CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-918

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA # :	21-918
Drug Name:	Ciprofloxacin Otic Solution, 0.2%
Indication(s):	Otitis Externa
Applicant:	Parexel (acting as US Agent on behalf of Laboratorios SALVAT, S.A.)
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Biometrics Division:	Division of Biometrics IV
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Documents Reviewed:	\\CDSESUB1\N21918\N_000\2005-06-09
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1. EXECUTIVE SUMMARY

1.1 Introduction

This NDA submission (NDA 21918) seeks to gain approval for the use of Ciprofloxacin Otic Solution 0.2% as twice daily treatment of otitis externa (OE). This NDA is submitted as a 505 (b) (2) using Cipro HC (Ciprofloxacin hydrochloride and hydrocortisone otic suspension) as the reference listed drug (RLD). In contrast to the RLD, the proposed drug product (Ciprofloxacin Otic Solution 0.2%) consists of a single active ingredient, Ciprofloxacin hycrochloride, and is devoid any corticosteroid component. This NDA submission utilizes Ciprofloxacin data from published data sources and references previous Agency determinations regarding the safety and efficacy of Ciprofloxacin. Data from one pivotal Phase III, randomized, evaluator blinded, multi-center study (CIPROT III/03 IA 02) is included in the submission. Study CIPROT III/03 IA 02 was conducted under IND 67173 and involved 630 adult and pediatric subjects in both the United States and Spain to demonstrate non-inferiority of the proposed drug product to comparator, Polymyxin B/Neomycin/Hydrocortisone (PNH) within a 10% non-inferiority margin.

1.2 Conclusions and Recommendations

Pivotal Study CIPROT III/03 IA 02 achieved both co-primary endpoints by demonstrating the non-inferiority (within a 10% margin) of Ciprofloxacin Otic Solution 0.2% therapy to comparator therapy (PNH) for the treatment of otitis externa (OE) in both the Clinical Intent-to-treat (ITT) and Clinical Per-Protocol (CPP) analysis populations. According to the FDA analysis, comparisons of clinical cure rates at Test of Cure (TOC) with Ciprofloxacin vs. PNH were: 86.6% vs. 81.1%, a 5.6% (-0.9%, 12.1%) treatment difference (95% CI) in the CPP population and 81.4% vs. 76.7%, a 4.7% (-1.6%, 11.1%) treatment difference (95% CI) in the CITT population (Table 5). Non-inferiority of Ciprofloxacin therapy to PNH therapy within a 10% margin was demonstrated since the lower limit of the 95% CI of the treatment difference (Ciprofloxacin – PNH) was greater than -10% in both the CPP and CITT population analyses.

Secondary analyses in the overall population were generally consistent with the primary analysis and show Ciprofloxacin Otic Solution 0.2% therapy as non-inferior (within a 10% margin) to PNH therapy for endpoints which include: proportions of subjects with Clinical Cure at Visit 3 (end of treatment (EOT)), Clinical Improvement at Visit 4 (TOC), Clinical + Microbiological Cure at Visit 3 and at Visit 4. Proportions of subjects with resolution of otalgia and improvement in otalgia at Visit 3 and at Visit 4 were generally similar between Ciprofloxacin and PNH.

The Sponsor concluded that Ciprofloxacin Otic Solution 0.2% administered twice daily (bid) for 7 days was non-inferior (within a 10% margin) to PNH administered 3 times daily (tid) for the treatment of OE in children, adolescents, and adults. The Statistical Reviewer, however, did not agree with the Sponsor's conclusion with respect to adults (18 years old or older). While this

study provides strong overall evidence regarding the non-inferiority of Ciprofloxacin therapy to PNH therapy for children and adolescents, this study raises doubts about the efficacy of Ciprofloxacin otic in the treatment of adults with OE. As required by 21 CFR 314.50(d)(5)(v), *post-hoc* analyses were conducted by gender, age, and racial subgroups. For non-adults, the comparison of clinical cure rates at TOC with Ciprofloxacin vs. PNH were: 93.9% vs. 78.7%, a treatment difference (95% CI) of 15.1% (7.0, 23.2) in the CPP population. This contrasts with results for adults with 76.0% vs. 83.6%, a -7.6% (-18.4%, 3.1%) treatment difference (95% CI). See Table 9 that shows consistent results in the CITT population. Additional sensitivity analyses are included in Section 4. Separate comparisons for adults and non-adults are highly relevant due to results from two previous studies [1,2] included in the Sponsor's submission which suggested lower efficacy rates in adults treated with PNH, Ciprofloxacin, Cipro HC or ofloxacin. The FDA's previous findings of effectiveness for Cipro HC otic, the RLD, also showed lower efficacy rates in adult patients for both the Cipro HC and PNH treatment arms. Based on the clear differences in adult and non-adult populations and the magnitude of treatment differences found in favor of PNH therapy, both inferential evidence and direct evidence of non-inferiority of Ciprofloxacin therapy in an adult population were not considered to be substantial. The Statistical Reviewer feels that the difference in results for non-adults and adults warrant mention in the label even though the clinical relevance is unclear.

