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:	19-537 S049
Drug Name:	Cipro (Ciprofloxacin Hydrochloride)
Indication(s):	Complicated Urinary Tract Infection and Acute Pyelonephritis
Applicant:	Bayer
Date(s):	Received 09/25/03; user fee (6 months) 03/25/04
Review Priority:	Priority
Biometrics Division:	Division of Biometrics III
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Keywords: NDA review, clinical studies, noninferiority, safety study, pediatric written request response

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

It is the opinion of this reviewer that Cipro has not been shown to be noninferior to the comparator in terms of the arthropathy endpoint at day +42 or one-year post-treatment. In fact, the data suggests that the risk of arthropathy (as defined in the protocol) is higher with the use of Cipro than with the control. It is also the opinion of this reviewer that noninferiority of the efficacy of Cipro (in terms of clinical success and bacteriologic eradication) relative to that of the comparator has been demonstrated.

1.2 Brief Overview of Clinical Studies

In response to a Written Request Letter, the sponsor has submitted the results of one controlled clinical trial investigating the efficacy and safety of Cipro for the treatment of complicated urinary tract infection (cUTI) and acute pyelonephritis and one observational study investigating the safety of Cipro. Both were conducted in a pediatric population including children ages 1 to 17 years. These studies are denoted in the pediatric written request and throughout this review as "Study #1" and "Study #3", respectively. The study numbers assigned by the sponsor are 100169 and 100225 for Study #1 and Study #3, respectively.

Study 1 is titled, "A prospective, randomized study to compare ciprofloxacin (either as oral suspension or as IV or sequential IV → oral suspension therapy) versus control regimens (either trimethoprim/sulfamethoxazole oral suspension, cefixime oral suspension, IV ceftazidime, sequential IV ceftazidime → trimethoprim/sulfamethoxazole oral suspension therapy or sequential IV ceftazidime → PO cefixime) in the treatment of pediatric patients with complicated urinary tract infections or pyelonephritis". The primary objective of this study was to determine the musculoskeletal safety of Cipro relative to the comparator among pediatric patients with cUTI or pyelonephritis. A secondary objective of this trial was to assess the neurological safety of these dosage regimens in this patient population. A detailed statistical review of this study is contained in this document.

Study 3 is titled, "A prospective, open-label, non-randomized, naturalistic, long-term safety surveillance, observational study of either ciprofloxacin (either as oral suspension, oral tablets or sequential IV → oral therapy or purely IV therapy) or a non-quinolone antibiotic (either as oral suspension, oral tablets or sequential IV → oral therapy or purely IV therapy) in the treatment of pediatric patients with infectious diagnoses". The primary objective of this observational study was to obtain long-term post-exposure, follow-up safety data to determine the potential long-term incidence of arthropathy, if any, associated with Cipro or non-quinolone antibiotic therapy in pediatric patients with various infectious diagnoses. A co-primary objective was to determine the short- and long-term neurological system tolerability of courses of Cipro or non-quinolone antibiotic therapy. This reviewer is in agreement with the sponsor that the baseline differences between the non-randomized treatment groups in this study preclude legitimate by-treatment group comparisons, therefore this study is discussed only briefly within this document.

1.3 Statistical Issues and Findings

This review considers the results of one controlled clinical trial (Study #1) and one observational study (Study #3). This reviewer is in agreement with the sponsor that the baseline differences between the non-randomized treatment groups in Study #3 preclude legitimate by-treatment group comparisons, therefore this section will focus on the results of Study #1 only.

In Study #1, the arthropathy rates by day +42 were 9.3% (31/335) and 6.0% (21/349) for the Cipro and control groups, respectively. The 95% confidence interval for the difference between treatment groups was (-0.8%, 7.2%), indicating that Cipro is not noninferior to the comparator in terms of arthropathy at this time point (since the pre-specified noninferiority margin of 6% is not excluded from the interval). In fact, the interval suggests that Cipro is associated with a higher arthropathy rate than the comparator since the interval is primarily above zero. Similar conclusions are indicated for the one-year time point. The arthropathy rates by one-year post-treatment were 13.7% (45/335) and 9.5% (33/349) for the Cipro and control groups, respectively. The 95% confidence interval for the difference between treatment groups was (-0.6%, 9.1%), indicating that Cipro is not noninferior to the comparator in terms of arthropathy at the one-year follow-up time point. In fact, once again, the interval suggests that Cipro is associated with a higher arthropathy rate than the comparator since the interval is primarily above zero. The efficacy (including clinical success and bacteriologic eradication endpoints) of Cipro was evaluated as secondary objectives of Study #1. Regardless of the analysis group utilized, the results consistently indicated that Cipro was noninferior to the comparator in terms of clinical success and bacteriologic eradication at both the test-of-cure and follow-up time points.

2. INTRODUCTION

2.1 Overview

In response to a Written Request Letter, the sponsor has submitted the results of one controlled clinical trial investigating the efficacy and safety of Cipro for the treatment of complicated urinary tract infection (cUTI) and acute pyelonephritis and one observational study investigating the safety of Cipro. Both were conducted in a pediatric population including children ages 1 to 17 years. These studies are denoted in the pediatric written request and throughout this review as "Study #1" and "Study #3", respectively. The study numbers assigned by the sponsor are 100169 and 100225 for Study #1 and Study #3, respectively.

