CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-537

STATISTICAL REVIEW(S)

July 18, 2003

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/Serial Number:	21-537
Drug Name:	CIPRODEX® OTIC SUSPENSION (ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension)
Indication:	1. Acute otitis media with tympanostomy tubes
	2. Acute otitis externa
Sponsor:	Alcon, Inc
Dates:	Submission Date: 9/23/2002; Received Date: 9/25/2002; PDUFA Date: 7/25/2003; Review Completion Date: 7/18/2003
Review Status:	Standard Review
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Joel Jiang, Ph.D.
Concurring Reviewers:	Daphne Lin, Ph.D., Statistical Team Leader
	Mohammad Huque, Ph.D., Statistical Division Director
Medical Division:	Division of Anti-infective Drug Division (HFD-520)
Clinical Team:	Medical Officer: Tom Smith, M.D.
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Project manager:	LT. Daniel Nguyen, HFD-520

Keywords: NDA review, clinical studies, efficacy evaluation, statistical analysis

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Reviewer's Note: Throughout the review, the following terms are abbreviated and referred to as: AOE = acute otitis externa; AOMT = acute otitis media with tympanostomy tubes; BID = twice daily; Ciprodex = Ciprodex® Otic suspension (ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension); EOT = end of treatment; Floxin = FLOXIN Solution (ofloxacin 0.3%); EOT = end of treatment, FU = follow-up; ITT = intent-to-treat; MITT = modified intent-to-treat; MO = Medical Officer, MPP = microbiologic per-protocol; PP = per-protocol; TID = three times daily; TOC = test of cure.

Confidence intervals for differences in outcome rates (Ciprodex minus control) are reported as $_{n1,n2}(l, u)_{p1,p2}$, *where* n_1 *is the number of Ciprodex subjects,* n_2 *is the number of control subjects, l and u are the lower and upper bounds of the 95% confidence interval, respectively,* p_1 *is the response rate in Ciprodex subjects, and* p_2 *is the response rate in control subjects.*

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

This NDA submission was to evaluate the efficacy and safety of Ciprodex in the treatments of AOMT and AOE, and each indication was supported by two pivotal studies.

For the treatment of AOMT, Study C99-59 showed that Ciprodex was superior to Ciprofloxacin in time to cessation of otorrhea. Study C00-52 showed therapeutic non-inferiority to the approved comparator Floxin, but did not its superiority. These studies support the efficacy claim of Ciprodex (3 drops BID for 7 days) for the AOMT indication.

For the treatment of AOE, both studies C98-18 and C98-19 showed therapeutic non-inferiority to the approved comparator Cortisporin. These studies support the efficacy claim of Ciprodex (3 drops BID for children and 4 drops BID for adults for 7 days) for the AOE indication.

In addition, all of the four pivotal studies demonstrated that Ciprodex and its comparators provided substantially comparable safety profiles

Based on the above findings, it is the opinion of this reviewer to conclude that the accessible data from four pivotal studies of this submission supported the use of Ciprodex with proposed treatment regimen in the treatments of AOMT and AOE and the trial provided sufficient evidence to confirm that Ciprodex as an effective and safe medicine in these two indications.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submits this NDA in order to obtain approval to market its Ciprodex® Otic suspension (ciproflxacin 0.3% and dexamethasone 0.1% otic suspension) for the topical treatment of otic bacterial infections and inflammation, that is, AOMT and AOE. Ciprodex contains the synthetic broad-spectrum antibacterial agent, ciprofloxacin hydrochloride, combined with the anti-inflammatory corticosteroid and dexamethasone, in a sterile, preserved suspension for otic use.

ACUTE OTITIS MEDIA WITH TYMPANOSTOMY TUBES

Acute otorrhea is the most common complication after insertion of tympanostomy tubes with reported postoperative incidence rates of 10% to 50%. The vast majority (90% to 95%) of AOMT cases involve pediatric subjects between 1 and 12 years of age. In general, such subjects will experience between two to six episodes of AOMT characterized by purulent or mucopurulent discharge. Microorganisms commonly isolated from AOMT subjects include: *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus,* and *Pseudomonas aeruginosa*

In the treatment of AOMT, the Ciprodex therapy of antibiotic and steroid is expected to be effective for the relief of pain in AOE subjects for cessation of otorrhea, and for the reduction and prevention of persistent middle ear mucosal changes in rats with experimental AOMT.

To support the indication of AOMT, two pivotal phase III studies (C99-59 and C00-52 were submitted for review. Both studies were randomized, observer-blind, multicenter, active-controlled, parallel-group study. The study population included pediatric subjects aged from 6 months to 12 years of age, with a patent tympanostomy tube, clinically diagnosed with acute otitis media and otorrhea of 3 weeks or less duration, visible by the parent/guardian.

Study C99-59

Eligible subjects who met the entry qualifications were randomized (Day 1) in an equal ratio (1:1) to one of two treatments: Ciprodex (3 drops BID for 7 days) and Ciloxan (3 drops BID for 7 days). The study was approximately three weeks in duration with four scheduled visits: Visit 1 on Day 1 (baseline), Visit 2 on Days 3-5 (during treatment), Visit 3 on Days 8-10 (EOT) and Visit 4 on Days 14-17 (TOC). According to the inclusion/exclusion criteria, 201 subjects (103 Ciprodex and 98 Ciloxan) were enrolled, randomized, received study drug and were evaluable for the safety analyses. Nine of the 201 subjects (3 Ciprodex and 6 Ciloxan) were excluded from the ITT data set due to no on-therapy FU visit. Of the 192 subjects evaluable for ITT analysis, 157 subjects (84 Ciprodex and 73 Ciloxan) were evaluable from MO's PP set. It was initiated on March 10, 2000 and completed on February 2, 2001.

The primary objective of the study was to demonstrate therapeutic superiority of Ciprodex relative to Ciloxan for the time to cessation of otorrhea. The primary efficacy variable was the time to cessation of otorrhea in ITT subjects. The Log-rank test (Kaplan-Meier survival analysis) was used to compare median time to cessation between Ciprodex and Ciloxan.

The safety evaluation was conducted on all subjects who were randomized into the study and received at least one dose of study drug. The safety analysis is based on the extent of exposure to study drug and adverse events.

Study C00-52

Eligible subjects who met the entry qualifications were randomized (Day 1) in an equal ratio (1:1) to one of two treatments: Ciprodex (4 drops BID for 10 days) and Floxin (5 drops BID for 7 days). The study was approximately three weeks in duration with four scheduled visits:

Visit 1 on Day 1 (baseline), Visit 2 on Days 3-5 (during treatment), Visit 3 on Days 11-13 (EOT) and Visit 4 on Days 18-21 (TOC). According to the inclusion/exclusion criteria, 599 subjects (297 Ciprodex and 302 Floxin) were enrolled, randomized, received study drug and were evaluable for the safety and ITT analyses. Of the 599 subjects evaluable for ITT analysis, 456 subjects (236 Ciprodex and 220 Floxin) were evaluable from MO's PP set. It was initiated on February 14, 2001 and completed on May 20, 2002.

The primary objective of the study was to demonstrate therapeutic non-inferiority of Ciprodex to Floxin. The primary efficacy variables were the proportions of subjects in each treatment group with clinical cure and microbiologic success at the TOC visit. Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical cure rates or microbiologic success rate at TOC between Ciprodex and Floxin for PP and ITT subjects or MPP and MITT subjects. A delta value of 0.1 is defined as a non-inferiority margin.

The safety evaluation was conducted on all subjects who were randomized into the study and received at least one dose of study drug. The safety analysis is based on the extent of exposure to study drug and adverse events.

ACUTE OTITIS EXTERNA

AOE is a diffuse cellulitis and bacterial infection of the external auditory meatus that may involve underlying structures, the skin of the pinna, and regional lymph nodes. Subjects with AOE usually complain of unilateral ear pain, itchiness, and discharge, and the auricle is often tender to palpation. Mild to moderate erythema and a foul-smelling grayish-green discharge are present. The external auditory canal may be edematous and, in its most severe form, may obscure erythema. Typical bacterial pathogens include Pseudomonas aeruginosa, Staphylococcus aureus, and Proteus and Streptococcus spp.

In the treatment of AOE, the expected benefits of Ciprodex therapy include elimination of organisms susceptible to ciprofloxacin, decrease or cessation of otic discharge, reduction of inflammation, and a more rapid reduction in ear pain.

To support the indication of AOE, two pivotal phase III studies (C98-18 and C98-19) were submitted for review. Both studies were randomized, observer-blind, multicenter, active-controlled, parallel-group study. The study population included subjects aged 1 year and older, with a clinical diagnosis of moderate to severe AOE. In both studies, randomized subjects were administered Ciprodex 3 drops BID for children and 4 drops BID for adults for 7 days, and returned for three FU visits on Day 3, Day 8, and Day 18 (TOC visit).

Study C98-18

Eligible subjects who met the entry qualifications were randomized (Day 1) in an equal ratio (1:1:1) to one of three treatments: Ciprodex (3 drops BID for children and 4 drops BID for adults for 7 days), Ciloxan (3 drops BID for children and 4 drops BID for adults for 7 days),

and Cortisporin (3 drops TID for children and 4 drops TID for adults for 7 days). According to the inclusion/exclusion criteria, 909 subjects (305 Ciprodex, 305 Ciloxan, and 299 Cortisporin) were enrolled, randomized, received study drug and were evaluable for the safety and ITT analyses. Of the 909 subjects evaluable for ITT analysis, 785 subjects (262 Ciprodex, 274 Ciloxan, and 249 Cortisporin) were evaluable from MO's PP set. It was initiated on April 17, 1998 and completed on May 15, 2000.

The primary objectives of the study were to demonstrate therapeutic non-inferiority of Ciprodex to both Ciloxan and Cortisporin for clinical cure rates, also therapeutic non-inferiority of Ciloxan to Cortisporin for clinical cure rates, and superiority of Ciprodex relative to Ciloxan for the time to cessation of ear pain. The primary efficacy variable for the non-inferiority claim was the proportion of subjects in each treatment group with clinical cure at the TOC visit. The comparisons of Ciprodex to Ciloxan and Cortisporin and of Ciloxan to Cortisporin required testing of therapeutic non-inferiority. Bonferroni's approach was applied for this multiple comparison. Statistical evaluation of efficacy was primarily based upon the two-sided 98.3% confidence interval of the difference in clinical cure rates at TOC between Ciprodex, Ciloxan and Cortisporin for PP and ITT subjects. A delta value of 0.1 is defined as a non-inferiority margin. The primary efficacy measure for the superiority claim was the time to cessation of ear pain. The Log-rank test (Kaplan-Meier survival analysis) was used to compare median time to cessation of pain between Ciprodex and Ciloxan.

The safety evaluation was conducted on all subjects who were randomized into the study and received at least one dose of study drug. The safety analysis is based on the extent of exposure to study drug and adverse events.

Study C98-19

Eligible subjects who met the entry qualifications were randomized (Day 1) in an equal ratio (1:1) to one of two treatments: Ciprodex (3 drops BID for children and 4 drops BID for adults for 7 days) and Cortisporin (3 drops TID for children and 4 drops TID for adults for 7 days). According to the inclusion/exclusion criteria, 468 subjects (232 Ciprodex and 236 Cortisporin) were enrolled, randomized, received study drug and were evaluable for the safety and ITT analyses. Of the 468 subjects evaluable for ITT analysis, 410 subjects (202 Ciprodex and 208 Cortisporin) were evaluable from MO's PP set. It was initiated on April 16, 1998 and completed on July 12, 1999.

The primary objective of the study was to demonstrate therapeutic non-inferiority of Ciprodex to Cortisporin. The primary efficacy variable were the proportions of subjects in each treatment group with clinical cure and microbiologic success at the TOC visit. Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical cure rates or microbiologic success rate at TOC between Ciprodex, Ciloxan and Cortisporin for ITT and PP subjects or MITT and MPP subjects. A delta value of 0.1 is defined as a non-inferiority margin.

The safety evaluation was conducted on all subjects who were randomized into the study and received at least one dose of study drug. The safety analysis is based on the extent of exposure to study drug and adverse events.

1.3 STATISTICAL ISSUES AND FINDINGS

The comparisons of statistical interest in this study were conducted between Ciprodex and its comparators. The reviewer employed the following methodologies in primary statistical analyses of efficacy and safety for four pivotal studies.

There were two types of variables in statistical evaluation of efficacy, proportion of subject clinical response or microbiologic response, and time to event.

A two-sided 95% confidence interval was constructed for the difference in proportions between the Ciprodex's group and its comparators' groups. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. The evaluation of whether non-inferior or superiority in efficacy was declared was judged based upon the lower confidence limit for the difference in proportion (Ciprodex – its comparator) and the delta value. With respect to these two indications, the delta value 0.1 is considered a clinically acceptable non-inferiority margin. The assessment of clinical response was primarily performed on PP and ITT populations, and microbiologic response on MPP and MITT populations. In the study with three treatment groups, Bonferroni's adjustment in the Type I error probability was applied for the multiple comparison. Non-inferiority between pairs of three treatments was assessed by computing the two-sided 98.3% confidence interval (95% family confidence interval) of the difference in clinical cure rates. Subgroup analyses by demographic characteristics were also performed for primary efficacy variables. Homogeneity of treatment effect was evaluated by Breslow-Day's test.

Statistical superiority on time to event was estimated and analyzed by Kaplan-Meier estimator and Log-rank test on an ITT basis. Subgroup analyses by demographic characteristics were also performed for time to event of ITT population. Stratified log-rank test was used to compare the two treatments while controlling for demographics.