1.3 Brief Overview of Study CIPROT III/03 IA 02

Study CIPROT III/03 IA is a pivotal Phase III, randomized, evaluator blinded, multi-center study comparing Ciprofloxacin Otic Solution (0.25 mL bid for 7 days) to Polymyxin B/Neomycin/Hydrocortisone (PNH) (4 drops bid for subjects thirteen years and older, 3 drops bid for subjects 12 years and under). Study CIPROT III/03 IA 02 was conducted under IND 67173 and involved 630 adult and pediatric subjects in both the United States and Spain to demonstrate non-inferiority of the proposed drug product to comparator, PNH within a 10% non-inferiority margin. Clinical efficacy was assessed at visit 4, the Test of Cure (TOC) visit, which occurred 14–16 days after the first dose of the study drug was received. The primary outcome was Sponsor assessment of clinical response at TOC evaluated in the CPP and CITT populations as co-primary endpoints.

1.4 Statistical Issues and Findings

The main statistical issue in Study CIPROT III/03 IA 02 is that overall study results, as well as results from other studies included in the Sponsor's submission, were highly inconsistent across the adult and non-adult patient subgroups treated with Ciprofloxacin. Consequently both patient subgroups were analyzed separately in a *post-hoc* analysis. While results in the non-adult patient subgroup showed strong evidence of non-inferiority, results in the adult patient subgroup provided contradictory results. The strength of the evidence leads to a concern that the adult subgroup comes from a different distribution than the non-adult and that ciprofloxacin may be inferior to PNH in treating OE in adults. Since this is a *post-hoc* analysis, the clinical meaning is unclear but the difference in results between adults and non-adults warrant mention on the product label.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Ciprofloxacin is a fluoroquinolone antibiotic with broad-spectrum antibacterial activity. It is a well characterized compound that is used intravenously, orally, and topically to treat a variety of infections.

2.1.2 Rationale for Drug Product Development

Ciprofloxacin is marketed worldwide for the treatment of systemic and topical infections, including otitis externa. Otic Ciprofloxacin products approved in the U.S. for this indication include Cipro HC, a combination of Ciprofloxacin and hydrocortisone, with a prescribed dose of 3 drops BID for 7 days, for a total daily dose of approximately 0.6 mg Ciprofloxacin. More recently, Ciprodex, a combination of Ciprofloxacin and dexamethasone, was approved to treat otitis externa with a prescribed daily dose of 0.84 mg Ciprofloxacin, also for 7 days. SALVAT's proposed formulation of Ciprofloxacin Otic Solution 0.2% provides a total dose of approximately 1.0 mg/day.

2.2 Data Sources

- Files of \\CDSESUB1\N21918\N_000\2005-06-09

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Primary Objective: The Sponsor's primary objective was to determine whether the proportion of subjects with Clinical Cure (assessed at TOC) after 7 days of twice-daily treatment with Ciprofloxacin otic solution 0.2% was non-inferior to the proportion with Clinical Cure after 7 days of three-times-daily treatment with PNH otic solution in children, adolescents, and adults with acute diffuse otitis externa.

Design: This was a randomized, parallel-group, evaluator-blinded, active-controlled, multicenter study comparing Ciprofloxacin otic solution 0.2% with PNH otic solution in the treatment of acute diffuse OE in children, adolescents, and adults.

The visit schedule is shown in Table 1. Clinical efficacy was assessed at the Test of Cure (TOC) visit.