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neurological safety of these dosage regimens in this patient population. A detailed statistical review of this study is contained in this document.

Study 3 is titled, "A prospective, open-label, non-randomized, naturalistic, long-term safety surveillance, observational study of either ciprofloxacin (either as oral suspension, oral tablets or sequential IV → oral therapy or purely IV therapy) or a non-quinolone antibiotic (either as oral suspension, oral tablets or sequential IV → oral therapy or purely IV therapy) in the treatment of pediatric patients with infectious diagnoses". The primary objective of this observational study was to obtain long-term post-exposure, follow-up safety data to determine the potential long-term incidence of arthropathy, if any, associated with Cipro or non-quinolone antibiotic therapy in pediatric patients with various infectious diagnoses. A co-primary objective was to determine the short- and long-term neurological system tolerability of courses of Cipro or non-quinolone antibiotic therapy. The data included in this submission are the results of an interim analysis including available one-year post-treatment follow-up data. This reviewer is in agreement with the sponsor that the baseline differences between the non-randomized treatment groups in this study preclude legitimate by-treatment group comparisons, therefore this study is discussed only briefly within this document.

2.2 Data Sources

In response to a Written Request Letter, the sponsor has submitted the results of one controlled clinical trial investigating the efficacy and safety of Cipro for the treatment of complicated urinary tract infection (cUTI) and acute pyelonephritis and one observational study investigating the safety of Cipro. Both were conducted in a pediatric population including children ages 1 to 17 years. The following data sets were submitted electronically and utilized in the review of this study.

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All submitted data sets were found to be clearly documented and well organized.

3. STATISTICAL EVALUATION

Study Design, Protocol, and Protocol Amendments (Study #1)

This trial was a prospective, randomized, double-blind, active-controlled, parallel group, multinational, pediatric protocol. The primary objective of this study was to determine the musculoskeletal safety of Cipro relative to the comparator among pediatric patients with cUTI or pyelonephritis. A secondary objective of this trial was to assess the neurological safety of these dosage regimens in this patient population. Additional secondary objectives included the evaluation of clinical and microbiological response data at the test-of-cure visit and first follow-up evaluation.

Patients aged at least 1 year and <17 years, diagnosed with cUTI or pyelonephritis were enrolled. The study centers included 27 sites in the United States, four in Canada, five in South Africa, nine in Argentina, three in Peru, six in Germany, one in Costa Rica, and six in Mexico. Patients were stratified prior to randomization based on whether, in the opinion of the clinical investigator, IV therapy was initially warranted. Patients were then randomized to receive either Cipro or control antibiotics according to a 1:1 randomization. In the oral therapy stratum, ciprofloxacin oral suspension was compared to control regimens (cefixime or TMP/SMX suspension [in Canada only]). In the IV therapy stratum, purely IV ciprofloxacin or IV ciprofloxacin followed by ciprofloxacin oral suspension were compared to control regimens (IV ceftazidime or sequential IV ceftazidime followed by PO cefixime or TMP/SMX [in Canada only]). See Table 1 for a more detailed description of the regimens. Patients with a history of Pseudomonas infections or those in whom Pseudomonas was isolated on pretherapy culture were to remain on IV therapy for the entire course of study, regardless of assigned regimen, to ensure adequate antimicrobial coverage for this organism. Data from each stratum and each dose level within the strata were pooled to perform comparisons between the control and experimental regimens.

Table 1: Method of Assignment of Patients	
Oral Therapy Stratum	
Regimen A	Oral ciprofloxacin at doses of 10 to 20 mg/kg every 12 hours (maximum of 1500 mg per day) to complete 10 to 21 days inclusive of total oral therapy.
Regimen B	Oral cefixime at a dose of 4 mg/kg every 12 hours for patients weighing <50 kg and less than or equal to 12 years of age. Patients weighing >50 kg and over 12 years of age were treated with the recommended adult dose of 200 mg every 12 hours. Therapy duration was 10 to 21 days. OR In Canada, oral TMP/SMX at a dose of 4 mg/kg trimethoprim/20 mg sulfamethosazole every 12 hours. In older children and adolescents weighing ≥ 40 kg, the total daily dose of trimethoprim was not to exceed 320 mg and the total daily dose of sulfamethoxazole was not to exceed 1600 mg. Therapy duration was 10 to 21 days.
IV Therapy Stratum	
Regimen A	Intravenous ciprofloxacin at doses of 6 to 10 mg/kg every 8 hours (maximum of 1200 mg per day). Therapy duration was 10 to 21 days OR Intravenous ciprofloxacin at doses of 6 to 10 mg/kg every 8 hours (maximum of 12 mg per day) followed by oral ciprofloxacin at doses of 10 to 20 mg/kg every 12 hours (maximum of 1500 mg per day) to complete 10 to 21 days inclusive of total therapy.
Regimen B	Intravenous ceftazidime at a dose of 30-45 mg/kg every 8 hours (maximum of 6 grams per day). Therapy duration was 10 to 21 days. OR Intravenous ceftazidime at a dose of 30-45 mg/kg every 8 hours (maximum of 6 grams per day) followed by oral cefixime at a dose of 4 mg/kg every 12 hours for patients weighing <50 kg and less than or equal to 12 years of age. Patients weighing >50 kg and over 12 years of age were treated with the recommended adult dose of 200 mg every twelve hours. Dosing continued for 10 to 21 days inclusive of total therapy. OR In Canada, intravenous ceftazidime at a dose of 30-45 mg/kg every 9 hours (maximum of 6 grams per day) followed by oral TM/SMX at a dose of 4 mg/kg trimethoprim/20 mg sulfamethoxazole every 12 hours. In older children and adolescents weighing ≥40 kg, the total daily dose of trimethoprim was not to exceed 320 mg and the total daily dose of sulfamethoxazole was not to exceed 1600 mg (in Canada). Dosing continued for 10 to 21 days inclusive of total therapy.

