drops of 0.3% (0.75mg/0.25ml) Children Single dose	Serum :30-120 minutes	Serum: n=3 range: <2-13 ng/mL
	Test 4. Chronic Suppurative otitis media	10 drops of 0.1% (0.50mg/0.5 ml) Single dose	Otorrhea: 10 minutes	Otorrhea: n=3 range: 106.5-826.5 µg/mL

III *Formulation:*

The formulation used in the study consists of 0.3% ofloxacin, 0.0025% benzalkonium chloride and 0.9% sodium chloride. The pH of the solution was adjusted by HCL or NaOH.

The solutions used for pharmacokinetic and clinical studies are the same lots and manufactured by However, the market product is planned to be manufactured by Parke-Davis but the formulation is the same. Associated with the site changes, manufacture size and apparatus changed from L and from BFS[1] to BTC[2], respectively. An official request for waiver of bioequivalency testing as discussed with Agency on August 1, 1995, and confirmed by the Agency at the meeting was included in the submission. The Lot # of the solution used in Study 8280A-PRT001 was 2071-PRC. No bioequivalency study was performed. The summary of formulation development is given in Appendix I.

IV *Assay:*

COMMENTS:

1. The steady state concentration (C_{ss}) of ofloxacin was calculated based on the known pharmacokinetics data following iv infusion and oral administration. C_{ss} would have been 17.25 ng/mL following administration of ofloxacin otic solution at dose of 1.5mg assuming the bioavailability were similar to the oral administration based on the fact that C_{ss} was 4.6 μg/mL following oral administration of ofloxacin tablet at dose of 400 mg. Similarly, the C_{ss} would have been 20.63 ng/mL to 27 ng/mL assuming the 100% bioavailability following the administration of otic solution based on the fact that the serum peak concentration of ofloxacin at steady state were from 5.5 μg/mL to 7.2 μg/mL, respectively in two studies following intravenous doses of 400 mg of ofloxacin q 12 hours. Therefore, based on the calculation above, the serum ofloxacin concentration is expected to be at least 100 times lower following administration of otic solution. It is considered to be safe with respect to the systemic toxicity following the administration of otic solution.
2. It is worthwhile to point out that the most of subjects in the studies were adults. Only 4 children (age under 12) were included in only Study 8280A-PRT001.
3. The technique to administer otic solution was very important. The improper technique could result in the absence of fluorescence in the pharynx, the indicator of

[1] BFS: Blow-fill-seal unitary bottle/tip system (white opaque, low-density polyethylene) and cap (white opaque, polypropylene).

[2] BTC: White opaque, low-density, polyethylene bottle, white opaque, low-density polyethylene controlled drop-size tip and polyprolylene screw cap with extended tip.

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middle ear exposure to ofloxacin, like the case in one study group in Study 8280A-PRT004. It should be suggested to push the tragus forward instead of pull the auricle down in order to facilitate the penetration of the solution into the middle ear region.

Labeling Comments (to be sent to Sponsor)

In pharmacokinetics section of CLINICAL PHARMACOLOGY paragraph:

/S/

Jenny Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

RD/FT signed by Frank Pelsor, Pharm.D., Team Leader /S/

cc:
Division File: NDA 20-799
HFD-520 (C. McDonald, MO)
HFD-520 (B. Duvall-Miller)
HFD-340 (Viswanathan)
HFD-880 (Division File)
HFD-880 (F. Pelsor, TL)
HFD-880 (J Zheng, Reviewer)
CDR (attn: B. Murphy)

APPENDIX I

Study Summaries

Study No: Protocol 8280A-PRT004 Vol:23-24

Title: Single dose, double-blind, placebo-controlled, parallel group study to assess the pharmacokinetics and penetration of ofloxacin otic solution through a tympanostomy tube in adults without active otitis media.

Investigator and study center:

Objective: To determine the pharmacokinetic profile of ofloxacin after a single dose administration of ofloxacin otic solution, and to determine the time to penetration of ofloxacin from the external ear canal through a patent tympanostomy tube to the middle ear as determined by the presence or absence of fluorescence in the pharynx and bitter taste experience after dosing.