Table 1: Visit Schedule

Visit number	Visit name	Schedule per Study Protocol
1	Baseline	Day 1
2	OT (telephone contact)	Day 3-4
3	EOT	Day 8-10
4	TOC	Day 15-17

Source: Section 9.1 of Sponsor's study report,
Day numbers are measured from baseline.
OT- On treatment, EOT- End of Treatment, TOC- Test of Cure

Primary Efficacy Endpoint:

- Sponsor assessment of clinical response for the Clinical Per Protocol (CPP) population and Clinical ITT (CITT) populations at the Test of Cure (TOC) visit (Days 15-17).

Secondary Efficacy Endpoints:

- Clinical Cure at Visit 3
- Clinical Improvement at Visits 3,4
- Resolution of Otalgia at Visit 3,4
- Improvement of Otalgia at Visit 3,4
- Clinical + Microbiological Improvement at Visit 3,4

Populations Analyzed:

• CITT: All randomized subjects who received at least 1 dose of study medication. The treatment group of a patient was determined by the treatment to which the patient was randomized, not necessarily the treatment the patient received.

• CPP: All subjects in the CITT population who had no protocol violations.

• MITT: All subjects in the CITT population whose Visit 1 microbiological culture yielded 1 or more pathogens.

• MPP: All subjects in the CPP population whose Visit 1 microbiological culture yielded 1 or more pathogens and who had microbiological results (Eradication, Presumed Eradication, Persistence, or Superinfection) from Visit 3 and/or Visit 4.

Statistical Reviewer Comments: *Note that the 'ITT population' as defined in the Sponsor's submission does not include subjects who were randomized but did not receive at least one dose of treatment medication. Generally, the Division prefers that the 'ITT population' is defined to include all randomized subjects.*

3.1.2 Subject Disposition, Demographic and Baseline Characteristics

Subject Disposition

Disposition of subjects is summarized in Table 2. Six hundred sixty-six subjects were screened, of whom 630 entered the study and were randomized. Of the subjects who did not enter the study, most were excluded because their otitis did not meet the protocol requirements for acute diffuse otitis externa. Study medication was distributed to 54 study centers, 48 in the US and 6 in Spain. Subjects were randomized at 47 study centers, 42 in the US and 5 in Spain.

The large majority of subjects, 95% of subjects in both treatment groups, completed the study. Of subjects who withdrew before completing the study, the largest proportion was lost to follow-up. Three subjects in each treatment group were withdrawn because of adverse events. Consent was withdrawn by 1 patient in the Ciprofloxacin group and 5 subjects in the PNH group. Three subjects in the Ciprofloxacin group and 1 in the PNH group were withdrawn because of treatment failure.

Table 2: Subject Evaluation Groups, Number (%) of Subjects

Evaluation Group (All Randomized Subjects)	Ciprofloxacin (N=318)	PNH (N=312)	Total (N=630)
Safety*	319 (100.3)	309 (99.9)	628 (99.7)
Clinical Intent-to-Treat (CITT)	318 (100.0)	309 (99.0)	627 (99.5)
Clinical Per Protocol (CPP)	247 (77.7)	243 (77.9)	490 (77.8)
Microbiological ITT (MITT)	232 (73.0)	217 (69.6)	449 (71.3)
Microbiological PP (MPP)	174 (54.7)	174 (55.8)	348 (55.2)

Source: Sponsor's Statistical Table 3

* Patient 105-020 did not sign a required document and was included in the Safety population but not in any of the efficacy analysis populations.

Statistical Reviewer Comments: *Of the 630 subjects enrolled, 627 subjects were treated with either Ciprofloxacin or PNH. Of these treated subjects, 490 (77.8%) were included in the Clinical Per Protocol population at TOC.*

Demographics and Baseline Characteristics:

Demographic characteristics of the Safety population are summarized in Table 3. Mean age was approximately 24 years; median age was 14 years in the Ciprofloxacin group and 15 years in the PNH group. Slightly less than half of the subjects were 12 years old or younger. Slightly more than half of the subjects were under 18 years old. Almost three-quarters of the subjects participated in the study in the US, and the remainder participated in Spain. The majority (approximately 87%) of subjects were Caucasian; approximately 7% were Hispanic; approximately 3% were black; and the remainder were Asian or of other ethnic groups.