Assessment of Arthropathy (Primary Objective)

Arthropathy was the primary outcome variable for safety in this study. The primary timepoint for analysis was Day +28 to +42.

Patients were to undergo musculoskeletal and neurological examinations on Day 2 to 5 during therapy, with additional on-therapy visits every 2 to 5 days during an extended treatment course. The patients were evaluated again at the Day +5 to +9 post-therapy test-of-cure (TOC) visit and the Day +28 to +42 follow-up (first follow-up) visit. In-office visits were to be conducted at the 3-month and 1-year time points. Interim telephone calls were conducted at the 6- and 9-month time points.

The definition of arthropathy was generally considered as any condition affecting a joint or periarticular tissue where there is historical and/or physical evidence for structural damage and/or functional limitation that may have been temporary or permanent. Patients with any pre-treatment baseline musculoskeletal exam abnormalities were to be excluded from the study. The musculoskeletal condition of each patient was evaluated by either rheumatologists or trained physical therapists at the site who were experienced in musculoskeletal examinations. This included assessments of the appearance, structure, and function of all joints (with special emphasis on weight-bearing joints and the shoulder girdle). Patients who developed evidence of musculoskeletal abnormalities, regardless of the degree of severity, were to undergo magnetic resonance imaging (MRI); or other appropriate imaging studies of the affected joint. Initially, a computer program was used to identify patients with potential cases of arthropathy. Patients who met any one of the five conditions below were flagged.

1. Patients with any musculoskeletal adverse events, as identified by the COSTART coding system (COSTART codes between 7000000 and 7999999).
2. Patients with changes in gait/joint exams, identified as those patients with decreases in range of motion which were in the lowest 1% of all changes seen in the population.
3. Patients with abnormal gait/joint appearances, as determined by the investigators.
4. Patients with abnormal stance or swing, as determined by the investigators.
5. Patients with a 10 degree or greater decrease from baseline on any range of motion exam. (Note: If range of motion was the only finding, the case was not highlighted).

Prior to declaring a clean database and breaking the study blind, investigator terms for adverse events were reviewed by a Bayer medical physician. Those adverse events that could potentially relate to musculoskeletal events, but due to coding conventions would not be identified by the computer program, were selected as additional potential cases of arthropathy. These included all cases of adverse events that coded to COSTART terms of leg pain, hand pain, arm pain, and abnormal gait. Additionally, decreased range of motion and movement in the hip coded to movement disorder, therefore, all events of movement disorder were also highlighted. Similarly, since ankle and hand swelling are coded to peripheral edema, these events were also highlighted. Finally, selected accidental injuries were highlighted if they related to joints or the extremities. By the end of the study, 116 patients (71 (21%) Cipro and 45 (13%) comparator) were identified by the computer program as potential cases of arthropathy. Twenty-five additional subjects (8 (3%) Cipro and 17 (6%) comparator) were identified by the Bayer medical physician's review. In total, there were 141 potential cases of arthropathy highlighted.

An "Independent Pediatric Safety Committee" (IPSC) was established by the sponsor with the purpose of reviewing the 141 highlighted potential cases of arthropathy to determine the

likelihood that arthropathy had occurred (i.e., definite, probably, possible, none), the relationship of the arthropathay to study drug therapy (i.e., definite, probably, possible, none, not assessable), and if there were any pre-existing conditions that may/may not have been exacerbated during the study. The IPSC was formed in September of 1999 and included a pediatric infectious diseases expert and a pediatric rheumatology expert. The committee began reviewing cases in early 2001. In February 2001, a pediatric neurologist was added to the IPSC and in October 2001, a pediatric orthopedic surgeon began participating in the review of cases. The IPSC's determination regarding the occurrence of arthropathy was used in the data analysis. The members of the IPSC were blinded to treatment assignment.

A two-sided 95% confidence interval for the weighted difference between treatment groups in arthropathy incidence rates (documented up to the first follow-up visit) was to be constructed using Mantel-Haenszel weights reflecting IV or oral administration. The difference was to be constructed as P(e) minus P(s), where P(e) is the arthropathy incidence rate for the experimental Cipro arm, and P(s) is the arthropathy incidence rate for the control therapy. "Equivalence" was defined as the upper limit of the two-sided 95% confidence interval for the weighted difference in arthropathy incidence rates being less than 6%. Stratum by treatment interaction was to be assessed using a Breslow-Day or Zelen's test. The analysis of arthropathy incidences was to be completed using the "valid for safety" group of patients.