Design of Study: This was a two-site, double-blind, single dose, placebo controlled, randomized parallel group, outpatient study. Subjects 18 years of age or older with tympanostomy tubes in place and no signs or symptoms of middle or external ear infection and who met all inclusion/exclusion criteria were to be randomized in a 2:1 ratio to receive one dose (10 drops) of either ofloxacin 0.3% otic solution (1.5 mg) or placebo otic solution, respectively. It was planned that 24 subjected would be enrolled into the study and the 12 subjects would be randomly assigned to receive ofloxacin otic solution and the 8 subjects to receive placebo solution.

Formulations:	Test product:	Ofloxacin 0.3% otic solution
		Batch number: QSA1
		Dosing: 10 drops (1.5 mg)
	Reference:	Placebo otic solution
		Batch number: QKW1
		Dosing: 10 drops

Sample collection: 5 ml of blood was collected into a heparinized tube at 0 (predose), 0.5, 1, 2, 4 and 6 hours following administration of otic solution through the external auditory canal. Except the plasma concentration analysis, the presence or absence of fluorescence in subject's oropharynx, presence or absence of taste sensation in the oropharynx was observed by fluorescence detection and the time to penetration of ofloxacin from the external ear canal through a patent tympanostomy tube to the middle ear, the time of first taste sensation were documented. The presence of fluorescence was observed for 30 minutes at 5 minutes interval.

Assay Validation:

Specificity: The specificity of the method was satisfactory based on the submitted chromatogram.
Linearity: 1.07-107.33 ng/mL
Limit of Quantitation (LOQ): 1.00 ng/ml
Intra-day precision: The CV% of within runs (n=6) were less than 10% for the all quality control samples.
Inter-day precision: The CV% of between runs (n=6) were less than 10% for the quality control samples. However, the six values for each quality control sample were from the three duplicate samples (see comment).
Accuracy: The relative error of the quality control samples in guinea pig serums were less than 5% (n=6).
Recovery: The recoveries of ofloxacin in guinea pig serum at concentrations of 2.99 ng/mL, 39.92 ng/mL and 79.84 ng/mL were 68.94%, 93.09%, and 90.68%, respectively. The recovery of internal standard was 77.3%.
Stability: Ofloxacin was stable in human serum at 22°C for 4 hours and even 43.2 hours. It was also stable after 3 cycles of freeze-thaw in both guinea pig and human serum. Ofloxacin and its internal standard were also stable in potassium dihydrogen orthophosphate at -22°C for 182 days and 97 days, respectively.

Data Analysis: Continuous variables (age, time to fluorescence, time to taste sensation, vital signs) were analyzed using 2-way ANOVA. The Cochran-Mantel-Haenszel test was used to analyze the discrete variable: race, gender, presence of fluorescence, presence of taste sensation.
The pharmacokinetic parameters of interest include: AUC_{0-6} (or log AUC_{0-6}), elimination half life, C_{max}, T_{max}, elimination constant. The AUC_{0-6} was calculated by trapezoidal rule to respective last data point. C_{max} and T_{max} were reported from the plasma Vs concentration time curve.

Results: 25 subjects enrolled into and completed the study. 24 were randomized in a 2:1 ratio to receive ofloxacin or placebo while one subject was treated in an open label fashion in order to audit for possible protocol deviation at one site where no fluorescence in the oropharynx or taste alteration in any of the subjects enrolled were reported. It was concluded that the probable explanation for the result may have been the technique the sub-investigator used in pumping the tragus.
Demographic characteristics were similar for the two treatment groups in term of race, gender, age.
Pharmacokinetics Results:
Pharmacokinetic calculations were possible for five out of seventeen ofloxacin treated subjects. No placebo treated subjects had detectable serum levels of ofloxacin. The ofloxacin concentrations in plasma for each individual was shown in Table 1 of Appendix II. The summary of pharmacokinetic parameters are shown in the following table.