The reviewer's efficacy analyses primarily focused on MO's outcome assessment and population definition, which used a slightly different algorithm for efficacy assessment and a little different definition for population inclusion.

Descriptive statistics was used in safety evaluation based on extent of exposure to study drug and adverse events.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics of randomized subjects.

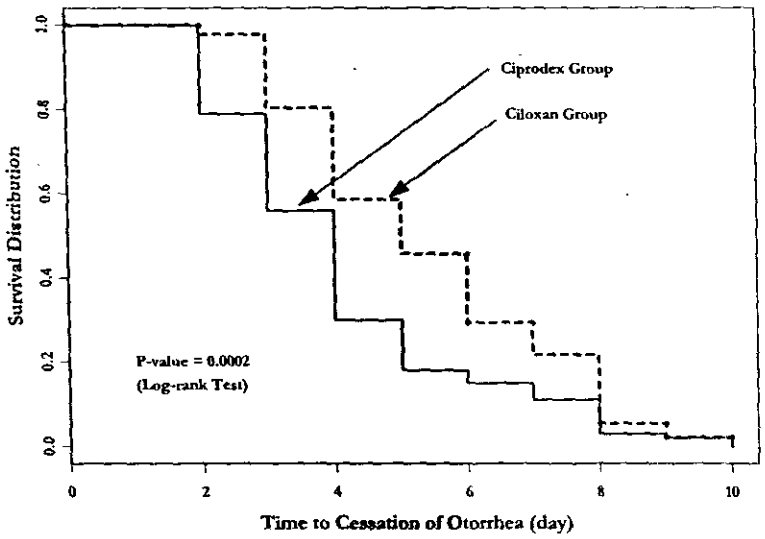
Quantitative variables were assessed using the t-test, and qualitative variables were assessed using chi-square test.

All tests were two-sided and used a 5% level of significance. A 15% level of significance was applied to the test of homogeneity.

ACUTE OTITIS MEDIA WITH TYMPANOSTOMY TUBES

Study C99-59

Ciprodex was superior to ciloxan for time to cessation of otorrhea for ITT subjects (P-value by log-rank test: 0.0025). For the ciprodex treatment group, cessation of otorrhea occurred one day earlier compared to the Ciloxan treatment group (median time of 4 days for Ciprodex versus 5 days for Ciloxan).

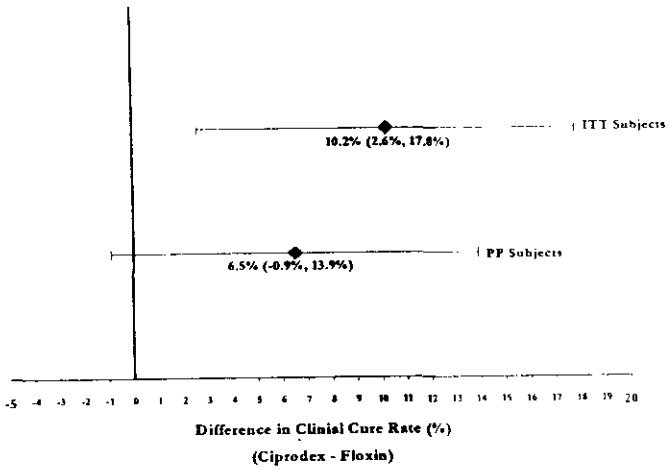


Study C00-52

For PP population, a total of 202/236 (85.6%) Ciprodex subjects were considered clinical cure, while 174/220 (79.1%) Floxin subjects were considered clinical cure. The efficacy results demonstrated therapeutic non-inferiority of Ciprodex to Floxin (6.5%, 95%CI: -0.9%, 13.9%).

For ITT population, a total of 226/297 (76.1%) Ciprodex subjects were considered clinical cure, while 199/302 (65.9%) Floxin subjects were considered clinical cure. The efficacy results demonstrated therapeutic superiority of Ciprodex over Floxin (10.2%, 95% CI: 2.6%, 17.8%).

The results of confidence intervals in MPP and MITT subsets also showed Ciprodex was non-inferior or superior to Floxin with respect to microbiologic success rates at TOC.



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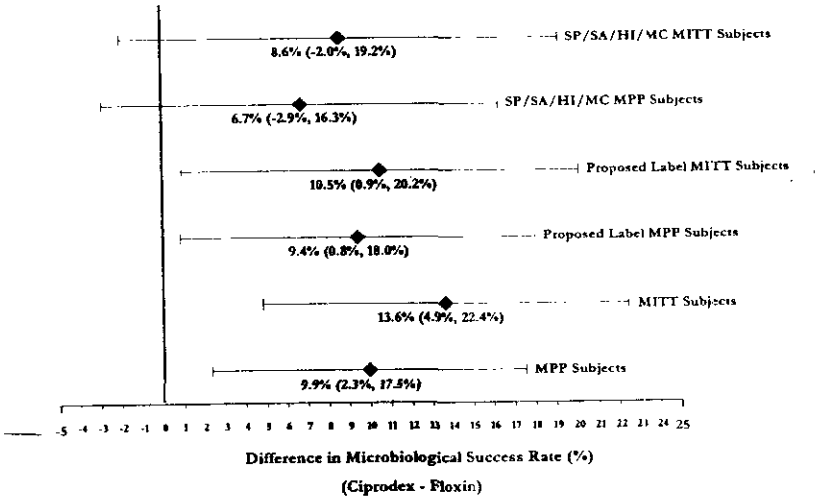


Note: SP/SA/HI/MC/PA: *S. pneumoniae, S. aureus, H. influenzae, M. catarrhalis, or P. aeruginosa*
Proposed label: Any organism in proposed label

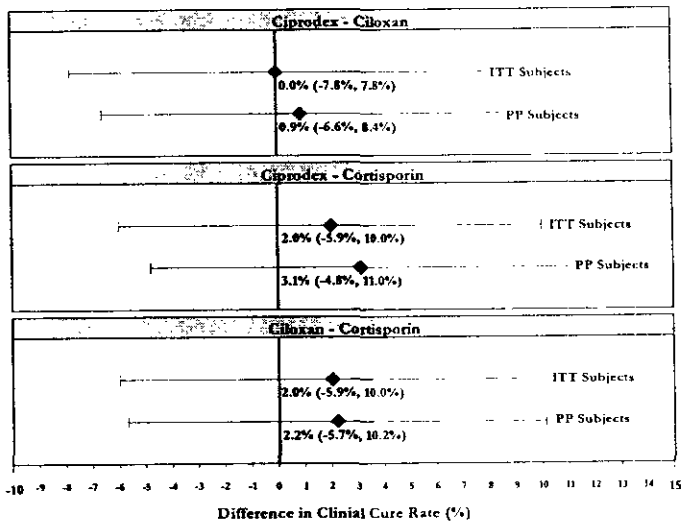
ACUTE OTITIS EXTERNA

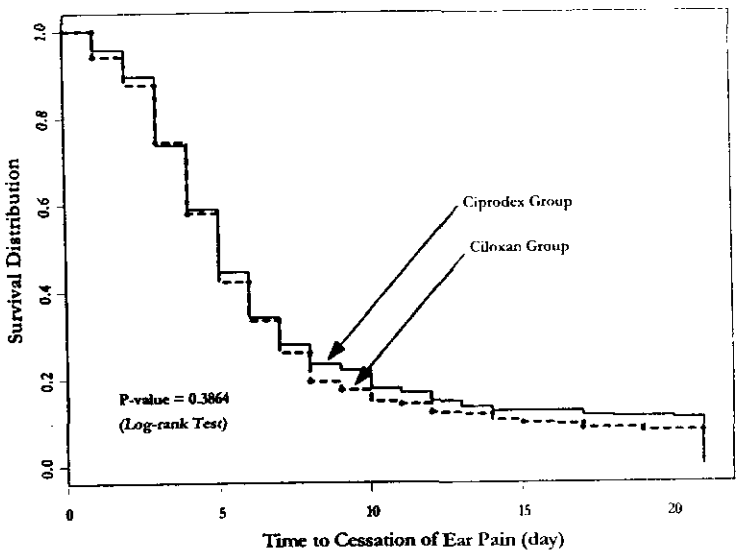
Study C98-18

For PP population, a total of 227/262 (86.6%) Ciprodex subjects were considered clinical cure, while 235/274 (85.8%) Ciloxan subjects and 208/249 (83.5%) Cortisporin subjects were considered clinical cure. The efficacy results demonstrated therapeutic non-inferiority of Ciprodex to Ciloxan (0.9%, 98.3% CI: -6.6%, 8.4%) and Cortisporin (3.1%, 98.3% CI: -4.8%, 11.0%). The result also showed the therapeutic non-inferiority of Ciloxan to Cortisporin (2.2%, 98.3% CI: -5.7%, 10.2%).

For ITT population, a total of 250/305 (82.0%) Ciprodex subjects were considered clinical cure, while 250/305 (82.0%) Ciloxan subjects and 239/299 (79.9%) Cortisporin subjects were considered clinical cure. The efficacy results demonstrated therapeutic non-inferiority of Ciprodex to Ciloxan (0%, 98.3% CI: -7.8%, 7.8%) and Cortisporin (2.0%, 98.3% CI: -5.9%, 10.0%). The result also showed the therapeutic non-inferiority of Ciloxan to Cortisporin (2.0%, 98.3% CI: -5.9%, 10.0%).

Ciprodex failed to demonstrate a significant benefit of time to cessation of ear pain over Ciloxan in ITT subjects (P-value by Log-rank test: 0.3864). The median time to end of pain was 5.0 days for both groups.



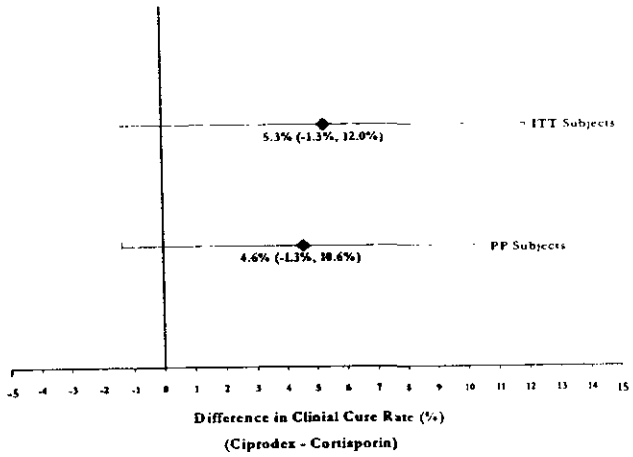


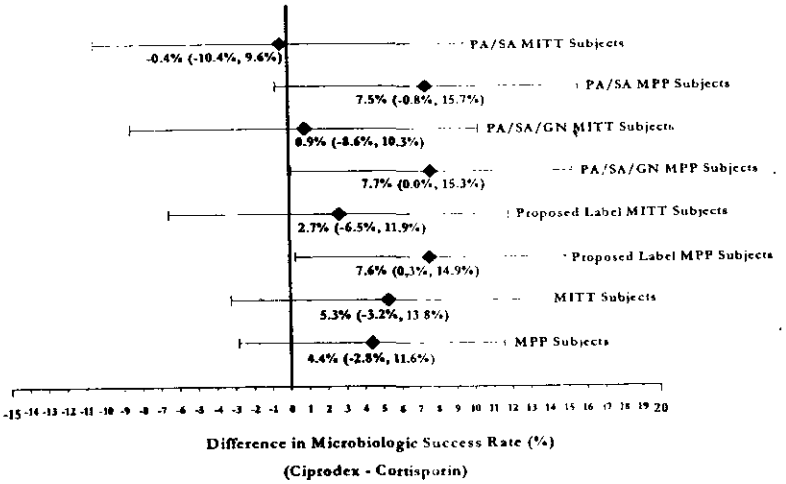
Study C98-19

For PP population, a total of 189/202 (93.6%) Ciprodex subjects were considered clinical cure, while 185/208 (88.9%) Cortisporin subjects were considered clinical cure. The efficacy results demonstrated therapeutic non-inferiority of Ciprodex to Cortisporin (4.6%, 95% CI: -1.3%, 10.6%).

For ITT population, a total of 206/232 (88.8%) Ciprodex subjects were considered clinical cure, while 197/236 (83.5%) Cortisporin subjects were considered clinical cure. The efficacy results demonstrated therapeutic non-inferiority of Ciprodex to Cortisporin (5.3%, 95% CI: -1.3%, 12.0%).

The results of confidence intervals in MPP and MITT subsets also showed Ciprodex was non-inferior or superior to Cortisporin with respect to microbiologic success rates at TOC.





Note: PA/SA: *P. aeruginosa or S. aureus*
PA/SA/GN: *P. aeruginosa, S. aureus*, or other Gram-negative bacteria
Proposed label: Any organism in proposed label

2 INTRODUCTION

2.1 OVERVIEW

The sponsor submits this NDA in order to obtain approval to market Ciprodex for the treatments of AOMT and AOE, respectively. Two pivotal phase III controlled studies for each indication were completed and presented as evidence to support that Ciprodex was safe and efficacious for the two indications when compared with its comparators. Statistical review focuses on these comparative clinical trials which formed the basis of this application.

ACUTE OTITIS MEDIA WITH TYMPANOSTOMY TUBES

Study C99-59

Primary Objectives

To demonstrate therapeutic superiority of Ciprodex to Ciloxan in the cessation of otorrhea.