Assessment of Neurologic Safety (Secondary Objective)

Neurological safety was a secondary safety outcome and was assessed through the collection of neurological system adverse events through 1-year post-therapy. Comparison of incidence rates of all types of adverse events (including neurologic adverse events) was to be done in a descriptive manner. Events were to be tabulated by type and frequency at the first follow-up and at the one-year follow-up using the "valid for safety" group.

Assessment of Clinical and Microbiological Response (Secondary Objectives)

The evaluation of clinical and microbiological response at the test-of-cure visit and first follow-up evaluation were additional secondary considerations.

Clinical responses determined at the TOC visit (Day +5 to Day +9) were defined as follows.

Cure: resolution of signs and symptoms related to the current infection and not requiring further antibiotic therapy;
Failure: persistent fever or flank pain or insufficient reduction in severity of the signs and symptoms of infection to qualify as resolution, requiring a modification of the antibacterial therapeutic regimen;
Indeterminate: patients in whom a clinical assessment was not possible for various reasons, including early withdrawal due to adverse events, protocol violations, etc.

Clinical responses determined at the first follow-up visit were defined as follows.

Sustained cure: resolution of clinical signs and symptoms maintained throughout the follow-up period not requiring further antibiotic therapy;
Failure: patients carried forward from the Day +5 to +9 post-therapy visit;
Relapse: initial resolution or partial resolution of signs and symptoms through assessment at Day +5 to +9 following treatment but with reappearance of infection-related complaints requiring further antibiotic therapy;
Indeterminate: patients in whom a clinical assessment was not possible for various reasons, including early withdrawal due to adverse events, protocol violations, etc.

A two-sided 95% confidence interval for the weighted difference between treatment groups in clinical success rates was to be constructed using Mantel-Haenszel weights based on IV or oral administration. The difference was to be constructed as P(e) minus P(s), where P(e) is the clinical success rate for the experimental ciprofloxacin arm, and P(s) is the clinical success rate for the control therapy. Non-inferiority was defined as the lower limit of the two-sided 95% confidence interval for the weighted difference in clinical success rates being greater than -12%. Stratum by treatment interaction was to be assessed using a Breslow-Day or Zelen's test. The analysis of clinical success was to be completed using the "clinically valid" group as well as using the "valid for safety" group of patients. Missing and indeterminate data were to be treated as failures in the analysis utilizing the "valid for safety" group.

Bacteriologic response was assigned at the test-of-cure visit using the following definitions.

Eradication: causative organism(s) in numbers $<10^4$ CFU/mL ($<10^3$ CFU/mL for intermittent catheterization samples and $<10^2$ CFU/mL for specimens obtained by suprapubic aspiration);
Persistence: causative organism(s) in numbers $\geq 10^4$ CFU/mL ($\geq 10^3$ CFU/mL for intermittent catheterization samples and $\geq 10^2$ CFU/mL for specimens obtained by suprapubic aspiration);
Indeterminate: the bacteriological response to the study drug was not evaluable for any reason (eg, the pretreatment culture was negative, post-treatment culture was not performed):
Superinfection: response was assessed when all of the following criteria were met

- The isolation of a pathogen other than the original pathogen from a specimen taken while the patient was on study drug.
- The presence of signs and symptoms of complicated UTI or pyelonephritis.
- The infection required alternative antimicrobial therapy.

Superinfections were considered microbiological failures and were assessed separately.
New Infection: appearance of new causative organism(s) other than the original microorganism found at a level $\geq 10^5$ CFU/mL (either by MSU or by indwelling urethral catheter), $\geq 10^4$ CFU/mL (by intermittent urethral catheterization) or $\geq 10^3$ CFU/mL (by suprapubic aspiration) if present anytime after treatment was completed.

Bacteriologic response determined on the first follow-up visit used the following definitions.

Long-term, Sustained Eradication: causative organism(s) in numbers $<10^4$ CFU/mL (for MSU or indwelling uretheral catheterization), $<10^3$ CFU/mL (for intermittent catheterization samples) and $<10^2$ CFU/mL (For specimens obtained by suprapubic aspiration);
Persistence: A urine culture, taken any time after the completion of therapy, with $>10^4$ CFU/mL of the original uropathogen. These patients were carried forward from the Day +5 to +9 post-therapy visit;
Recurrence: eradication on Day +5 to +9 following therapy, but reappearance of the initial causative organism(s) in numbers $\geq 10^4$ CFU/mL ($\geq 10^3$ CFU/mL for intermittent catheterization samples and $\geq 10^2$ CFU/mL for specimens obtained by suprapubic aspiration);
New Infection: appearance of new causative organism(s) other than the original microorganism found at a level $\geq 10^5$ CFU/mL (either by MSU or by indwelling urethral catheter), $\geq 10^4$ CFU/mL (by intermittent urethral catheterization) or $\geq 10^3$ CFU/mL (by suprapubic aspiration) if present anytime after treatment was completed.
Indeterminate: no evaluation possible for any reason.