	Number of Subject	Original Value Mean ± SD	Log Value Mean ± SD
AUC_{0-6}	5	17.7 ± 7.05	2.80 ± 0.50
C_{max} (ng/mL)	5	4.1 ± 1.36	1.30 ± 0.43
T_{max} (hour)	5	0.8 ± 0.27	NA

The concentration of ofloxacin in the serum of subjects was measurable but not greatly above the LOQ of the analytical method (1 ng/mL) after delivery to the external auditory canal in subjects with tympanostomy tubes. However, when ofloxacin is given to subjects orally at therapeutic dosages for systemic infections, the concentrations of drug in the plasma are in the mg/mL range; i.e., about a thousand times the concentration observed in this study. Therefore, the systemic exposure by the otic route in subjects with tympanostomy tubes is an extremely small fraction relative to the exposure following a therapeutic oral dose.

Fluorescence and Taste Results:

No subjects had presence of fluorescence at baseline. Eight of 17 ofloxacin treated subjects and 0 out of 8 placebo treated subjects had fluorescence at one or more time points. All of the 8 subjects who had fluorescence were from site 401. A significantly higher percentage of subjects in the ofloxacin group had presence of fluorescence than the placebo group at each post-dose time point except at 20 minutes after dosing. The maximum number of subjects with detectable fluorescence was at 10 and 15 minutes after dosing. The results are summarized in the following table.

Evaluation	Ofloxacin	Placebo	P-value
Baseline	0	0	
5 min post-dose	6 (35%)	0	0.019*
10 min post-dose	7 (41%)	0	0.006**
15 min post-dose	7 (41%)	0	0.006**
20 min post-dose	4 (24%)	0	0.097#
25 min post-dose	5 (29%)	0	0.047*
30 min post-dose	6 (35%)	0	0.019*

*: $P<0.05$;
**: $P<0.01$;
#: $0.05<p<0.1$

Time to fluorescence and taste sensation evaluations are summarized in the table below. The mean time to fluorescence was 8.1 minutes in ofloxacin treated subjects. Three ofloxacin treated subjects experienced bitter taste. No placebo treated subjects experienced bitter taste. The mean time to first taste sensation was 7.5 minutes for the ofloxacin group and was not computed for the placebo group because there were no subjects in that group who experienced a taste sensation during the study. Any comparison between the two sites with respect to taste sensation was not possible because all 4 subjects who met the taste sensation criteria came from the same site (401).

Assessment		Ofloxacin	Placebo	P-value
Time to fluorescence (minutes)	N	8	0	
	Mean ± SD	8.1±7.04		
Taste Sensation (# of subjects)	None	13 (76%)	8 (100%)	0.324
	Salty	1 (6%)	0	
	Bitter	3 (18%)	0	
Time to First Taste (minutes)		7.5 ± 4.36		

Conclusions:

1. The concentration of ofloxacin in the serum was a very small fraction of the concentration of ofloxacin in the plasma after systemic administration. This demonstrates that topical delivery of the drug to the middle ear minimizes systemic exposure when compared to systemic administration.
2. It is highly likely that ingestion of the drug plays a prominent role in the absorption of the drug since most of the subjects who had measurable levels of drug in the serum also had fluorescence apparent in the pharynx.
3. If the drug was administered correctly (pushing inward on the tragus instead of pulling downward on the auricle), the fluorescence could be detected in the pharynx, indicating that the middle ear was exposed to the ofloxacin.
4. The technique of pumping the tragus was very important on how the drug penetrates through a tympanostomy tube.
5. The calculated $t_{1/2}$ of the drug in serum was greater than 4 hours, only slightly shorter than the collection time of the last serum sample after dosing (6 hours). Therefore, the accurate estimation of $AUC_{0-\infty}$ is not possible.

Comments:

1. The between-batch precision and accuracy were not appropriately evaluated using pig serum. The sponsor used the three duplicate quality control samples instead of the six separate batches.
2. The procedures for stability study (SOP No. AL-G1538-03, SOP No. AL-G1538-04, SOP No. AL-G1538-04.A01) and recovery study (SOP No. AL-G1540-03) should be included in the submission.
3. The term should be replaced by because the tubes were used for the blood collection.