Study Design

This was a multicenter, active-controlled, randomized, subject-masked, parallel group study comparing the safety and efficacy of Ciprodex to Ciloxan in the treatment of pediatric subjects, from 6 months to 12 year of age, presenting with post tympanostomy acute otitis media and otorrhea. The study was approximately two weeks in duration with four scheduled visits: Day 1 (baseline), Days 3-5 (during treatment), Days 8-10 (EOT) and Days 14-17 (TOC). Eligible subjects who met the entry qualifications were subsequently enrolled and randomized in a ratio 1:1 to receive either Ciprodex or Ciloxan. The dosing regimen and route of administration were identical for both treatment groups; three drops topically applied BID for 7 days. It was initiated on March 10, 2000 and completed on February 2, 2001.

Study C00-52

Primary Objectives

To demonstrate the non-inferiority of Ciprodex to Floxin in clinical and microbiological responses at TOC.

Study Design

This was a multicenter, active-controlled, randomized, observer-masked, parallel group study comparing the safety and efficacy of Ciprodex to Floxin in the treatment of pediatric subjects, from 6 months to 12 year of age, presenting with post-tympanostomy acute otitis media and otorrhea. The study was approximately three weeks in duration with four scheduled visits: Day 1 (baseline), Days 3-5 (during treatment), Days 11-13 (EOT) and Days 18-21 (TOC). Eligible subjects who met the entry qualifications were subsequently enrolled and randomized in a ratio 1:1 to receive either Ciprodex or Floxin. Both drugs were topically administered BID into the infected ear(s) with the following dosages according to treatment; 4 drops for 7 days for the Ciprodex group or 5 drops for 10 days for the Floxin group. It was initiated on February 14, 2001 and completed on May 20, 2002

ACUTE OTITIS EXTERNA

Study C98-18

Primary Objectives

To demonstrate:

- Therapeutic non-inferiority of Ciprodex to Ciloxan based on clinical response at TOC;
- Therapeutic non-inferiority of Ciprodex to Cortisporin based on clinical response at TOC;
- Therapeutic non-inferiority of Ciloxan to Cortisporin based on clinical response at TOC;
- Therapeutic superiority of Ciprodex to Ciloxan for time to cessation of ear pain.

Study Design

This was a randomized, observer-masked, multicenter, parallel group study comparing the safety and efficacy of Ciprodex, Ciloxan, and Cortisporin in subjects with moderate to severe AOE. Eligible subjects who met the entry qualifications were randomized (Day 1) in an equal ratio (1:1:1) to one of three treatments: Ciprodex (BID), Ciloxan (BID), and Cortisporin (TID). Randomized subjects were treated with study drug for 7 days and returned for three follow-up visits on Day 3, Day 8, and Day 18 (TOC visit). It was initiated on April 17, 1998 and completed on May 15, 2000.

Study C98-19

Primary Objectives

To demonstrate:

- Therapeutic non-inferiority of Ciprodex to Cortisporin based on clinical response at TOC;
- Therapeutic non-inferiority of Ciprodex to Cortisporin based on microbiological eradication of disease-specific organisms at TOC.

Study Design

This was a randomized, observer-masked, multicenter, parallel group study comparing the safety and efficacy of Ciprodex and Cortisporin in subjects with moderate to severe AOE. Eligible subjects who met the entry qualifications were randomized (Day 1) in an equal ratio (1:1) to one of three treatments: Ciprodex (BID) and Cortisporin (TID). Randomized subjects were treated with study drug for 7 days and returned for three FU visits on Day 3, Day 8, and Day 18 (TOC visit). It was initiated on April 16, 1998 and completed on July 12, 1999.

2.2 DATA SOURCES

This submission contains data from four pivotal studies performed by the sponsor, two studies to support the AOMT indication (C99-59 and C00-52) and two studies to support the AOE indication (C98-18 and C98-19).

The submitted datasets for Studies C99-59, C00-52, C98-18, and C98-19 can be found respectively under:
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The four pivotal studies are described in Table 1.

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TABLE 1. LISTING OF CLINICAL TRIALS			
Study	Population	Test Drugs	Enrollment
ACUTE OTITIS MEDIA WITH TYMPANOSTOMY TUBES			
C99-59	Pediatric subjects 6 months and older	Ciprodex, 3 drops BID x 7 days; Ciprofloxacin, 3 drops BID x 7 days	103 Ciprodex 98 Ciprofloxacin
C00-52	Pediatric subjects 6 months and older	Ciprodex, 4 drops BID x 7 days; Floxin, 5 drops BID x 10 days	297 Ciprodex 302 Floxin
ACUTE OTITIS EXTERNA			
C98-18	Pediatric subjects 1 year and older; adults	Ciprodex, 3 drops (ped) or 4 drops (adult) BID x 7 days; Ciprofloxacin, 3 drops (ped) or 4 drops (adult) BID x 7 days; Cortisporin, 3 drops (ped) or 4 drops (adult) TID x 7 days	305 Ciprodex 305 Ciprofloxacin 299 Cortisporin
C98-19	Pediatric subjects 1 year and older; adults	Ciprodex, 3 drops (ped) or 4 drops (adult) BID x 7 days; Cortisporin, 3 drops (ped) or 4 drops (adult) TID x 7 days	232 Ciprodex 236 Cortisporin

A review by random sample method of at least 10% of the CRF stratified by treatment group was conducted to validate the sponsor's efficacy data and to check for agreement with investigators' evaluability and outcome assessments. The MO did not concur with some efficacy outcomes assessed by the sponsor, and also disagreed with some aspects of evaluability evaluated by the sponsor. Please refer to MO's review for detailed descriptions.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

ACUTE OTITIS MEDIA WITH TYMPANOSTOMY TUBES

Study C99-59

The statistical objective of this study was to demonstrate the superiority of Ciprodex relative to Ciloxan in the cessation of otorrhea.

The efficacy evaluation was focused primarily on the time to cessation of otorrhea as noted and recorded by the parent/guardian in the subject's diary. This was defined as the first day on which the otorrhea was noted as absent by the parent/guardian for one or both enrolled ears and subsequently remained absent.

Four subject populations were defined by the sponsor as ITT, MITT , PP, and MPP. The MO defined his PP and MPP subjects and reclassified efficacy outcomes after checking for agreement with investigators' evaluability and outcome assessments. The primary efficacy variable under analysis was time to cessation of otorrhea for the ITT population.

The number and the proportion of subjects included in each evaluation group are presented in Table 2. Nine of the randomized subjects were excluded from ITT due to no baseline visit (Day1), when the first dose of drug was administered as scheduled in the protocol plan. The most common reasons for exclusion from PP analyses were "Excluded Concomitant Medication" and "Missed Visit". The major discrepancy on evaluability and outcome assessments between the MO and the sponsor came about from the subjects who were discontinued from the study and prescribed alternative therapy. The only notable differences with respect to the percentage of subjects in these evaluation groups was that there were greater number of discontinuation due to treatment failure in the Ciloxan arm, who were excluded from sponsor's PP group.

TABLE 2: STUDY C99-59: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Number of Subjects	
	Ciprodex	Ciloxan
All Randomized Subjects	103	98
ITT Subjects	100 (100%)	92 (100%)
MO's SP/SA/HI/MC/PA MITT Subjects	60 (60.0%)	54 (58.7%)
MO's Proposed Label MITT Subjects	77 (77.0%)	69 (75.0%)
MITT Subjects	87 (87.0%)	80 (87.0%)
MO's PP Subjects	84 (84.0%)	73 (79.3%)
Sponsor's PP Subjects	80 (80.0%)	61 (66.3%)
MO's SP/SA/HI/MC/PA MPP Subjects	48 (48.0%)	45 (48.9%)
MO's Proposed Label MPP Subjects	64 (64.0%)	55 (59.8%)
Sponsor's MPP Subjects	73 (73.0%)	64 (69.6%)

SP/SA/HI/MC/PA: *S. pneumoniae, S. aureus, H. influenzae, M. catarrhalis, or P. aeruginosa*
Proposed label: Any organism in proposed label

Data for demographics and baseline characteristics are described for ITT subjects in Table 3. The two treatment groups were comparable and no statistically significant differences were detected with regard to these characteristics.

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TABLE 3: STUDY C99-59: BASELINE DEMOGRAPHICS IN ITT SUBJECTS

Variables	Ciprodex (N=100)	Ciloxan (N=92)	P-value
Age (yrs.)			
Range (Min, Max)	(0, 12)	(0, 11)	
Mean ± SD	2.6 ± 2.6	2.2 ± 2.1	*0.291
Distribution			
≥ 0 year and ≤ 12 years	100 (100%)	92 (100%)	NA
> 13 years and < 18 years	0 (0%)	0 (0%)	
Gender			
Male	57 (57.0%)	47 (51.1%)	0.411
Female	43 (43.0%)	45 (48.9%)	
Race			
White	82 (4%)	72 (78.3%)	0.779
Black	8 (58%)	8 (8.7%)	
Other	10 (38%)	12 (13.0%)	
Enrolled Ear			
Right Only	38 (38.0%)	36 (39.1%)	0.403
Left Only	37 (37.0%)	40 (43.5%)	
Both	25 (25.0%)	16 (17.4%)	
Worst Ear			
Right	40 (40.0%)	42 (45.7%)	0.429
Ledt	60 (60.0%)	50 (54.4%)	
Haemophilus Vaccination			
No	19 (19.0%)	17 (18.5%)	0.765
Yes	68 (68.0%)	66 (71.4%)	
Unknown	13 (13.0%)	9 (9.8%)	
Pneumococcal Vaccination			
No	79 (79.0%)	71 (77.2%)	0.906
Yes	8 (8.0%)	7 (7.6%)	
Unknown	13 (13.0%)	14 (15.2%)	

* By t test. ^ By Fisher's exact test. All others in the table, by chi-square test.

In ITT population, the median time to cessation of otorrhea in those receiving Ciprodex was 4 days versus 5 days for those receiving Ciloxan, which are shown in Table 4. Ciprodex displayed its superiority to Ciloxan in time to cessation of otorrhea (p-value = 0.0025).

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TABLE 4: STUDY C99-59: DAYS TO CESSATION OF OTORRHEA OF ITT SUBJECTS AT TOC VISIT		
Cessation of Otorrhea (day)	Ciprodex (N=100)	Ciloxan (N=92)
Mean	4.1	5.4
Median	4.0	5.0
Std	2.0	2.0
Min/Max	2/10	2/10
P-Value by Log-rank Test	0.0025	

The secondary analyses are presented in Tables 5, 6, 7, and 8 for the clinical responses of PP and ITT subjects as per MO's and sponsor's at the TOC visit, respectively. The confidence interval results showed Ciprodex was therapeutically non-inferior or marginally non-inferior to Ciloxan with respect to clinical cure rates at TOC.

TABLE 5: STUDY C99-59: CLINICAL RESPONSES OF PP SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Ciprodex (N=84)	Ciloxan (N=73)
Cured	76 (90.5%)	58 (79.5%)
Not Cured	8 (9.5%)	15 (20.5%)
Difference in Cure Rate Ciprodex vs. Ciloxan:	11.0%, 95% C.I.: -1.5%, 23.5%	

TABLE 6: STUDY C99-59: CLINICAL RESPONSES OF PP SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Ciprodex (N=80)	Ciloxan (N=61)
Cured	76 (95.0%)	60 (98.4%)
Not Cured	4 (5.0%)	1 (1.6%)
Difference in Cure Rate Ciprodex vs. Ciloxan:	-3.4%, 95% C.I.: -10.5%, 3.8%	

TABLE 7: STUDY C99-59: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Ciprodex (N=100)	Ciloxan (N=92)
Cured Not Cured	89 (89.0%) 11 (11.0%)	70 (76.1%) 22 (23.9%)
Difference in Cure Rate Ciprodex vs. Ciloxan:	12.9%, 95% C.I.: 1.2%, 24.6%	

TABLE 8: STUDY C99-59: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Ciprodex (N=100)	Ciloxan (N=92)
Cured Not Cured	91 (91.0%) 9 (9.0%)	82 (89.1%) 6 (10.9%)
Difference in Cure Rate Ciprodex vs. Ciloxan:	1.9%, 95% C.I.: -7.7%, 11.4%	

The secondary analyses in Tables 9, 10, 11, and 12 present clinical cure rates and microbiologic success rates from MPP subsets and MITT subsets, respectively. The results all supported the non-inferiority of Ciprodex to Ciloxan.