The analysis of bacteriological response was to be performed on the "microbiologically valid" group of subjects as well as on the "microbiologically valid for safety" group. The statistical procedures and noninferiority definition for the bacteriologic endpoint were to be identical to those described above for the clinical endpoint.

The "clinically valid" subgroup was defined in the protocol as including all subjects for whom the following criteria are met and documented on the case report form.

- Infectious diagnosis must be supported by signs and symptoms of complicated urinary tract infection or pyelonephritis.
- All inclusion/exclusion criteria are met.
- Urinary tract infection must have been confirmed pre-treatment (colony count of $\geq 10^5$ CFU/ml of a causative organism by the midstream urine collection or indwelling urinary catheter methods, colony count of $\geq 10^4$ CFU/ml from clean intermittent urethral catheterization specimens or $\geq 10^3$ CFU/ml from a suprapubic aspiration sample)
- At least 6 days (18 IV doses OR 12 oral doses OR a combination) of study drug must have been taken unless the patient was a treatment failure.
- The study drug must have been given for a minimum of 48 hours (6 IV doses or 4 PO doses) if the treatment result was a failure.
- No other antimicrobial agent, active against the causative organism, must have been administered concomitantly with the study drug.
- A clinical evaluation must have been performed at the Test of Cure (day +5-+9) visit unless the patient was an early clinical failure. An indeterminate designation at Test-of-Cure will invalidate the patient for efficacy evaluation.

Definition of the "microbiologically valid" group is not clearly provided in the protocol; however, it is indicated that the "microbiologically valid" group includes those subjects who are included in the "clinically valid" group and have microbiological response data.

A modified intent-to-treat (mITT) analysis including all patients who received at least one dose of study drug and had a baseline pathogen was not protocol-specified but will be conducted by this reviewer for the efficacy endpoints. Patients with missing or indeterminate efficacy evaluations will be included and counted as failures in all efficacy analyses carried out in the mITT population. It is division policy to consider the results of an intent-to-treat group or mITT group of at least as much importance as that of groups such as the "clinically valid" group or "microbiologically valid" group for non-inferiority trials. Therefore this review will include discussion of the results from both the mITT and "clinically valid" or "microbiologically valid" analysis groups.

The protocol originally specified that 436 pediatric patients would be enrolled into the study. This sample size was calculated using the methods of Rodary[1], based on the previously described primary analysis methods and the following assumptions.

- The true arthropathy rate for each treatment group is 1.5%,
- The smallest clinically meaningful difference between treatments (delta) is 6%, and
- The type I error rate is 0.025 (one-sided).

Under these assumptions, a study of this size would afford 99.8% power to reject the null hypothesis of inequivalence in terms of the arthropathy endpoint. Using an assumed true clinical success rates of 90% in both groups and a clinically meaningful difference (delta) of 12%, the sample size of 436 patients calculated for the arthropathy comparison would have provided 93.5% power (at alpha=0.025, one-sided) to reject the null hypothesis after accounting for an 80% patient validity rate for the clinical success endpoint. However, after consultation with the FDA in August of 2001, the sample size was increased to 640 patients. The increase was not

[1] Rodary C, Com-Nougue C, Tournade MF. How to establish equivalence between treatments: a one-sided clinical trial in pediatric oncology. *Stat Me*d. 1989;8:593-8.

justified by a statistical argument rather according to the protocol amendment, it was supported by the FDA's "interest in more comparative (quinolone versus non-quinolone) safety data in pediatric patients". Since the study already had adequate power with the original sample size, this change resulted in very high power for all planned treatment group comparisons under the assumptions described above.