Study No: Protocol 8280A-PRT005 Vol:26

Title: Single dose, double-blind, placebo-controlled, parallel group study to assess the pharmacokinetics and penetration of ofloxacin otic solution through a tympanostomy tube in adults with suppurative otitis media with otorrhea.

Investigator and study center:

Objective: To determine the pharmacokinetic profile of ofloxacin after a single dose administration of ofloxacin otic solution, and to determine the time to penetration of ofloxacin from the external ear canal through a patent tympanostomy tube to the middle ear in subjects with suppurative otitis media with otorrhea as determined by the presence or absence of fluorescence and bitter taste in the pharynx after dosing.

Design of Study: This was a multi-center, double-blind, single dose, placebo controlled, randomized parallel group, outpatient study. Subjects 18 years of age or older with tympanostomy tubes in place and a diagnosis of suppurative otitis media with otorrhea and who met all inclusion/exclusion criteria were to be randomized in a 2:1 ratio to receive one dose (10 drops) of either ofloxacin 0.3% otic solution (1.5 mg) or placebo otic solution, respectively. It was planned that 24 subjected would be enrolled into the study and the 12 subjects would be randomly assigned to receive ofloxacin otic solution and the 8 subjects to receive placebo solution.

Formulations:

Test product:	Ofloxacin 0.3% otic solution
	Batch number: QSAI
	Dosing: One dose 1.5 mg (10 drops)
Reference:	Placebo otic solution
	Batch number: QKWI
	Dosing: One dose (10 drops)

Sample collection: 5 ml of blood was collected into a heparinized tube at 0 (predose), 0.5, 1, 2, 4 and 6 hours following administration of otic solution through the external auditory canal. Except the plasma concentration analysis, the presence or absence of fluorescence in subject's oropharynx, presence or absence of taste sensation in the oropharynx was observed by fluorescence detection and the time to penetration of ofloxacin from the external ear canal through a patent tympanostomy tube to the middle ear, the time of first taste sensation were documented. The presence of fluorescence was observed for 30 minutes at 5 minutes interval.

Assay Validation:

Specificity: The specificity of the method was satisfactory based on the submitted chromatogram.
Linearity: 1.07-107.33 ng/mL
Limit of Quantitation (LOQ): 1.00 ng/ml
Intra-day precision: The CV% of within runs (n=6) were less than 10% for the all quality control samples.
Inter-day precision: The CV% of between runs (n=6) were less than 10% for the quality control samples. However, the six values for each quality control sample were from the three duplicate samples (see comment).
Accuracy: The relative error of the quality control samples in guinea pig serums were less than 5% (n=6).
Recovery: The recovery of ofloxacin in guinea pig serum at concentrations of 2.99 ng/mL, 39.92 ng/mL and 79.84 ng/mL were 68.94%, 93.09%, and 90.68%, respectively. The recovery of internal standard was 77.3%.
Stability: Ofloxacin was stable in human serum at 22°C for 4 hours and even 43.2 hours. It was also stable after 3 cycles of freeze-thaw in both guinea pig and human serum. Ofloxacin and its internal standard were also stable in potassium dihydrogen orthophosphate at -22°C for 182 days and 97 days, respectively.

Data Analysis: Continuous variables (age, time to fluorescence, time to taste sensation, vital signs) were analyzed using 2-way ANOVA. The Cochran-Mantel-Haenszel test was used to analyze the discrete variable: race, gender, presence of fluorescence, presence of taste sensation.
The pharmacokinetic parameters of interest include: AUC_{0-6} (or log AUC_{0-6}), elimination half life, C_{max}, T_{max}, elimination constant. The AUC_{0-6} was calculated by trapezoidal rule to respective last data point. C_{max} and T_{max} were reported from the plasma vs concentration time curve.

Results: Seven subjects (5 ofloxacin and 2 placebo) were enrolled at 2 sites (501 and 504). No subjects were enrolled at site 505. Demographic characteristics were similar for the two treatment groups. The ofloxacin plasma concentrations were included in Table 2 of Appendix II. The pharmacokinetics of ofloxacin was summarized in the following table.