TABLE 9: STUDY C99-59: MICROBIOLOGIC SUCCESS RATES AT TOC VISIT IN SUBSETS OF MPP SUBJECTS			
MPP Subset	Ciprodex	Ciloxan	95% C.I.
MO's SP/SA/HI/MC/PA MPP Subjects	43/48 (89.6%)	34/45 (75.6%)	(-3.4%, 31.4%)
MO's Proposed Label MPP Subjects	59/64 (92.2%)	43/55 (78.2%)	(-0.4%, 28.4%)
MO's MPP Subjects	66/73 (90.4%)	51/64 (79.7%)	(-2.7%, 24.1%)
Sponsor's MPP Subjects	68/72 (90.4%)	51/55 (79.7%)	(-8.6%, 12.0%)

TABLE 10: STUDY C99-59: MICROBIOLOGIC SUCCESS RATES AT TOC VISIT IN SUBSETS OF MITT SUBJECTS			
MITT Subset	Ciprodex	Ciloxan	95% C.I.
MO's SP/SA/HI/MC/PA MITT Subjects	44/60 (73.3%)	34/54 (63.0%)	(-8.5%, 29.2%)
MO's Proposed Label MITT Subjects	61/77 (79.2%)	43/69 (62.3%)	(0.9%, 32.9%)
MO's MITT Subjects	68/87 (78.2%)	51/80 (63.8%)	(-0.4%, 29.3%)
Sponsor's MITT Subjects	73/87 (83.9%)	58/80 (72.5%)	(-2.3%, 25.1%)

TABLE 11: STUDY C99-59: CLINICAL CURE RATES AT TOC VISIT IN SUBSETS OF MPP SUBJECTS			
MPP Subset	Ciprodex	Ciloxan	95% C.I.
MO's SP/SA/HI/MC/PA MPP Subjects	43/48 (89.6%)	34/45 (75.6%)	(-3.4%, 31.4%)
MO's Proposed Label MPP Subjects	58/64 (90.6%)	43/55 (78.2%)	(-2.3%, 27.2%)
MO's MPP Subjects	65/73 (89.0%)	51/64 (79.7%)	(-4.3%, 23.0%)
Sponsor's MPP Subjects	68/72 (94.4%)	54/55 (98.2%)	(-11.7%, 4.2%)

TABLE 12: STUDY C99-59: CLINICAL CURE RATES AT TOC VISIT IN SUBSETS OF MITT SUBJECTS			
MITT Subset	Ciprodex	Ciloxan	95% C.I.
MO's SP/SA/HI/MC/PA MPP Subjects	53/60 (88.3%)	40/54 (74.1%)	(-1.7%, 30.3%)
MO's Proposed Label MPP Subjects	69/77 (89.6%)	52/69 (75.4%)	(0.6%, 27.9%)
MO's MPP Subjects	76/87 (87.4%)	62/80 (77.5%)	(-2.9%, 22.6%)
Sponsor's MPP Subjects	78/87 (89.7%)	72/80 (90.0%)	(-10.7%, 10.0%)

Table 13 shows pathogen microbiologic success rates for those isolated baseline pathogens proposed in the label.

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TABLE 13: STUDY C99-59: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF MO'S MPP SUBJECTS AT TOC VISIT

Baseline Isolate Pathogen	Ciprodex	Ciloxan
Gram-positive		
Staphylococcus aureus	17/17 (100%)	10/12 (83%)
Streptococcus pneumoniae	16/21 (76.2%)	13/19 (68.4%)
Gram-negative		
Haemophilus influenzae	4/4 (100%)	8/9 (88.9%)
Moraxella catarrhalis	4/4 (100%)	NA
Pseudomonas aeruginosa	11/11 (100%)	8/13 (61.5%)

Study C00-52

The statistical objective of this study was to demonstrate the non-inferiority of Ciprodex relative to Floxin in clinical and microbiological response at the TOC visit.

The efficacy evaluation was focused primarily on the proportion of subjects at the TOC visit as clinically cured based on a 4-point scale (resolved/cured, improved, not changed and worsened) in which resolved/cured was defined as the complete absence of otorrhea, and the proportion of subjects for whom disease-specific pathogens presented at enrollment were eradicated at the TOC visit. The microbiological response was documented as success (eradication) or failure at the TOC visit.

Four subject populations were defined by the sponsor as ITT subjects, MITT subjects, PP subjects, and MPP subjects. The MO defined his PP and MPP subjects and reclassified efficacy outcomes after checking for agreement with investigators' evaluability and outcome assessments. The primary efficacy variables under analysis were clinical cure rate in PP and ITT populations, and microbiologic success rate in MPP and MITT populations.

The number and the proportion of subjects included in each evaluation group are presented in Table 14. The most common reasons for exclusion from PP analyses was "Missed Visit". The major discrepancy on evaluability and outcome assessments between the MO and the sponsor came about from the subjects who were discontinued from the study because of the development of otitis media in the non-study ear or of other manifestations of upper respiratory infection, and prescribed alternative therapy. There were no notable differences for two treatment groups with respect to the percentage of subjects included in each evaluation group.

TABLE 14: STUDY C00-52: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Number of Subjects	
	Ciprodex	Floxin
All Randomized Subjects	297	302
ITT Subjects	297 (100%)	302 (100%)
MO's SP/SA/HI/MC/PA MITT Subjects	148 (49.8%)	164 (54.3%)
MO's Proposed Label MITT Subjects	178 (59.9%)	188 (62.3%)
MITT Subjects	208 (70.0%)	216 (71.5%)
MO's PP Subjects	236 (79.5%)	220 (72.8%)
Sponsor's PP Subjects	232 (78.1%)	220 (72.8%)
MO's SP/SA/HI/MC/PA MPP Subjects	126 (42.4%)	129 (42.7%)
MO's Proposed Label MPP Subjects	151 (50.8%)	150 (49.7%)
Sponsor's MPP Subjects	181 (60.9%)	170 (56.3%)

SP/SA/HI/MC/PA: *S. pneumoniae, S. aureus, H. influenzae, M. catarrhalis, or P. aeruginosa*
Proposed label: Any organism in proposed label

Data for demographics and baseline characteristics are described for ITT subjects in Table 15. There appeared to be a statistically imbalance in the gender composition of the treatment population and the proportion of male subject was greater in the Floxin arm. The two treatment groups were comparable and no statistically significant differences were detected with regard to the other characteristics.

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TABLE 15: STUDY C00-52: BASELINE DEMOGRAPHICS IN ITT SUBJECTS

Variables	Ciprodex (N=297)	Floxin (N=302)	P-value
Age (yrs.)			
Range (Min, Max)	(0, 12)	(0, 11)	
Mean ± SD	2.5 ± 2.4	2.4 ± 2.3	*0.425
Distribution			
≥ 0 year and < 12 years	294 (99.0%)	302 (100%)	0.080
≥ 12 years and < 18 years	3 (1.0%)	0 (0%)	
Gender			
Male	172 (57.9%)	201 (66.6%)	0.029
Female	125 (42.1%)	102 (33.4%)	
Race			
White	242 (81.5%)	244 (80.8%)	0.977
Black	16 (5.4%)	17 (5.6%)	
Other	39 (13.1%)	41 (13.6%)	
Enrolled Ear			
Right Only	122 (41.1%)	125 (41.4%)	0.251
Left Only	114 (38.4%)	100 (33.1%)	
Both	61 (20.5%)	77 (25.5%)	
Worst Ear			
Right	166 (55.9%)	178 (58.9%)	0.451
Ledt	131 (44.1%)	124 (41.1%)	
Haemophilus Vaccination			
No	64 (21.6%)	61 (20.2%)	0.669
Yes	185 (62.3%)	184 (60.9%)	
Unknown	48 (16.2%)	57 (18.9%)	
Pneumococcal Vaccination			
No	161 (54.2%)	155 (51.3%)	0.776
Yes	83 (28.0%)	89 (29.5%)	
Unknown	53 (17.9%)	58 (19.2%)	

* By t test. All others in the table, by chi-square test.

The primary efficacy analyses are presented in Tables 16, 17, 18, and 19 for the clinical responses of PP and ITT subjects as per MO's and sponsor's at the TOC visit, respectively. The confidence interval results showed Ciprodex was therapeutically non-inferior to Floxin with respect to clinical cure rates of MO's PP population at TOC. The results from the other three sets supported the superiority claim of Ciprodex to its comparator.

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TABLE 16: STUDY C00-52: CLINICAL RESPONSES OF PP SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Ciprodex (N=236)	Floxin (N=220)
Cured	202 (85.6%)	174 (79.1%)
Not Cured	34 (14.4%)	46 (20.9%)
Difference in Cure Rate Ciprodex vs. Floxin:	6.5%, 95% C.I.: -0.9%, 13.9%	

TABLE 17: STUDY C00-52: CLINICAL RESPONSES OF PP SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Ciprodex (N=232)	Floxin (N=220)
Cured	204 (87.9%)	170 (77.3%)
Not Cured	28 (12.1%)	50 (22.7%)
Difference in Cure Rate Ciprodex vs. Floxin:	10.7%, 95% C.I.: 3.3%, 18.0%	

TABLE 18: STUDY C00-52: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Ciprodex (N=297)	Floxin (N=302)
Cured	226 (76.1%)	199 (65.9%)
Not Cured	71 (23.9%)	103 (34.1%)
Difference in Cure Rate Ciprodex vs. Floxin:	10.2%, 95% C.I.: 2.6%, 17.8%	

TABLE 19: STUDY C00-52: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Ciprodex (N=297)	Floxin (N=302)
Cured	222 (74.7%)	185 (61.3%)
Not Cured	75 (25.3%)	117 (38.7%)
Difference in Cure Rate Ciprodex vs. Floxin:	13.5%, 95% C.I.: 5.8%, 21.2%	

The primary efficacy analyses are presented in Tables 20 and 21 for the microbiologic responses of MPP and MITT subjects as per MO's and sponsor's at the TOC visit, respectively. The confidence interval results showed Ciprodex was therapeutically non-

inferior or superior to Floxin with respect to microbiologic success rates at TOC.

TABLE 20: STUDY C00-52: MICROBIOLOGIC SUCCESS RATES AT TOC VISIT IN SUBSETS OF MPP SUBJECTS			
MPP Subset	Ciprodex	Floxin	95% C.I.
MO's SP/SA/HI/MC/PA MPP Subjects	111/126 (88.1%)	105/129 (81.4%)	(-2.9%, 16.3%)
MO's Proposed Label MPP Subjects	136/151 (90.1%)	121/150 (80.7%)	(0.8%, 18.0%)
MO's MPP Subjects	165/181 (91.2%)	139/170 (81.8%)	(1.7%, 17.1%)
Sponsor's MPP Subjects	165/180 (90.7%)	139/170 (79.4%)	(2.3%, 17.5%)

TABLE 21: STUDY C00-52: MICROBIOLOGIC SUCCESS RATES AT TOC VISIT IN SUBSETS OF MITT SUBJECTS			
MITT Subset	Ciprodex	Floxin	95% C.I.
MO's SP/SA/HI/MC/PA MITT Subjects	112/148 (75.7%)	110/164 (67.1%)	(-2.0%, 19.2%)
MO's Proposed Label MITT Subjects	138/178 (77.5%)	126/188 (67.0%)	(0.9%, 20.2%)
MITT Subjects	167/208 (80.3%)	144/216 (66.7%)	(4.9%, 22.4%)

The secondary analyses in Tables 22 and 23 present clinical cure rates from MPP and MITT subsets, respectively. Most results supported the superiority claim of Ciprodex to Floxin. Table 24 shows pathogen microbiologic success rates for those isolated baseline pathogens proposed in the label.

TABLE 22: STUDY C00-52: CLINICAL CURE RATES AT TOC VISIT IN SUBSETS OF MPP SUBJECTS			
MPP Subset	Ciprodex	Floxin	95% C.I.
MO's SP/SA/HI/MC/PA MPP Subjects	109/126 (86.5%)	102/129 (79.1%)	(-2.6%, 17.4%)
MO's Proposed Label MPP Subjects	133/151 (88.1%)	117/150 (78.0%)	(1.0%, 19.1%)
MO's MPP Subjects	162/181 (89.5%)	135/170 (79.4%)	(2.0%, 18.2%)
Sponsor's MPP Subjects	162/180 (90.0%)	133/170 (78.2%)	(3.6%, 19.9%)

TABLE 23: STUDY C00-52: CLINICAL CURE RATES AT TOC VISIT IN SUBSETS OF MITT SUBJECTS

MITT Subset	Ciprodex	Floxin	95% C.I.
MO's SP/SA/HI/MC/PA MITT Subjects	117/148 (79.1%)	112/164 (68.3%)	(0.4%, 21.1%)
MO's Proposed Label MITT Subjects	143/178 (80.3%)	129/188 (68.6%)	(2.3%, 21.1%)
MO's MITT Subjects	172/208 (82.7%)	149/216 (69.0%)	(5.2%, 22.2%)
Sponsor's MITT Subjects	165/208 (79.3%)	138/216 (63.9%)	(6.5%, 24.4%)

TABLE 24: STUDY C00-52: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF MO'S MPP SUBJECTS AT TOC VISIT

Baseline Isolate Pathogen	Ciprodex	Floxin
Gram-positive		
Staphylococcus aureus	32/35 (91.4%)	31/33 (93.9%)
Streptococcus pneumoniae	23/24 (95.8%)	32/38 (84.2%)
Gram-negative		
Haemophilus influenzae	22/24 (91.7%)	25/28 (89.3%)
Moraxella catarrhalis	6/7 (85.7%)	7/8 (87.5%)
Pseudomonas aeruginosa	36/37 (97.3%)	23/26 (88.5%)

ACUTE OTITIS EXTERNA

Study C98-18

The comparisons of statistical interest in this study were conducted between Ciprodex, Ciloxan and Cortisporin, which was designed to demonstrate the non-inferiority in clinical response at TOC of Ciprodex to Ciloxan, Ciprodex to Cortisporin, and Ciloxan to Cortisporin, and the superiority of Ciprodex to Ciloxan in the cessation of ear pain.

The primary efficacy variable analyzed was the proportion of subjects at the TOC visit as clinically cured based on a 4-point scale (cured, improved, not changed and worsened). Subjects who had a recurrence or incomplete cure were not reported as cured.

Another primary efficacy variable analyzed in this study was the time to cessation of ear pain. In AOE, pain is a direct result of inflammation, thus, anti-inflammatory effects were measured as cessation of pain. Cessation of ear pain was defined as the first day on which there was no use of analgesics in the prior 24 hours, the diary pain score was zero, and the score remained at zero for all subsequent visits. This clinical efficacy variable from the

subject's perspective was the assessment of pain as recorded in a subject diary. Ear pain was assessed on a 4-point scale (none to severe) twice-daily until the TOC visit.