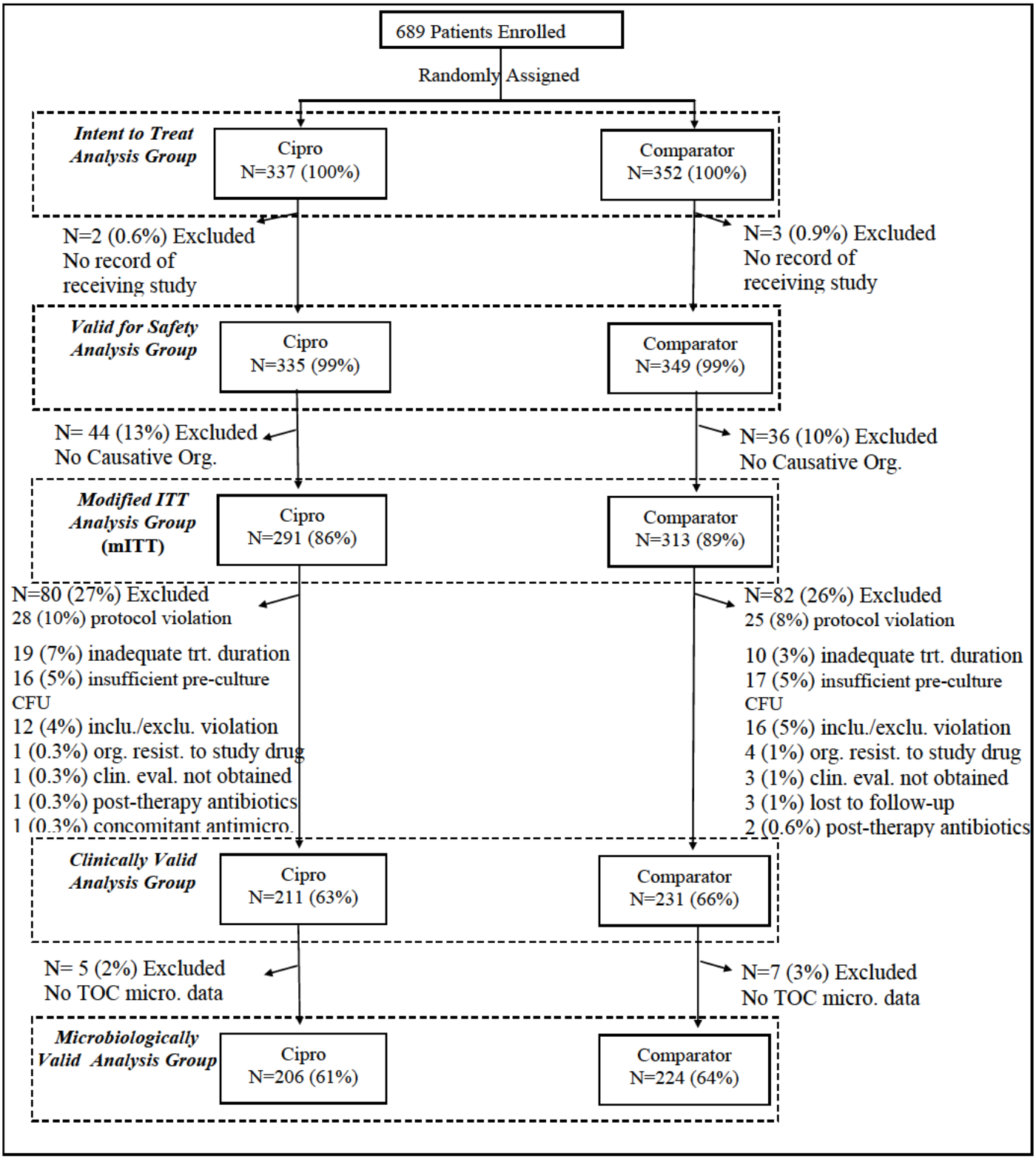
Results (Study #1)

This study enrolled 689 patients at 61 centers in eight countries. Three hundred thirty seven were randomly assigned to treatment with Cipro and 352 were randomly assigned to the control group. Patient inclusion in and exclusion from the "valid for safety", "clinically valid", and "mirobiologically valid" analysis groups as they were defined in the protocol are described in Figure 1. In addition, a modified intent-to-treat (mITT) analysis group including all patients who received at least one dose of study drug and had a baseline pathogen is included. Although it was not a protocol-specified analysis group, the results for this group will be included in this review as it is the approach commonly implemented by the Division of Special Pathogens and Immunologic Drug Products.

As indicated in Figure 1, five subjects were excluded from the valid for safety analysis group, as there was no record of them receiving study medication. The only reason for further exclusions from the mITT analysis group in both treatments groups was no causative organism. The Cipro group had a slightly higher rate of patients (13%) with no causative organisms than the comparator group (10%). Further exclusions from the sponsor's "clinically valid" analysis group were made for the follow reasons; protocol violation, inadequate treatment duration, insufficient pre-culture CFU, inclusion or exclusion criteria violation, organism resistant to study drug, required clinical evaluation not obtained, post-therapy antibiotics, concomitant antimicrobial therapy, non-adherence to dosing regimen and lost-to-follow-up. The rates of these exclusions were fairly balanced across treatment groups. Finally, five Cipro patients and seven comparator patients were excluded from the sponsor's "microbiologically valid" analysis group since microbiological response data was not available for these subjects.

It is interesting to note that the rate of inclusion in the clinically valid analysis group varied by country of enrollment. Although, these rates were fairly balanced across treatment groups they were dramatically lower in the United States, Canada, and Germany (within 35% to 55% in each treatment groups in all cases) than in Argentina, Costa Rica, Mexico, Peru and South Africa (within 61% to 85% in each treatment group in all cases).

Figure 1: Patient Disposition and Analysis Groups



Demographic and baseline variables (including causative orgainsm) for the clinically valid and valid for safety analysis groups are summarized in Table 2. The majority of patients in both treatment groups and in both the clinically valid and valid for safety analysis groups were female. Regardless of treatment assignment or analysis group, most patients fell into one of three racial categories, Caucasian, Hispanic, or Uncodable. According to the study report, further inspection of uncodable races revealed these patients were of Mestizo (mixed European and native South American) descent. In both analysis groups, approximately half of the patients in each treatment group were being treated for pyelonephritis, the others were receiving treatment for cUTI. There were numerically more patients in the Cipro group than in the comparator group with severe infections (7% vs. 3% in the clinically valid analysis group, 7% vs. 4% in the valid for safety group). This difference was marginally statistically significant in each of the analysis groups ($p=0.083$ and $p=0.068$ for the clinically valid group and valid for safety group, respectively). Average infection duration was similar for both treatment groups in both analysis groups. With the exception of the infection severity, the distributions of the demographic and baseline variables were not statistically significantly different across treatment groups in either analysis group.