Pharmacokinetics Results:

Parameters		AUC_{0-6} (ng/ml•hours)	C_{max} (ng/ml)	T_{max} (hours)
Number of Subjects		3	3	3
Original Values	Mean±SD	20.8±13.20	5.4±3.45	1.3±0.58
Log Values	Mean±SD	2.8±0.93	1.5±0.78	

Fluorescence and Taste Results:

No subjects had presence of fluorescence in the placebo treatment group. The percentage of subjects who had presence of fluorescence was similar for the two treatment groups at each post-dose time point.

Evaluation	Ofloxacin	Placebo	P-value
Baseline	0	0	
5 min post-dose	2 (40%)	0	0.317
10 min post-dose	3 (60%)	0	0.083
15 min post-dose	3 (60%)	0	0.083
20 min post-dose	1 (20%)	0	0.564
25 min post-dose	1 (20%)	0	0.564
30 min post-dose	1 (20%)	0	0.564

Time to fluorescence and taste sensation evaluations are summarized in the table below.

Assessment		Ofloxacin	Placebo	P-value
Time to fluorescence (minutes)	N	3	0	
	Mean ± SD	6.7±2.89		
Taste Sensation (# of subjects)	None	4 (80%)	2 (100%)	0.564
	Bitter	1 (20%)	0	
Time to First Taste (minutes)	N	1		
		1 ± 1.00		

Three of 5 ofloxacin treated subjects and 0 out of 2 placebo treated subjects had fluorescence at one or more time points. All of the three subjects who had fluorescence were from site 501.

Conclusion:

1. The concentration of ofloxacin in the plasma was a very small fraction of the concentration of ofloxacin in the plasma after systemic administration of the usual therapeutic doses.
2. Following delivery of ofloxacin to the middle ear by tympanostomy tube, the appearance of fluorescence in the pharynx of the most patients with otorrhea, demonstrated that the middle ear had been exposed to ofloxacin.

Comments:

1. Only seven subjects were included in the study. The conclusion from the study should be evaluated carefully.
2. Among the only 5 patients, fluorescence was detected in 3 (60%) patients. If the presence of fluorescence can be used as the indicator of the middle ear exposure to ofloxacin, the absence of fluorescence indicates the failure of delivery of the medicine into the middle ear, which could result in the treatment failure.

Study No: Protocol 8280A-PRT001 Vol:29

Title: Pharmacokinetic study of otorrhea in patients with chronic suppurative otitis media treated with ofloxacin otic solution.

Investigator:
Study Sites:

Objective: 1. To evaluate the concentration of ofloxacin in otorrhea and serum in patients with chronic suppurative otitis media (CSOM) and perforated ear drum treated with topical ofloxacin 0.3% otic solution; and
2. To evaluate the concentration of ofloxacin in mucous membranes and serum in patients with CSOM, perforated eardrum, and requiring middle ear surgery, after administration of topical ofloxacin 0.3% otic solution.

Design of Study: This was a multi-center, non-comparative, single dose, pharmacokinetic evaluation of the concentration of ofloxacin in otorrhea, serum and middle ear mucosa in subjects with chronic suppurative otitis media. The investigators were to have collectively enrolled a group of 30 subjects (20 adults and 10 children, Group A) who had chronic suppurative otitis media and a perforated eardrum. In addition, a second group (Group B) of 10 adults and 10 children were to have been enrolled if they had CSOM, a perforated eardrum and required middle ear surgery. Subjects could be either hospitalized or ambulatory.

Formulations: Test product: Ofloxacin 0.3% otic solution
Batch number: 2071-PRC
Dosing: One dose 1.5 mg (10 drops) for adults and children ≥12 years of age; 0.75 mg (5 drops) for children <12 years of age.