Four subject populations were defined as ITT subjects, MITT subjects, PP subjects, and MPP subjects. The primary efficacy analysis was conducted on both the ITT and the PP subject populations for the non-inferiority claim, and the ITT subject populations for the superiority claim.

The number and the proportion of subjects included in each evaluation group are presented in Table 25. The most common reasons for exclusion from PP analyses was "Excluded Concomitant Disease". The major discrepancy on evaluability and outcome assessments between the MO and the sponsor came about from the subjects who were discontinued from the study and prescribed alternative therapy. There were no notable differences for two treatment groups with respect to the percentage of subjects included in each evaluation group.

TABLE 25: STUDY C98-18: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Number of Subjects		
	Ciprodex	Ciloxan	Cortisporin
All Randomized Subjects	305	305	299
ITT Subjects	305 (100%)	305 (100%)	299 (100%)
MO's PA/SA MITT Subjects	184 (60.3%)	178 (58.4%)	180 (60.2%)
MO's PA/SA/GN MITT Subjects	211 (69.2%)	204 (66.9%)	204 (68.2%)
MO's Proposed Label MITT Subjects	236 (77.4%)	232 (76.1%)	229 (76.6%)
MITT Subjects	267 (87.5%)	261 (85.6%)	257 (86.0%)
MO's PP Subjects	262 (85.9%)	274 (89.8%)	249 (83.3%)
Sponsor's PP Subjects	238 (78.0%)	246 (80.7%)	228 (76.3%)
MO's PA/SA MPP Subjects	159 (52.1%)	162 (53.1%)	150 (50.2%)
MO's PA/SA/GN MPP Subjects	181 (59.3%)	185 (60.7%)	169 (56.5%)
MO's Proposed Label MPP Subjects	199 (65.2%)	209 (68.5%)	190 (63.5%)
MO's MPP Subjects	229 (75.1%)	236 (77.4%)	217 (72.6%)
Sponsor's MPP Subjects	207 (75.1%)	214 (77.4%)	200 (72.6%)

PA/SA: *P. aeruginosa or S. aureus*
PA/SA/GN: *P. aeruginosa, S. aureus*, or other Gram-negative bacteria
Proposed label: Any organism in proposed label

Data for demographics and baseline characteristics are described for ITT subjects in Table 26. The two treatment groups were comparable and no statistically significant differences were detected with regard to these characteristics.

TABLE 26: STUDY C98-18: BASELINE DEMOGRAPHICS IN ITT SUBJECTS

Variables	Ciprodex (N=305)	Ciloxan (N=305)	Cortisporin (N=299)	P-value
Age (yrs.)				
Range (Min, Max)	(1, 81)	(1, 88)	(2, 85)	
Mean ± SD	21.1 ± 17.3	20.6 ± 17.9	21.1 ± 16.9	*0.920
Distribution				
≥ 0 years and < 13 years	141 (46.2%)	158 (51.8%)	148 (49.5%)	0.607
≥ 13 years and < 65 years	156 (51.2%)	137 (44.9%)	144 (48.2%)	
≥ 65 years	8 (2.6%)	10 (3.3%)	7 (2.3%)	
Gender				
Male	144 (47.2%)	126 (41.3%)	133 (44.5%)	0.340
Female	161 (52.8%)	179 (58.7%)	166 (55.5%)	
Race				
White	271 (88.9%)	259 (84.9%)	250 (83.6%)	0.411
Black	13 (4.3%)	16 (5.3%)	16 (5.4%)	
Other	21 (6.9%)	30 (9.8%)	33 (11.0%)	
Enrolled Ear				
Right Only	149 (48.9%)	142 (46.6%)	145 (48.5%)	0.581
Left Only	137 (44.9%)	133 (43.6%)	128 (42.8%)	
Both	19 (6.2%)	30 (9.8%)	26 (8.7%)	
Worst Ear				
Right	140 (45.9%)	137 (44.9%)	131 (43.8%)	0.875
Left	165 (54.1%)	168 (55.1%)	168 (56.2%)	
Previous AOE				
No	200 (65.6%)	207 (67.9%)	201 (67.2%)	0.825
Yes	105 (34.4%)	98 (32.1%)	98 (32.8%)	

* By ANOVA. All others in the table, by chi-square test.

The primary analyses are presented in Tables 27, 28, 29, and 30 for the clinical responses of PP and ITT subjects as per MO's and sponsor's at the TOC visit, respectively. The confidence interval results demonstrated Ciprodex was non-inferior to both Ciloxan and Cortisporin with respect to clinical cure rates at TOC. Meantime, Ciloxan was shown to be non-inferior to Cortisporin with regard to clinical cure rate at TOC.

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TABLE 27: STUDY C98-18: CLINICAL RESPONSES OF PP SUBJECTS AT TOC VISIT BY MO			
Clinical Response	Ciprodex (N=262)	Ciloxan (N=274)	Cortisporin (N=249)
Cured	227 (86.6%)	235 (85.8%)	208 (83.5%)
Not Cured	35 (13.4%)	39 (14.2%)	41 (16.5%)
Difference in Cure Rate			
Ciprodex vs. Ciloxan:	0.9%, 98.3% C.I.: -6.6%, 8.4%		
Ciprodex vs. Cortisporin:	3.1%, 98.3% C.I.: -4.8%, 11.0%		
Ciloxan vs. Cortisporin:	2.2%, 98.3% C.I.: -5.7%, 10.2%		

TABLE 28: STUDY C98-18: CLINICAL RESPONSES OF PP SUBJECTS AT TOC VISIT BY SPONSOR			
Clinical Response	Ciprodex (N=238)	Ciloxan (N=246)	Cortisporin (N=228)
Cured	227 (95.4%)	235 (95.5%)	208 (91.2%)
Not Cured	11 (4.6%)	11 (4.5%)	20 (8.8%)
Difference in Cure Rate			
Ciprodex vs. Ciloxan:	-0.2%, 98.3% C.I.: -5.1%, 4.8%		
Ciprodex vs. Cortisporin:	4.2%, 98.3% C.I.: -1.8%, 10.1%		
Ciloxan vs. Cortisporin:	4.3%, 98.3% C.I.: -1.6%, 10.2%		

TABLE 29: STUDY C98-18: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT BY MO			
Clinical Response	Ciprodex (N=305)	Ciloxan (N=305)	Cortisporin (N=299)
Cured	250 (82.0%)	250 (82.0%)	239 (79.9%)
Not Cured	55 (18.0%)	55 (18.0%)	60 (20.1%)
Difference in Cure Rate			
Ciprodex vs. Ciloxan:	0.0%, 98.3% C.I.: -7.8%, 7.8%		
Ciprodex vs. Cortisporin:	2.0%, 98.3% C.I.: -5.9%, 10.0%		
Ciloxan vs. Cortisporin:	2.0%, 98.3% C.I.: -5.9%, 10.0%		

TABLE 30: STUDY C98-18: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT BY SPONSOR			
Clinical Response	Ciprodex (N=305)	Ciloxan (N=305)	Cortisporin (N=299)
Cured	251 (82.3%)	250 (82.0%)	242 (80.9%)
Not Cured	54 (17.7%)	55 (18.0%)	57 (19.1%)
Difference in Cure Rate			
Ciprodex vs. Ciloxan:	0.3%, 98.3% C.I.: -7.4%, 8.1%		
Ciprodex vs. Cortisporin:	1.4%, 98.3% C.I.: -6.5%, 9.2%		
Ciloxan vs. Cortisporin:	1.0%, 98.3% C.I.: -6.9%, 8.9%		

Another primary analysis for time to no pain is presented in Tables 31. In ITT population, the median times to cessation of ear pain in those receiving Ciprodex and Ciloxan were all 5 days. Time to cessation of ear pain was not shown significantly different between Ciprodex and Ciloxan (p-value=0.3864).

TABLE 31: STUDY C98-18: DAYS TO CESSATION OF EAR PAIN OF ITT SUBJECTS AT TOC VISIT		
Cessation Of Ear Pain (day)	Ciprodex (N=305)	Ciloxan (N=305)
Mean	7.1	6.7
Median	5.0	5.0
Std	5.7	5.3
Min/Max	1/21	1/21
P-Value by Log-rank Test	0.3864	

The secondary analyses in Tables 32, 33, 34, and 35 present clinical cure rates and microbiologic success rates from MPP and MITT subsets, respectively. Almost all supported the non-inferiority claim of Ciprodex to its comparators across these MPP and MITT subsets , though only a few just marginally missed non-inferiority margin. Ciloxan consistently showed non-inferior to Cortisporin.

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TABLE 32: STUDY C98-18: MICROBIOLOGIC SUCCESS RATES AT TOC VISIT IN SUBSETS OF MPP SUBJECTS

MPP Subset	Ciprodex	Ciloxan	Cortisporin	98.3% C.I.
MO's PA/SA MPP Subjects	139/159 (87.4%)	142/162 (87.7%)	126/150 (84.0%)	1. (-9.7%, 9.2%) 2. (-6.8%, 13.6%) 3. (-6.5%, 13.8%)
MO's PA/SA/GN MPP Subjects	161/181 (89.0%)	162/185 (87.6%)	145/169 (85.8%)	1. (-7.2%, 10.0%) 2. (-5.9%, 12.2%) 3. (-7.5%, 11.0%)
MO's Proposed Label MPP Subjects	175/199 (87.9%)	182/209 (87.1%)	163/190 (85.8%)	1. (-7.5%, 9.2%) 2. (-6.6%, 10.9%) 3. (-7.4%, 10.0%)
MO's MPP Subjects	198/229 (86.5%)	205/236 (86.9%)	184/217 (84.8%)	1. (-8.4%, 7.6%) 2. (-6.7%, 10.1%) 3. (-6.2%, 10.4%)
Sponsor's MPP Subjects	198/207 (95.7%)	205/214 (95.8%)	184/200 (92.2%)	1. (-5.3%, 5.1%) 2. (-2.5%, 9.9%) 3. (-2.3%, 9.9%)

For 98.3% C.I. calculation, 1, 2, and 3 mean Ciprodex vs. Ciloxan, Ciprodex vs. Cortisporin, and Ciloxan vs. Cortisporin, respectively.

TABLE 33: STUDY C98-18: MICROBIOLOGIC SUCCESS RATES AT TOC VISIT IN SUBSETS OF MITT SUBJECTS

MITT Subset	Ciprodex	Ciloxan	Cortisporin	98.3% C.I.
MO's PA/SA MITT Subjects	156/184 (84.8%)	151/178 (84.8%)	139/180 (77.2%)	1. (-9.6%, 9.5%) 2. (-2.8%, 17.9%) 3. (-2.8%, 18.0%)
MO's PA/SA/GN MITT Subjects	179/211 (84.8%)	173/204 (84.8%)	161/204 (78.9%)	1. (-8.9%, 8.9%) 2. (-3.6%, 15.4%) 3. (-3.7%, 15.5%)
MO's Proposed Label MITT Subjects	198/236 (83.9%)	196/232 (84.5%)	181/229 (79.0%)	1. (-9.1%, 7.9%) 2. (-4.2%, 13.9%) 3. (-3.6%, 14.5%)
MO's MITT Subjects	223/267 (83.5%)	223/261 (85.4%)	203/257 (79.0%)	1. (-9.8%, 6.0%) 2. (-4.0%, 13.1%) 3. (-2.0%, 14.9%)
Sponsor's MITT Subjects	224/267 (83.9%)	228/261 (87.4%)	208/257 (80.9%)	1. (-11.1%, 4.2%) 2. (-5.4%, 11.3%) 3. (-1.6%, 14.5%)

For 98.3% C.I. calculation, 1, 2, and 3 mean Ciprodex vs. Ciloxan, Ciprodex vs. Cortisporin, and Ciloxan vs. Cortisporin, respectively.

TABLE 34: STUDY C98-18: CLINICAL CURE RATES AT TOC VISIT IN SUBSETS OF MPP SUBJECTS

MPP Subset	Ciprodex	Ciloxan	Cortisporin	98.3% C.I.
MO's PA/SA MPP Subjects	137/159 (86.2%)	142/162 (87.7%)	123/150 (82.0%)	1. (-11.1%, 8.1%) 2. (-6.5%, 14.8%) 3. (-4.7%, 16.0%)
MO's PA/SA/GN MPP Subjects	159/181 (87.8%)	162/185 (87.6%)	142/169 (84.0%)	1. (-8.5%, 9.0%) 2. (-5.7%, 13.3%) 3. (-5.9%, 13.0%)
MO's Proposed Label MPP Subjects	173/199 (86.9%)	181/209 (86.6%)	159/190 (83.7%)	1. (-8.2%, 8.9%) 2. (-5.9%, 12.4%) 3. (-6.1%, 12.0%)
MO's MPP Subjects	198/229 (86.5%)	206/236 (87.3%)	182/217 (83.9%)	1. (-8.8%, 7.1%) 2. (-5.9%, 11.1%) 3. (-4.9%, 11.8%)
Sponsor's MPP Subjects	198/207 (95.7%)	206/214 (96.3%)	182/200 (91.0%)	1. (-5.7%, 4.5%) 2. (-1.8%, 11.1%) 3. (-1.0%, 11.5%)

For 98.3% C.I. calculation, 1, 2, and 3 mean Ciprodex vs. Ciloxan, Ciprodex vs. Cortisporin, and Ciloxan vs. Cortisporin, respectively.