Table 3: Demographic Characteristics: Safety Population

		Ciprofloxacin (N=319)	PNH (N=309)	Total (N=628)
Age, years	Mean (SD)	23.5 (18.8)	23.9 (18.6)	23.7 (18.7)
	Median	14	15	15
	Min, Max	2, 83	2, 76	2, 83
Age category, n (%)	≤12 years	145 (45.5)	131 (42.4)	276 (43.9)
	>12 years	174 (54.5)	178 (57 6)	352 (56.1)
	<18 years	175 (54.9)	161 (52.1)	336 (53.5)
	≥18 years	144 (45.1)	148 (47.9)	292 (46.5)
Sex, n (%)	Male	176 (55.2)	140 (45.3)	316 (50.3)
	Female	143 (44.8)	169 (54.7)	312 (49.7)
Country, n (%)	United States	233 (73.0)	222 (71.8)	455 (72.5)
	Spain	86 (27.0)	87 (28.2)	173 (27.5)
Race, n (%)	Caucasian	281 (88.l)	266 (86.1)	547 (87.1)
	Hispanic	21 (6.6)	22 (7.1)	43 (6.8)
	Black	11 (3.4)	10 (3.2)	21 (3.3)
	Asian	2 (0.6)	4 (1.3)	6 (1.0)
	Other	4 (1.3)	7 (2.3)	11 (1.8)

Source: Sponsor's Statistical Table 4.1.5

Statistical Reviewer Comments: *The age and ethnic compositions of the two treatment groups were similar. There was a slightly higher percentage of male subjects in the Ciprofloxacin arm than in the PNH arm (approximately 55% vs. 45%). The demographic characteristics of the CPP and CITT populations were similar to those of the Safety population.*

Protocol Deviations:
Subjects with any of the following deviations from the protocol were excluded from the CPP and MPP populations:

• Violation of any of the inclusion or exclusion criteria.

• Use of prohibited concomitant medications (unless the prohibited medication was used for treatment of otitis externa due to lack of efficacy of the treatment assigned to the patient at randomization).

• Failure to complete Visit 3 and Visit 4 (unless the patient's outcome was Clinical Failure at an earlier visit than Visit 4).

• Attendance at Visit 3 or Visit 4 outside the specified evaluation window.

• Compliance with study treatment not between 80% and 120% (Subjects with Clinical Failure were included if they had compliance rates between 80% and 120% during the first 3 days of study treatment).

Protocol deviations are summarized in Table 4. Approximately 22% of subjects in each treatment group had protocol violations that caused them to be excluded from the CPP and MPP populations. More than 1 deviation could be reported for an individual patient. The types of violations observed were very similar between treatment groups. The most common violations were non-compliance with study medication, use of prohibited concomitant medications and occurrence of Visit 3 and/or Visit 4 outside the allowed time windows.

Table 4: Summary of Protocol Deviations

	Number (%) of Subjects		
Category	Ciprofloxacin	PNH	Total
Subjects with protocol violations	71 (22.3)	69 (22.1)	140 (22.2)
Type of violation:			
Non-compliant with study medication	26 (8.2)	26 (8.3)	52 (8.3)
Used prohibited concomitant medication	29 (9.1)	21 (6.7)	50 (7.9)
Visit 3 and/or Visit 4 outside window*	17 (5.3)	20 (6.4)	37 (5.9)
Did not complete Visit 3 and Visit 4	14 (4.4)	13 (4.2)	27 (4.3)
Violation of inclusion or exclusion criteria	5 (1.6)	5 (1.6)	10 (1.6)
Other	0	2 (0.6)	2 (0.3)

Source: Sponsor's Statistical Table 2

Statistical Reviewer Comments: *The primary reason for these protocol deviations was non-compliance with study medication. Protocol violations were similar for both treatment groups.*

3.1.3 Statistical Methodologies

Primary Efficacy Assessment: Clinical efficacy was analyzed in the CPP and CITT populations using 95% confidence intervals comparing the proportion of Subjects with a clinical response of success (Sponsor assessed clinical cure at TOC). The confidence intervals on the differences in proportions were computed using the normal approximation to the binomial distribution. The agreed upon non-inferiority margin was -10%.

Additional Efficacy Assessments: Additional efficacy analyses included the following secondary endpoints:

- Clinical Cure at Visit 3
- Clinical Improvement at Visits 3,4
- Resolution of Otalgia at Visit 3,4
- Improvement of Otalgia at Visit 3,4
- Clinical + Microbiological Improvement at Visit 3,4