Sample collection: Group A: A minimum of 4 otorrheal samples were taken from the affected study ear; i.e., just before dosing, then at 30 minutes and at least two other time points at either 2, 4, 6 and 8 hours after application of ofloxacin; Venous blood samples were to be obtained at baseline and 0.5 hours after dosing (adults only), and at the time of the last otorrheal sampling (adults and children); Group B: Middle ear mucosa and serum samples were taken at one and two hours after application of ofloxacin otic solution.

Assay Validation:

Specificity: The specificity of the methods were satisfactory based on the submitted chromatogram. There is no interference peaks at the retention time of ofloxacin and the internal standard for both serum and otorrhea samples.
Limit of Quantitation (LOQ): 1.00 ng/ml for serum, 1μg/g for otorrhea, and 0.5 μg/g for mucosa.
Linearity and intra-day precision and accuracy (n=5):

	Serum	Otorrhea	Mucosa
Linearity	1 ng/mL-100ng/mL	1 μg/g-3500μg/g	0.5 μg/g-300μg/g
Precision	2.90% @ 3 ng/mL;	3.28% @ 3 μg/g;	0.62% @ 1.5μg/g;
	1.23% @ 40.00 ng/mL;	1.79% @ 1500μg/g;	0.46% @ 150μg/g;
	0.44% @ 80.00 ng/mL	0.70% @ 3000μg/g	1.43% @ 250μg/g
Accuracy	91.51% @ 3 ng/mL;	88.27% @ 3 μg/g;	99.27% @ 1.5μg/g;
	91.58% @ 40.00 ng/mL;	97.99% @ 1500μg/g;	99.56% @ 150μg/g;
	92.52% @ 80.00 ng/mL	98.98% @ 3000μg/g	98.94% @ 250μg/g

Inter-day precision and accuracy: The assay was conducted only three times on different days. The CV were less than 10% for all quality control samples of serum, otorrhea, and mucosa at low, medium and high levels. The relative error of the all quality control samples of serums, otorrhea, and mucosa at low, medium and high levels were less than 10% (n=3).
Recovery: The recovery of ofloxacin in serum, otorrhea, and mucosa were evaluated and summarized in following table.

	Ofloxacin		Internal Standard	
	Concentration	Recovery (%) n=5	Concentration	Recovery (%) n=15
Plasma	3.00 ng/ml 40.00 ng/ml 80.00 ng/ml	88.6±4.2 84.9±2.2 88.8±2.4	250.0 ng/ml	86.1±2.0
Otorrhea	3.0 μg/g 1500 μg/g 3000 μg/g	78.0±2.4 95.0±1.5 93.5±1.7	400.0 ng/ml	97.2±1.4
Mucous membrane	1.500 μg/g 150.0 μg/g 250.0 μg/g	86.9±2.6 97.0±4.1 101.0±5.9	150.0 ng/ml	93.9±5.6

Stability: Ofloxacin was found to be stable at room temperature for at least 24 hours and at -20°C for at least 6 months. Regarding freezing and thawing, the samples were found to be stable through 2 cycles.

Data Analysis: Summary statistics (mean ±standard deviation) were to be calculated for the concentrations of ofloxacin.

No pharmacokinetic parameters could be calculated because plasma were collected at limited time points (2 or 3 time points/individual).

Results: A total of 38 subjects were enrolled in the study (20 subjects in Group A and 18 subjects in Group B) and all completed the study. Only four patients were below 12 years old and they all are included in Group A. There are 9 patients who had detectable drug levels in specimens at baseline (7 in otorrhea and 2 in serum), including 3 patients who received ofloxacin 0.3% otic solution within 7 days prior to the study treatment, 4 patients who had been prescribed ofloxacin 0.3% otic solution more than 7 days prior to the study, 2 patients who might be prescribed ofloxacin solution without knowing it. For the purpose of pharmacokinetic analysis, patients were not excluded from the analysis unless the pre-dosing baseline levels exceeded more than 1/20 of the maximum levels. Based on the criterion, four patients were excluded from the analysis, including 2 patients in Group A and two patients in Group B.