TABLE 35: STUDY C98-18: CLINICAL CURE RATES AT TOC VISIT IN SUBSETS OF MITT SUBJECTS

MITT Subset	Ciprodex	Ciloxan	Cortisporin	98.3% C.I.
MO's PA/SA MITT Subjects	152/184 (82.6%)	150/178 (84.3%)	141/180 (78.3%)	1. (-11.6%, 8.2%) 2. (-6.2%, 14.8%) 3. (-4.5%, 16.3%)
MO's PA/SA/GN MITT Subjects	175/211 (82.9%)	172/204 (84.3%)	163/204 (79.9%)	1. (-10.6%, 7.8%) 2. (-6.6%, 12.7%) 3. (-5.1%, 14.0%)
MO's Proposed Label MITT Subjects	194/236 (82.2%)	193/232 (83.2%)	182/229 (79.5%)	1. (-9.8%, 7.8%) 2. (-6.4%, 11.9%) 3. (-5.4%, 12.8%)
MO's MITT Subjects	219/267 (82.0%)	220/261 (84.3%)	206/257 (80.2%)	1. (-10.4%, 5.9%) 2. (-6.7%, 10.4%) 3. (-4.3%, 12.6%)
Sponsor's MITT Subjects	220/267 (82.4%)	220/261 (84.3%)	208/257 (80.9%)	1. (-10.0%, 6.2%) 2. (-7.0%, 9.9%) 3. (-5.0%, 11.7%)

For 98.3% C.I. calculation, 1, 2, and 3 mean Ciprodex vs. Ciloxan, Ciprodex vs. Cortisporin, and Ciloxan vs. Cortisporin, respectively.

Table 36 shows pathogen microbiologic success rates for those isolated baseline pathogens proposed in the label.

TABLE 36: STUDY C98-18: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF MO'S MPP SUBJECTS AT TOC VISIT

Baseline Isolate Pathogen	Ciprodex	Ciloxan	Cortisporin
Gram-positive			
Staphylococcus aureus	17/18 (94.4%)	13/16 (81.3%)	17/17 (100%)
Gram-negative			
Pseudomonas aeruginosa	124/144 (86.1%)	132/150 (88.0%)	117/141 (83.0%)

Study C98-19

The comparisons of statistical interest in this study were conducted between Ciprodex and Cortisporin, which was designed to demonstrate the non-inferiority in clinical response and microbiologic response at TOC of Ciprodex to Cortisporin.

The primary efficacy variable analyzed was the proportion of subjects at the TOC visit as clinically cured based on a 4-point scale (cured, improved, not changed and worsened) in which cured was defined as the complete absence of otorrhea, and the proportion of subjects for whom disease-specific pathogens which, present at enrollment, were eradicated at the TOC visit. The microbiological response was documented as success (eradication) or failure at the TOC visit.

Four subject populations were defined as ITT subjects, MITT subjects, PP subjects, and MPP subjects. The primary efficacy analyses were conducted on clinical response at TOC in the ITT and the PP populations, and on microbiological eradication of disease-specific organisms at TOC of the MITT and the MPP populations.

The number and the proportion of subjects included in each evaluation group are presented in Table 37. The most common reasons for exclusion from PP analyses was "Excluded Concomitant Disease". The major discrepancy on evaluability and outcome assessments between the MO and the sponsor came about from the subjects who were discontinued from the study and prescribed alternative therapy. There were no notable differences for two treatment groups with respect to the percentage of subjects included in each evaluation group.

TABLE 37: STUDY C98-19: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Number of Subjects	
	Ciprodex	Cortisporin
All Randomized Subjects	232	236
ITT Subjects	232 (100%)	236 (100%)
MO's PA/SA MITT Subjects	150 (64.7%)	138 (58.5%)
MO's PA/SA/GN MITT Subjects	161 (69.4%)	159 (67.4%)
MO's Proposed Label MITT Subjects	171 (73.7%)	168 (71.2%)
MITT Subjects	197 (84.9%)	199 (84.3%)
MO's PP Subjects	202 (87.1%)	208 (88.1%)
Sponsor's PP Subjects	194 (83.6%)	199 (84.3%)
MO's PA/SA MPP Subjects	126 (54.3%)	123 (52.1%)
MO's PA/SA/GN MPP Subjects	136 (58.6%)	140 (59.3%)
MO's Proposed Label MPP Subjects	145 (62.5%)	145 (61.4%)
MO's MPP Subjects	172 (74.1%)	171 (72.5%)
Sponsor's MPP Subjects	173 (74.6%)	168 (71.2%)

PA/SA: *P. aeruginosa or S. aureus*
PA/SA/GN: *P. aeruginosa, S. aureus,* or other Gram-negative bacteria
Proposed label: Any organism in proposed label

Data for demographics and baseline characteristics are described for ITT subjects in Table 38. The two treatment groups were comparable and no statistically significant differences were detected with regard to these characteristics.

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TABLE 38: STUDY C98-19: BASELINE DEMOGRAPHICS IN ITT SUBJECTS

Variables	Ciprodex (N=232)	Cortisporin (N=236)	P-value
Age (yrs.)			
Range (Min, Max)	(2, 76)	(1, 90)	
Mean ± SD	22.4 ± 16.3	23.1 ± 18.2	*0.660
Distribution			
≥ 0 year and < 13 years	91 (39.2%)	103 (43.6%)	0.127
≥ 13 years and < 65 years	139 (59.1%)	126 (53.4%)	
≥ 65 years	2 (0.9%)	7 (3.0%)	
Gender			
Male	121 (52.2%)	116 (49.2%)	0.516
Female	111 (47.8%)	120 (50.9%)	
Race			
White	205 (88.4%)	204 (86.4%)	0.797
Black	6 (2.6%)	8 (3.4%)	
Other	21 (9.1%)	24 (10.2%)	
Enrolled Ear			
Right Only	100 (43.1%)	112 (47.5%)	0.174
Left Only	105 (45.3%)	108 (45.8%)	
Both	27 (11.6%)	16 (6.8%)	
Worst Ear			
Right	114 (49.1%)	115 (48.7%)	0.930
Left	118 (50.9%)	121 (51.3%)	
Previous AOE			
No	160 (69.0%)	164 (69.5%)	0.902
Yes	72 (31.0%)	72 (30.5%)	

* By t test. All others in the table, by chi-square test.

The primary analyses are presented in Tables 39, 40, and 41 for the clinical responses of PP and ITT subjects as per MO's and sponsor's at the TOC visit, respectively. The confidence interval results demonstrated Ciprodex was non-inferior to Cortisporin with respect to clinical cure rates at TOC.

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TABLE 39: STUDY C98-19: CLINICAL RESPONSES OF PP SUBJECTS AT TOC VISIT BY MO		
Clinical Response	Ciprodex (N=202)	Cortisporin (N=208)
Cured	189 (93.6%)	185 (88.9%)
Not Cured	13 (6.4%)	23 (11.1%)
Difference in Cure Rate Ciprodex vs. Cortisporin:	4.6%, 95% C.I.: -1.3%, 10.6%	

TABLE 40: STUD5.3Y C98-19: CLINICAL RESPONSES OF PP SUBJECTS AT TOC VISIT BY SPONSOR		
Clinical Response	Ciprodex (N=194)	Cortisporin (N=199)
Cured	189 (97.4%)	185 (93.0%)
Not Cured	5 (2.6%)	14 (7.0%)
Difference in Cure Rate Ciprodex vs. Cortisporin:	4.5%, 95% C.I.: -0.2%, 9.2%	

TABLE 41: STUDY C98-19: CLINICAL RESPONSES OF ITT SUBJECTS AT TOC VISIT		
Clinical Response	Ciprodex (N=232)	Cortisporin (N=236)
Cured	206 (88.8%)	197 (83.5%)
Not Cured	26 (11.2%)	39 (16.5%)
Difference in Cure Rate Ciprodex vs. Cortisporin:	5.3%, 95% C.I.: -1.3%, 12.0%	

Another primary analysis is shown in Tables 42 and 43 for the microbiologic responses of MPP and MITT subsets at the TOC visit, respectively. The confidence interval results demonstrated Ciprodex was non-inferior to Cortisporin with respect to microbiologic success rates at TOC.

TABLE 42: STUDY C98-19: MICROBIOLOGIC SUCCESS RATES AT TOC VISIT IN SUBSETS OF MPP SUBJECTS			
MPP Subset	Ciprodex	Cortisporin	95% C.I.
MO's PA/SA MPP Subjects	118/126 (93.7%)	106/123 (86.2%)	(-0.8%, 15.7%)
MO's PA/SA/GN MPP Subjects	128/136 (94.1%)	121/140 (86.4%)	(0.0%, 15.3%)
MO's Proposed Label MPP Subjects	137/145 (94.5%)	126/145 (86.9%)	(0.3%, 14.9%)
MO's MPP Subjects	158/172 (91.9%)	146/171 (85.4%)	(-0.8%, 13.8%)
Sponsor's MPP Subjects	158/173 (91.3%)	146/168 (86.9%)	(-2.8%, 11.6%)

TABLE 43: STUDY C98-19: MICROBIOLOGIC SUCCESS RATES AT TOC VISIT IN SUBSETS OF MITT SUBJECTS			
MITT Subset	Ciprodex	Cortisporin	95% C.I.
MO's PA/SA MITT Subjects	119/150 (79.3%)	110/138 (79.7%)	(-10.4%, 9.6%)
MO's PA/SA/GN MITT Subjects	129/161 (80.1%)	126/159 (79.2%)	(-8.6%, 10.3%)
MO's Proposed Label MITT Subjects	138/171 (80.7%)	131/168 (78.0%)	(-6.5%, 11.9%)
MO's MITT Subjects	161/197 (81.7%)	152/199 (76.4%)	(-3.2%, 13.8%)
Sponsor's MITT Subjects	162/197 (82.2%)	153/199 (76.9%)	(-3.1%, 13.8%)

The results of clinical cure rates at the TOC visit are shown in Tables 44 and 45 for MPP and MITT subsets, respectively. The results displayed consistently that Ciprodex was therapeutically non-inferior to Cortisporin. Table 46 gives pathogen microbiologic success rates for those isolated baseline pathogens proposed in the label.

TABLE 44: STUDY C98-19: CLINICAL CURE RATES AT TOC VISIT IN SUBSETS OF MPP SUBJECTS			
MPP Subset	Ciprodex	Cortisporin	95% C.I.
MO's PA/SA MPP Subjects	118/126 (93.7%)	108/123 (87.8%)	(-2.1%, 13.8%)
MO's PA/SA/GN MPP Subjects	127/136 (93.4%)	125/140 (89.3%)	(-3.2%, 11.4%)
MO's Proposed Label MPP Subjects	136/145 (93.8%)	128/145 (88.3%)	(-1.7%, 12.8%)
MO's MPP Subjects	159/172 (92.4%)	152/171 (88.9%)	(-3.2%, 10.3%)
Sponsor's MPP Subjects	168/173 (97.1%)	155/168 (92.3%)	(-0.5%, 10.2%)

TABLE 45: STUDY C98-19: CLINICAL CURE RATES AT TOC VISIT IN SUBSETS OF MITT SUBJECTS

MITT Subset	Ciprodex	Cortisporin	95% C.I.
MO's PA/SA MITT Subjects	136/150 (90.7%)	119/138 (86.2%)	(-3.7%, 12.5%)
MO's PA/SA/GN MITT Subjects	145/161 (90.1%)	137/159 (86.2%)	(-3.8%, 11.6%)
MO's Proposed Label MITT Subjects	154/171 (90.1%)	141/168 (83.9%)	(-1.6%, 13.9%)
MITT Subjects	179/197 (90.9%)	167/199 (83.9%)	(-0.1%, 13.9%)

TABLE 46: STUDY C98-19: PATHOGEN MICROBIOLOGIC SUCCESS RATES OF MO'S MPP SUBJECTS AT TOC VISIT

Baseline Isolate Pathogen	Ciprodex	Cortisporin
Gram-positive		
Staphylococcus aureus	21/23 (91.3%)	10/13 (76.9%)
Gram-negative		
Pseudomonas aeruginosa	99/105 (94.3%)	97/112 (86.6%)

3.2 EVALUATION OF SAFETY

ACUTE OTITIS MEDIA WITH TYMPANOSTOMY TUBES

Study C99-59

The safety of Ciprodex and Ciloxan was evaluated in 201 pediatric subjects with AOMT. No serious adverse events related to therapy and no deaths were reported during this study. Nineteen subjects (Ciprodex: 7; Ciloxan: 12) were discontinued from the study due to

adverse events, of which 18 were due to treatment-unrelated events. One Ciloxan subject was discontinued because of crying that was attributed to study treatment.

Adverse events were reported in 49 subjects receiving Ciprodex (47.6%) and in 51 receiving Ciloxan (52.0%). Adverse events determined by the investigators to be possibly, probably, or definitely related to trial treatment are listed in Table 47. The most frequently reported treatment-related adverse events in subjects receiving Ciprodex were ear discomfort (1.9%) and ear pain (1.9%). The most frequently reported treatment-related adverse event in subjects receiving Ciloxan was ear precipitate (3.1%).