The most common pre-therapy causative organism was *Escherichia coli*. Both treatment groups had similar distributions of most organisms with the exception of *Pseudomonas aeruginosa* (0 in the Cipro group versus 6 in the comparator group) for the clinically valid analysis group. Note though that in the valid for safety group (where the legitimacy of the original random treatment assignment is intact) this organism was balanced (8 in the Cipro group versus 8 in the comparator group). This indicates that there was a disproportionate exclusion of subjects with this pathogen from the clinically valid analysis group (0/8 (0%) and 6/8 (75%) for Cipro and control, respectively, $p=0.0022$). Exclusion of subjects with *Klebsiella Pneumoniae* from the clinically valid analysis group was also disproportionate in the two treatment groups (9/16 (56%) and 10/10 (100%) for Cipro and control, respectively, $p=0.0201$).

Table 2: Demographic and Baseline Variables Summary Statistics							
		Clinically Valid Analysis Group			Valid for Safety Analysis Group		
		Cipro N=211	Comp. N=231	By-trt. p-value[1]	Cipro N=335	Comp. N=349	By-trt. p-value[1]
Gender	**Male**	32 (15%)	33 (14%)	0.794	62 (19%)	65 (19%)	0.969
	Female	179 (85%)	198 (86%)		273 (81%)	284 (81%)	
Race	**Caucasian**	79 (37%)	87 (38%)	1.000	130 (39%)	134 (38%)	0.851
	Black	1 (<1%)	1 (<1%)		5 (1%)	7 (2%)	
	Asian	1 (<1%)	1 (<1%)		3 (<1%)	6 (2%)	
	Hispanic	65 (31%)	69 (30%)		102 (30%)	109 (31%)	
	Uncodable[2]	65 (31%)	73 (32%)		95 (28%)	93 (27%)	
Age	**Mean**	5.8	6.3	0.168	6.3	6.2	0.756
	Range	1.0 – 16.0	1.0 – 15.0		1.0 – 16.0	1.0 – 17.0	
Infection Type	**Pyelonephritis**	119 (56%)	137 (59%)	0.536	171 (51%)	183 (52%)	0.716
	Complicated UTI	92 (44%)	94 (41%)		164 (49%)	166 (48%)	
Infection Severity	**Mild**	50 (24%)	56 (24%)	0.083	76 (23%)	93 (27%)	0.068
	Moderate	146 (69%)	169 (73%)		234 (70%)	243 (70%)	
	Severe	15 (7%)	6 (3%)		25 (7%)	13 (4%)	
Infection Duration	**Mean**	11.3	11.3	0.850	11.3	11.2	0.592
	Range	7.0 – 21.0	10.0 – 21.0		5.0 – 21.0	7.0 – 21.0	
Pre-therapy Causative Organism	**Staphylococcus Sp.**	0	0		0	2	
	Staphylococcus Aureus	0	1		0	1	
	Staphylococcus saprophyticus	1	0		1	0	
	Staphylococcus Hyicus	0	1		0	1	
	Streptococcus Sp.	1	0		1	0	
	Streptococcus Pneumoniae	0	1		0	1	
	Streptococcus Viridans group	0	1		0	1	
	Enterococcus Sp.	2	0		4	2	
	Enterococcus faecalis	1	3		3	6	
	Gram-Positive Rods	0	1		0	1	
	Gram-Neg Rods Ferm. Entero.	1	0		1	0	
	Escherichia Coli	181	185		217	223	
	Klebsiella Pneumoniae	9	10		16	10	
	Klebsiella Oxytoca	0	3		0	5	
	Klebsiella Ozaenae	1	1		1	1	
	Proteus Mirabilis	2	5		5	12	
	Proteus Vulgaris	2	2		3	3	
	Enterobacter Cloacae	3	2		3	3	
	Serratia Sp.	0	1		0	1	
	Serratia Marcescens	0	1		0	2	
	Citrobacter Freundii	1	0		2	0	
	Morganella Morganii	1	2		1	3	
	Pantoea Agglomerans	4	5		5	5	
	Pseudomonas Aeruginosa	0	6		8	8	
	Pseudomonas Fluorescens	1	0		1	0	
	Acinetobacter Sp.	0	1		0	2	
	Mixed Culture	0	0		1	1	

1. P-values for categorical variables obtained using a chi-square test. P-values for continuous variables obtained using 1-way ANOVA.
2. According to the study report, further inspection of uncodable races revealed these patients were of Mestizo (mixed European and native South American descent.

Study Design, Protocol, and Protocol Amendments (Study #3 Interim Analysis)

This was an open-label, non-randomized, observational study of a group of pediatric patients receiving Cipro (either as oral suspension, oral tablets, or sequential IV to oral therapy or purely IV therapy) and another group of pediatric patients receiving a non-quinolone antibiotic (either as oral suspension, oral tablets, or sequential IV to oral therapy or purely IV therapy) for the treatment of a variety of infections.

The primary objective of the study was to estimate the long-term incidences of arthropathy associated with the use of Cipro and non-quinolone antibiotic therapy in pediatric patients. A co-primary objective was to determine the short- and long-term neurological system tolerability of courses of Cipro and non-quinolone antibiotic therapy in pediatric patients.