Group A:

Otorrhea: The plot and the concentrations of ofloxacin in otorrhea for each individual were shown in Figure 1 and Table 3 of Appendix II. The maximum concentrations of ofloxacin in otorrhea was achieved at 30 min (mean of 1762.4 μg/g) with rapid subsequent decline of the drug, but it was detected as long as 8 hours after application. Six bacterial strains were isolated from the middle ear, and the MIC of ofloxacin ranged from mg/mL. Therefore, otorrhea drug concentrations in 2 of 3 subjects covered the highest MICs of these pathogens at least up to 8 hours in patients whose otorrhea was measured after a single application.

Plasma: Individual data of plasma drug levels are listed in Table 4 of the Appendix II. Ofloxacin was detected in plasma of four patients out of the 12 patients from whom the plasma was collected. The range of the concentrations are from ng/mL.

Group B:

Mucosa: Individual data of mucosal drug levels are shown in Table 5 of the Appendix II. There was a high patient-to-patient variability in mucosal drug concentrations. Drug could be detected in 11 out of 16 patients who are evaluable for the analysis while no drug were detected in 5 out of the 16 patients. The drug concentration reached as high as μg/g in some patients.

Plasma: Individual data of drug levels were shown in Table 6 of the Appendix II. Plasma drug levels were detected in 7 out of 12 patients at 1 hour sampling. The highest plasma concentration measured was ng/mL. The drug levels were also detected at 2 hours after drug application in one case.

Conclusion:

1. The samples of otorrhea were collected from the external auditory canal in Group A so that it is uncertain whether the ofloxacin actually reached middle ear and the site of infection. Therefore, because of the uncertainty of the history of the otorrhea samples, the conclusions which can be drawn from them are limited. On the other hand, the elimination of drug from the otorrhea was probably not biologic, and clearance was

most likely related to simple loss from the site through the Eustachian tube and/or to the exterior through the external auditory canal.

2. The ofloxacin was detectable in mucosa membrane of the patients in Group B, which indicate the middle ear was exposed to the drug. However, the variability of ofloxacin concentrations in mucosa was high and no ofloxacin was detected in 5 out of 16 patients (31%).

Comments:

1. The working standard solutions were prepared to have the unit of μg/ml for ofloxacin assay in otorrhea and mucous membrane. It is not clear how it was converted to unit of μg/g. The raw data were suggested to be submitted.
2. It is not adequate to use only three quality control samples for validation of inter-assay precision and accuracy.
3. The procedure for assay recovery was not described in the submission.

Study No: 8280J-MET002 Vol: 29

Title: Ofloxacin concentration in the serum, mucous membrane of the middle ear and otorrhea after administration of ofloxacin otic solution

Investigator:

Objective: To investigate the distribution of ofloxacin into the serum and the mucous membrane of the middle ear.

Design of Study: It is non-comparative study. In two tests, multiple doses were given to the patients and in other two tests a single dose was given to the patients. Serum, mucous membrane or otorrhea samples were collected and the ofloxacin concentrations were measured.

Formulation: Test product: 0.3% or 0.5% or 0.1% ofloxacin otic solution
Batch number: unknown

Assay:

Results: The results were summarized in the following table.

Pharmacokinetic Parameters Of Ofloxacin From An Otic Solution

8280J-MET002	Test 1: Acute or chronic otitis media	10 drops of 0.5% (2.5mg/0.5 ml) Multiple dose	Serum: 30 or 60 or 75 or 90 minutes. Mucous membrane: 30 or 60 or 75 minutes.	Serum: n=11 range: ng/mL Mucous membrane: n=4 range: μg/g
	Test 2: Suppurative otitis media	10 drops of 0.3% (1.5 mg/0.5 ml) Multiple dose	Serum: 30 minutes	Serum: n=13 range ng/mL
	Test 3: Otitis media	5 drops of 0.3% (0.75mg/0.25ml) Children Single dose	Serum :30-120 minutes	Serum: n=3 range: ng/mL
	Test 4. Chronic Suppurative otitis media	10 drops of 0.1% (0.50mg/0.5 ml) Single dose	Otorrhea: 10 minutes	Otorrhea: n=3 range: μg/mL