TABLE 47: STUDY C99-59: FREQUENCY AND INCIDENCE OF TREATMENT-RELATED EVENTS

Adverse Event	Ciprodex (N=103) n (%)	Ciloxan (N=98) n (%)
Otic		
Discomfort, ear	2 (1.9)	1 (1.0)
Pain, ear	2 (1.9)	1 (1.0)
Pruritis, ear	1 (1.0)	1 (1.0)
Precipitate, ear		3 (3.1)
Nonotic		
Nervous system		
Crying	1 (1.0)	1 (1.0)
Special senses		
Taste perversion	1 (1.0)	

Study C00-52

The safety of Ciprodex and Floxin was evaluated in 599 pediatric subjects with AOMT. No serious adverse events related to therapy and no deaths were reported during this study. Seventy-eight subjects (Ciprodex: 32; Floxin: 46) were discontinued from the study due to adverse events, of which 76 were due to treatment-unrelated events.

Adverse events were reported in 137 subjects receiving Ciprodex (46.1%) and in 165 receiving Floxcin (54.6%). Adverse events determined by the investigators to be possibly, probably, or definitely related to trial treatment are listed in Table 48. The most frequently reported treatment-related adverse events in Ciprodex subjects were ear discomfort (3.4%) and ear pain (2.4%).

TABLE 48: STUDY C00-52: FREQUENCY AND INCIDENCE OF TREATMENT-RELATED EVENTS

Adverse Event	Ciprodex (N=297) n (%)	Floxin (N=302) n (%)
Otic		
Pain, ear	7 (2.4)	9 (3.0)
Discomfort, ear	10 (3.4)	3 (1.0)
Precipitate, ear	2 (0.7)	3 (1.0)
Device blockage	1 (0.3)	
Tinnitus	1 (0.3)	
Infection, superimposed ear		2 (0.7)
Irritation, ear		2 (0.7)
Pruritis, ear		2 (0.7)
Ear debris		1 (0.3)
Edema, eardrum		1 (0.3)
Hyperemia, eardrum		1 (0.3)
Nonotic		
Body as a whole		
Headache		1 (0.3)
Digestive system		
Monilia, oral	1 (0.3)	1 (0.3)
Diarrhea		1 (0.3)
Nervous system		
Irritability	2 (0.7)	
Dizziness	1 (0.3)	
Crying		1 (0.3)
Respiratory system		
Cough, increased		1 (0.3)
Skin and appendages		
Erythema	1 (0.3)	
Special senses		
Taste perversion	1 (0.3)	3 (1.0)

ACUTE OTITIS EXTERNA

Study C98-18

The safety of Ciprodex, Ciloxan, and Cortisporin was evaluated in 909 pediatric, adult, and elderly subjects with AOE. No serious adverse events related to therapy and no deaths were reported during the study. No subject discontinued from the study due to an adverse event related to therapy. Thirty-seven subjects (Ciprodex: 14, Ciloxan: 13, Cortisporin: 10) discontinued from the study due to adverse events, all of which were treatment-unrelated events.

Adverse events were reported in 121 subjects receiving Ciprodex (39.7%), 114 receiving Ciloxan (37.4%), and 115 receiving Cortisporin (38.5%). Adverse events determined by the investigators to be possibly, probably, or definitely related to trial treatment are listed in Table 49. The most common treatment-related adverse event in all study groups was ear pruritis.

TABLE 49: STUDY C98-18: FREQUENCY AND INCIDENCE OF TREATMENT-RELATED EVENTS

Adverse Event	Ciprodex (N=305)	Ciloxan (N=305)	Cortisporin (N=299)
	n (%)	n (%)	n (%)
Otic			
Pruritis, ear	5 (1.6)	4 (1.3)	4 (1.3)
Discomfort, ear	1 (0.3)		3 (1.0)
Hearing decreased	1 (0.3)		1 (0.3)
Ear debris	1 (0.3)		
Ear congestion		1 (0.3)	
Ear disorder			1 (0.3)
Pain, ear			1 (0.3)
Nonotic			
Body as a whole			
Headache		1 (0.3)	
Digestive system			
Nausea			1 (0.3)
Skin and appendages			
Erythema	2 (0.7%)		
Dermatitis		1 (0.3)	1 (0.3)

Study C98-19

The safety of Ciprodex and Cortisporin was evaluated in 468 pediatric, adult, and elderly subjects with AOE. No serious adverse events related to therapy and no deaths were reported during the study. Seventeen subjects (Ciprodex: 6, Cortisporin: 11) were discontinued from the study due to adverse events, of which 15 were due to treatment-unrelated events.

Adverse events were reported in 89 subjects receiving Ciprodex (38.4%) and in 96 receiving Cortisporin (40.7%). Adverse events determined by the investigators to be possibly, probably, or definitely related to trial treatment are listed in Table 50. The most common treatment-related adverse event in all study groups was ear pruritis.

TABLE 50: STUDY C98-19: FREQUENCY AND INCIDENCE OF TREATMENT-RELATED EVENTS

Adverse Event	Ciprodex (N=232)	Cortisporin (N=236)
	n (%)	n (%)
Otic		
Pruritis, ear	3 (1.3)	11 (4.7)
Ear congestion	2 (0.9)	4 (1.7)
Ear debris	2 (0.9)	2 (0.8)
Infection, superimposed ear	3 (1.3)	
Ear disorder	1 (0.4)	1 (0.4)
Pain, ear	2 (0.9)	
Discomfort, ear		3 (1.3)
Hearing, decreased		2 (0.8)
Erythema, canal		1 (0.4)
Nonotic		
None		

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4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

ACUTE OTITIS MEDIA WITH TYMPANOSTOMY TUBES

Study C99-59

The results of subgroup analyses showed in Tables 51. The test results did only reveal a statistically significance difference in favor of Ciprodex between the treatments in male subjects and white subjects, but not in other subgroups. The results by the log-rank test stratifying on gender and race, respectively, also provide supportive evidence that Ciprodex was superior to Ciloxan for time to cessation of otorrhea (p-values = 0.0022 and 0.0027).

TABLE 51: STUDY C99-59: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS IN ITT SUBJECTS

Subgroup	Ciprodex (N=100) Median (n)	Ciloxan (N=92) Median (n)	P-value Log-rank's	P-value Stratified Log-rank's
Gender				
Male	4.0 (57)	5.0 (47)	0.0063	0.0022
Female	4.0 (43)	5.0 (45)	0.1211	
Race				
White	4.0 (82)	5.0 (72)	0.0016	0.0027
Black	4.0 (8)	4.0 (8)	0.6640	
Other	4.0 (10)	6.5 (12)	0.3904	

Study C00-52

Subgroup analyses by gender and race for the clinical responses in ITT and PP populations are shown in Tables 52 and 53, respectively. Results were all consistent which means the treatment effects were homogeneous across all these demographic aspects.

TABLE 52: STUDY C00-52: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN PP SUBJECTS BY MO				
Subgroup	Ciprodex (N=236)	Floxin (N=220)	95% C.I.	P-value Breslow-Day's
Gender				
Male	114/134 (85.1%)	110/140 (78.6%)	(-3.3%, 16.3%)	0.9832
Female	88/102 (86.3%)	64/80 (80.0%)	(-5.9%, 18.4%)	
Race				
White	163/191 (85.3%)	142/178 (79.8%)	(-2.7%, 13.9%)	0.2607
Black	10/10 (100%)	9/13 (69.2%)	NA	
Other	29/35 (82.9%)	23/29 (79.3%)	(-18.9%, 26.0%)	

TABLE 53: STUDY C00-52: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO				
Subgroup	Ciprodex (N=297)	Floxin (N=302)	95% C.I.	P-value Breslow-Day's
Gender				
Male	129/172 (75.0%)	128/201 (63.7%)	(1.5%, 21.1%)	0.6829
Female	97/125 (77.6%)	71/101 (70.3%)	(-5.1%, 19.7%)	
Race				
White	181/242 (74.8%)	162/244 (66.4%)	(-0.1%, 16.9%)	0.2754
Black	14/16 (87.5%)	9/17 (52.9%)	NA	
Other	31/39 (79.5%)	28/41 (68.3%)	(-10.4%, 32.8%)	

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Study C98-18

Subgroup analyses by gender and race for the clinical responses in MO's PP population are shown in Tables 54, 55, and 56. A significant interaction for gender by treatment was seen when Ciloxan was compared with Cortisporin, where Ciloxan was more favored in males. Results were homogenous across all these demographic aspects. . Results by subgroups in ITT population are presented in Tables 57, 58, and 59. Significant heterogeneity of treatment effects existed only among the gender subgroup when Ciprodex was compared with Cortisporin, where Ciprodex was more favored in males.

TABLE 54: STUDY C98-18: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN PP SUBJECTS BY MO (1)				
Subgroup	Ciprodex (N=262)	Ciloxan (N=274)	98.3% C.I.	P-value Breslow-Day's
Age				
0 yr.~12 yrs.	114/125 (91.2%)	127/143 (88.8%)	(-7.1%, 11.9%)	0.1848
13 yrs~64 yrs.	108/130 (83.1%)	99/122 (81.1%)	(-10.4%, 14.3%)	
≥ 65 yrs.	5/7 (71.4%)	9/9 (100%)	NA	
Gender				
Male	113/129 (87.6%)	99/111 (89.2%)	(-12.3%, 9.1%)	0.5250
Female	114/133 (85.7%)	136/163 (83.4%)	(-8.5%, 13.0%)	
Race				
White	203/233 (87.1%)	203/237 (85.7%)	(-6.5%, 9.5%)	0.4959
Black	12/12 (100%)	14/14 (100%)	(-7.7%, 7.7%)	
Other	12/17 (70.6%)	18/23 (78.3%)	(-46.3%, 31.0%)	

TABLE 55: STUDY C98-18: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN PP SUBJECTS BY MO (2)				
Subgroup	Ciprodex (N=262)	Cortisporin (N=249)	98.3% C.I.	P-value Breslow-Day's
Age				
0 yr.~12 yrs.	114/125 (91.2%)	103/121 (85.1%)	(-4.6%, 16.7%)	0.2235
13 yrs~64 yrs.	108/130 (83.1%)	100/123 (81.3%)	(-10.5%, 14.1%)	
≥ 65 yrs.	5/7 (71.4%)	5/5 (100%)	NA	
Gender				
Male	113/129 (87.6%)	89/110 (80.9%)	(-5.5%, 18.9%)	0.3143
Female	114/133 (85.7%)	119/139 (85.6%)	(-10.8%, 11.0%)	
Race				
White	203/233 (87.1%)	176/210 (83.8%)	(-5.2%, 11.8%)	0.2416
Black	12/12 (100%)	11/13 (84.6%)	(-16.6%, 47.4%)	
Other	12/17 (70.6%)	21/26 (80.8%)	(-47.3%, 27.0%)	

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TABLE 56: STUDY C98-18: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN PP SUBJECTS BY MO (3)				
Subgroup	Ciloxan (N=274)	Cortisporin (N=249)	98.3% C.I.	P-value Breslow-Day's
Age				
0 yr.~12 yrs.	127/143 (88.8%)	103/121 (85.1%)	(-7.1%, 14.4%)	0.4932
13 yrs~64 yrs.	99/122 (81.2%)	100/123 (81.3%)	(-12.9%, 12.6%)	
≥ 65 yrs.	9/9 (100%)	5/5 (100%)	NA	
Gender				
Male	99/111 (89.2%)	89/110 (80.9%)	(-4.0%, 20.6%)	0.0975
Female	136/163 (83.4%)	119/139 (85.6%)	(-12.8%, 8.5%)	
Race				
White	203/237 (85.7%)	176/210 (83.8%)	(-6.8%, 10.5%)	0.2238
Black	14/14 (100%)	11/13 (84.6%)	(-16.0%, 46.8%)	
Other	18/23 (78.3%)	21/26 (80.8%)	(-34.3%, 29.3%)	

TABLE 57: STUDY C98-18: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO (1)				
Subgroup	Ciprodex (N=305)	Ciloxan (N=305)	98.3% C.I.	P-value Breslow-Day's
Age				
0 yr.~12 yrs.	125/141 (88.7%)	136/158 (86.1%)	(-7.3%, 12.4%)	0.7629
13 yrs~64 yrs.	120/156 (76.9%)	105/137 (76.6%)	(-12.2%, 12.8%)	
≥ 65 yrs.	5/8 (62.5%)	9/10 (90.0%)	NA	
Gender				
Male	124/144 (86.1%)	103/126 (81.7%)	(-7.1%, 15.9%)	0.1858
Female	126/161 (78.3%)	147/179 (82.1%)	(-14.8%, 7.1%)	
Race				
White	224/271 (82.7%)	212/259 (81.9%)	(-7.5%, 9.1%)	0.3345
Black	13/13 (100%)	15/16 (93.8%)	(-15.2%, 27.7%)	
Other	13/21 (61.9%)	23/30 (76.7%)	(-50.2%, 20.7%)	

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TABLE 58: STUDY C98-18: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO (2)				
Subgroup	Ciprodex (N=305)	Cortisporin (N=299)	98.3% C.I.	P-value Breslow-Day's
Age				
0 yr.~12 yrs.	125/141 (88.7%)	122/148 (82.4%)	(-4.3%, 16.8%)	0.2527
13 yrs~64 yrs.	120/156 (76.9%)	111/144 (77.1%)	(-12.5%, 12.1%)	
≥ 65 yrs.	5/8 (62.5%)	6/7 (85.7%)	NA	
Gender				
Male	124/144 (86.1%)	105/133 (78.9%)	(-4.5%, 18.8%)	0.1207
Female	126/161 (78.3%)	134/166 (80.7%)	(-13.8%, 8.8%)	
Race				
White	224/271 (82.7%)	200/250 (80.0%)	(-5.9%, 11.2%)	0.1941
Black	13/13 (100%)	14/16 (87.5%)	(-14.3%, 39.3%)	
Other	13/21 (61.9%)	25/33 (75.8%)	(-48.8%, 21.1%)	

TABLE 59: STUDY C98-18: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS BY MO (3)				
Subgroup	Ciloxan (N=305)	Cortisporin (N=299)	98.3% C.I.	P-value Breslow-Day's
Age				
0 yr.~12 yrs.	136/158 (86.1%)	122/148 (82.4%)	(-7.0%, 14.3%)	0.7629
13 yrs~64 yrs.	105/137 (76.6%)	111/144 (77.1%)	(-13.2%, 12.3%)	
≥ 65 yrs.	9/10 (90.0%)	6/7 (85.7%)	NA	
Gender				
Male	103/126 (81.7%)	105/133 (78.9%)	(-9.8%, 15.4%)	0.8393
Female	147/179 (82.1%)	134/166 (80.7%)	(-9.2%, 12.0%)	
Race				
White	212/259 (81.9%)	200/250 (80.0%)	(-6.9%, 10.6%)	0.8736
Black	15/16 (93.8%)	14/16 (87.5%)	(-24.5%, 37.0%)	
Other	23/30 (76.7%)	25/33 (75.8%)	(-28.0%, 29.8%)	

The test results (Tables 60) to times to cessation of ear pain demonstrated non-significance difference between Ciprodex and Ciloxan across all subgroups. The statistical evaluation by the log-rank test stratifying on age, gender, and race, respectively, provided supportive evidence that Ciprodex was unable to show its superiority to Ciloxan for time to cessation of ear pain (p-values = 0.6439, 0.3583, and 0.3649).

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TABLE 60: STUDY C98-18: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF TIME TO EAR PAIN IN ITT SUBJECTS				
Subgroup	Ciprodex (N=100) Median (n)	Ciloxan (N=92) Median (n)	P-value Log-rank's	P-value Stratified Log-rank's
Age				
0 yr.~12 yrs.	4.0 (141)	5.0 (158)	0.4316	0.6439
13 yrs~64 yrs.	6.0 (156)	6.0 (137)	0.2192	
≥ 65 yrs.	5.0 (8)	3.0 (10)	0.3200	
Gender				
Male	5.0 (144)	5.0 (126)	0.8970	0.3583
Female	5.0 (161)	5.0 (179)	0.1776	
Race				
White	5.0 (271)	5.0 (259)	0.3350	0.3649
Black	6.0 (13)	5.0 (16)	0.7898	
Other	6.0 (21)	6.0 (30)	0.8368	

Study C98-19

Subgroup analyses by gender and race for the clinical responses in PP and ITT populations are shown in Tables 61 and 62. Significant heterogeneity of treatment effects was detected only between the gender subgroups of MO's PP population, and the treatment effects more favored Ciprodex in male subjects.

TABLE 61: STUDY C98-19: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN MO's PP SUBJECTS				
Subgroup	Ciprodex (N=202)	Cortisporin (N=208)	95% C.I.	P-value Breslow-Day's
Age				
0 yr.~12 yrs.	77/79 (97.5%)	85/93 (91.4%)	(-1.8%, 13.9%)	0.3667
13 yrs~64 yrs.	110/121 (90.9%)	93/108 (86.1%)	(-4.4%, 14.0%)	
≥ 65 yrs.	2/2 (100%)	7/7 (100%)	NA	
Gender				
Male	99/104 (95.2%)	88/102 (86.3%)	(0.1%, 17.7%)	0.1321
Female	90/98 (91.8%)	97/106 (91.5%)	(-8.2%, 8.9%)	
Race				
White	167/179 (93.3%)	162/182 (89.0%)	(-2.1%, 10.7%)	0.7266
Black	6/6 (100%)	5/5 (100%)	NA	
Other	16/17 (94.1%)	18/21 (85.7%)	(-15.6%, 32.4%)	

TABLE 62: STUDY C98-19: SUBGROUP ANALYSES BY DEMOGRAPHICS CHARACTERISTICS OF CLINICAL RESPONSES IN ITT SUBJECTS

Subgroup	Ciprodex (N=232)	Cortisporin (N=236)	95% C.I.	P-value Breslow-Day's
Age				
0 yr.~12 yrs.	85/91 (93.4%)	90/103 (87.4%)	(-3.2%, 15.3%)	0.6467
13 yrs~64 yrs.	119/139 (85.6%)	100/126 (79.4%)	(-3.7%, 16.2%)	
≥ 65 yrs.	2/2 (100%)	7/7 (100%)	NA	
Gender				
Male	108/121 (89.3%)	93/116 (80.2%)	(-0.9%, 19.0%)	0.2950
Female	98/111 (88.3%)	104/120 (86.7%)	(-7.8%, 11.0%)	
Race				
White	182/205 (88.8%)	173/204 (84.8%)	(-3.1%, 11.0%)	0.3537
Black	6/6 (100%)	5/8 (62.5%)	NA	
Other	18/21 (85.7%)	19/24 (79.2%)	(-20.0%, 33.1%)	

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5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The following briefly lists and describes the statistical issues and its impact on the efficacy evaluation.

- In terms of uncertain pathogenicity in AOE, it is necessary to have exploratory analyses on several subsets of microbiologic population with different strings of isolated pathogens. The sponsor did not perform such analyses. The list of "defined pathogens" by the sponsor included many species not generally considered pathogens in AOE. According to the relevant draft guidance for AOE, subjects with microbiologic outcomes such as superinfection and reinfection should be included in the MPP analyses, but they were excluded in MPP analyses by the sponsor. The efficacy evaluation by this reviewer contained the analyses towards several subsets of microbiologic population and included subjects with microbiologic outcomes such as superinfection and reinfection in the MPP analyses, which provided a more accurate and complete description of efficacy (see Section 3.1).

- The multiplicity adjustment was ignored while multiple comparisons were performed by the sponsor. In Study 99-18, there were three treatment arms and pairwise comparison was planned between the treatment groups. However, no multiple adjustment approach was applied by the sponsor to maintain the overall Type I error. In addition, the sponsor did not use continuity correction in calculating confidence interval. Correction of analysis approaches were addressed and applied to efficacy evaluation.

- The sensitivity analyses were not conducted comprehensively by the sponsor, especially for dealing with discontinuation cases in PP analysis and relevant pathogen subsets in MPP analysis, which may weaken the robustness of study results. The protocol did not specify that all treatment failures should be carried forward in the per protocol analysis, regardless of whether there was a TOC visit, which may be a source of bias toward finding reliable efficacy evidence. For example, for those considered failure at EOT but without the TOC visit, their failures at EOT should be carried forward to TOC. The analyses by this reviewer incorporated treatment failures into the TOC outcomes.

- In regard to some aspects, the evaluability status of subjects was found not adequately or accurately recorded. For example, for some subjects classified as unevaluable by the sponsor because of "excluded concomitant medication", review of their CRFs revealed that many of these cases were actually treatment failures who were discontinued from the study and prescribed alternative therapy, which made them unevaluable by the sponsor. From the clinical perspective, these cases should be included as failures in the per protocol analysis. Thus, sponsor's results may inflate the treatment effect.

- The results from PP analysis in Study C00-52 did not demonstrate the superiority of Ciprodex over the approved comparator Cortisporin for the treatment of AOE as claimed by the sponsor. The data did demonstrate that Ciprodex was at least as effective as Cortisporin. In these four studies, the treatment regimen of Ciprodex in pediatric subjects was 3 drops BID for 7 days for the two indications, however, the dose of Ciprodex 4 drops BID for 7 days was proposed in sponsor's label.

Based on all the available data and the strength of statistical evidence from each of the four studies, the following summaries the evaluation by this reviewer. The conclusions presented in the review were drawn mainly focused on MO's redefined populations and reclassified outcomes, which was believed to provide a more accurate and validated interpretation and description for efficacy and safety of the studies.

ACUTE OTITIS MEDIA WITH TYMPANOSTOMY TUBE

This indication was primarily supported by two controlled studies (C99-59 and C00-52) to demonstrate the efficacy and safety of Ciprodex in the treatment of AOMT.

For statistical evaluation of efficacy, statistical non-inferiority on clinical response or microbiologic response was analyzed based upon the two-sided 95% confidence interval of the difference in clinical cure rates or microbiologic success rate at TOC between Ciprodex and its comparators for PP and ITT subjects, and statistical superiority on time to event was estimated and analyzed by Kaplan-Meier estimator and Log-rank test on an ITT basis.

STUDY C99-59

- Ciprodex was shown superior to Ciloxan in the time to cessation of otorrhea for ITT population (p-value = 0.0025).

- The safety profile of Ciprodex and it comparators appeared comparable.

STUDY C00-52

- The 95% confidence interval from PP subjects also demonstrated that Ciprodex was therapeutically non-inferior to Floxin $_{236,\ 220}(-0.9\%,\ 13.9\%)_{85.6\%,\ 79.1\%}$.

- The 95% confidence interval of the difference in clinical cure rates of Ciprodex minus Floxin for ITT subjects was $_{297,\ 302}(2.6\%,\ 17.8\%)_{76.1\%,\ 65.9\%}$, which demonstrated superiority of Ciprodex to Floxin in clinical cure rate at TOC.

- The safety profile of Ciprodex and it comparators appeared comparable.

ACUTE OTITIS EXTERNA

This indication was primarily supported by two controlled studies (C98-18 and C98-19) to demonstrate the efficacy and safety of Ciprodex in the treatment of AOE.

For statistical evaluation of efficacy, statistical non-inferiority on clinical response or microbiologic response was analyzed based upon the two-sided 95% confidence interval (family level) of the difference in clinical cure rates or microbiologic success rate at TOC between the Ciprodex's group and its comparators' groups for PP and ITT subjects, and statistical superiority on time to event was estimated and analyzed by Kaplan-Meier estimator and Log-rank test on an ITT basis.

STUDY C98-18

- The 98.3% confidence interval of the difference in clinical cure rates of Ciprodex minus Ciloxan and Ciprodex minus Cortisporin for PP subjects were $_{262,\ 274}(-6.6\%,\ 8.4\%)_{86.6\%,\ 85.8\%}$ and $_{262,\ 249}(-4.8\%,\ 11.0\%)_{86.6\%,\ 83.5\%}$, respectively. The results demonstrated Ciprodex was non-inferior to both Ciloxan and Cortisporin in clinical cure rate at TOC.

- The 98.3% confidence interval of the difference in clinical cure rates of Ciprodex minus Ciloxan and Ciprodex minus Cortisporin for ITT subjects were $_{305,\ 305}(-7.8\%,\ 7.8\%)_{82.0\%,\ 82.0\%}$ and $_{305,\ 299}(-5.9\%,\ 10.0\%)_{82.0\%,\ 79.9\%}$, respectively. The results demonstrated Ciprodex was non-inferior to both Ciloxan and Cortisporin in clinical cure rate at TOC.

- In both PP and ITT populations, Ciloxan was shown non-inferior to Cortisporin in clinical cure rate at TOC $_{274,\ 249}(-5.7\%,\ 10.2\%)_{85.8\%,\ 83.5\%}$ and $_{305,\ 299}(-5.9\%,\ 10.0\%)_{82.0\%,\ 79.9\%}$, respectively.

- Ciprodex failed to show superior to Ciloxan in the time to cessation of ear pain for ITT population (p-value = 0.3864).

- The safety profile of Ciprodex and it comparators appeared comparable.

STUDY C98-19

- The 95% confidence interval of the difference in clinical cure rates of Ciprodex minus Cortisporin for PP subjects were $_{202,\ 208}(-1.3\%,\ 10.6\%)_{93.6\%,\ 88.9\%}$, which demonstrated Ciprodex was non-inferior to Cortisporin in clinical cure rate at TOC.

- The 95% confidence interval of the difference in clinical cure rates of Ciprodex minus Cortisporin for ITT subjects were $_{232,\ 236}(-1.3\%,\ 12.0\%)_{88.8\%,\ 83.5\%}$, which demonstrated Ciprodex was non-inferior to Cortisporin in clinical cure rate at TOC.

- The safety profile of Ciprodex and it comparators appeared comparable.

5.2 CONCLUSIONS AND RECOMMENDATIONS

This NDA submission was to evaluate the efficacy and safety of Ciprodex in the treatment of AOMT and AOE, and each indication was supported by two pivotal studies.

For the treatment of AOMT, Study C99-59 showed that Ciprodex was superior to Ciprofloxacin in time to cessation of otorrhea. Study C00-52 showed therapeutic non-inferiority to the approved comparator Floxin. These studies support the efficacy claim of Ciprodex (3 drops BID for 7 days) for the AOMT indication.

For the treatment of AOE, the sponsor submitted two studies demonstrating that Ciprodex was non-inferior to the approved comparator Cortisporin for the treatment of AOE. Both studies showed therapeutic non-inferiority to the approved comparator Cortisporin. These studies support the efficacy claim of Ciprodex (3 drops BID for children and 4 drops BID for adults for 7 days) for the AOE indication.

In addition, all of the four pivotal studies demonstrated that Ciprodex and its comparators provided substantially comparable safety profiles

Based on the above findings, it is the opinion of this reviewer to conclude that the accessible data from four pivotal studies of this submission supported the use of Ciprodex with proposed treatment regimen in the treatment of AOMT and AOE, and the studies provided sufficient evidence to confirm that Ciprodex as an effective and safe medicine in these two indications.

6 APPENDICES

There is no appendix to this review.

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