Patients aged at least 2 months and <17 years were eligible for enrollment in the study. The study centers included 67 sites in the United States and one in Canada. The decision to treat with Cipro or a non-quinolone antibiotic was made prior to a patient's enrollment in the study and at the discretion of the investigator. After the investigator determined that a particular infant or child was suitable for treatment with Cipro or a non-quinolone antibiotic, the selection of study unit dose, total daily dose, duration of therapy, route of administration, and formulation was also left to the discretion of the investigator. Data from all dose levels, durations, and routes of administration were pooled for those receiving Cipro and those receiving a non-quinolone antibiotic.

Patients were to have routine physical examination including neurological assessment performed at the time of study enrollment. Within 72 hours prior to study enrollment, it was expected that a thorough history of musculoskeletal and neurological events, including events occurring during the time of ciprofloxacin or non-quinolone antibiotic administration which preceded study enrollment, were recorded in both source documents and on the study case report form. Patients also were to have a gait/joint examination to assess the range of motion of the weight-bearing joints (in particular, hip, knee and ankle) as well as the shoulder girdle. Parents/caregivers were also to be asked to complete a short questionnaire concerning their child's health status and to provide brief details of family history. For the non-quinolone antibiotic group, there was to be confirmation of no prior exposure to quinolone therapy. Patients were to return to the clinical site one month after the treatment course of Cipro or non-quinolone antibiotic for assessment of changes in gait or range of motion and to undergo a neurologic exam. Telephone interviews of the parents/caregivers were then conducted at 3, 6, 9, and 12 months post-treatment and quarterly each year thereafter for the purpose of long-term follow-up of musculoskeletal and neurological system status checks. Parents/caregivers were also provided with a phone number to call in the event that their child developed musculoskeletal or neurological symptoms.

As in study #1, the definition of arthropathy was generally considered as any condition affecting a joint or periatricular tissue where there is historical and/or physical evidence for structural damage and/or functional limitation that may have been temporary or permanent. This definition was seen as broad and inclusive of such phenomena as bursitis, enthesitis and tendonitis. The Independent Pediatric Safety Committee (IPSC) reviewed patient records and determined the arthropathy classification (i.e., definite, probable, possible, none), relationship of

arthropathy to study drug therapy (i.e., definite, probable, possible, none, not assessable), and if there were any pre-existing conditions that may/may not have been exacerbated during the study. The members of the IPSC were blinded to treatment assignment.

The primary population for tabular comparisons was the population of patients considered valid for safety. The primary outcomes of interest were the incidence of musculoskeletal and central nervous system adverse events occurring by day +28 to +42. These incidences were to be presented by treatment group with their 95% confidence intervals. No formal statistical comparisons between treatment groups were planned.

The data reported herein are the results of an interim analysis including one-year post-treatment follow-up data for all patients who had been contacted by telephone by June 30, 2003. The length of follow-up of subjects as part of this study is planned to be up to five years post-treatment. Pre-pubescent and pubescent children were to be followed for five years and post-pubescent children were to be followed for one year. Patients who experienced a musculoskeletal adverse event during therapy were to be followed for five years regardless of their stage of pubescence.

Results (Study #3 Interim Analysis)

Of the 1029 patients enrolled in the study, 994 (487 Cipro and 507 non-quinolone controls) were considered to have received at least one dose of study drug and were valid for the safety analysis. By June 30, 2003, 404 Cipro patients and 315 control patients would have been eligible for one-year post-treatment follow-up. Of these, 355 Cipro and 267 non-quinolone patients had been contacted by telephone for the one-year post-treatment follow-up and thus were included in this interim analysis.

3.1 Evaluation of Efficacy

Results for Clinical and Microbiological Response (Secondary Objectives, Study #1)

The clinical response at the test-of-cure visit in the overall group and in each of the strata is summarized in Table 3 for both the "clinically valid" and mITT analysis groups. The 95% confidence intervals for the by-treatment difference in the proportions of subjects with clinical success at the TOC visit (Cipro - comparator) in the "clinically valid" and mITT analysis group exclude the protocol specified noninferiority margin of -12%, indicating that Cipro is non-inferior to the comparator in terms of this endpoint. Interaction by strata was not detected in either analysis group.

Table 3				
Clinical Success at the Test-of-Cure Time Point				
	Clinically Valid Analysis Group		**mITT Analysis Group**	
	Cipro	**Comp.**	**Cipro**	**Comp.**
All Patients	**N=211**	**N=231**	**N=291**	**N=313**
Success[1]	202 (95.7%)	214 (92.6%)	225 (77.3%)	237 (75.7%)
95% C. I. for Diff. in Prop. (weighted by strata)[2]	(-1.3%, 7.3%)		(-5.2%, 8.2%)	
PO Stratum	**N=196**	**N=211**	**N=257**	**N=273**
Success[1]	188 (96.0%)	197 (93.4%)	205 (79.8%)	209 (76.6%)
97.5% C. I. for Diff. in Prop.[3]	(-2.8%, 8.0%)		(-4.9%, 11.2%)	
IV Stratum	**N=15**	**N=20**	**N=34**	**N=40**
Success[1]	14 (93.3%)	17 (85.0%)	20 (58.8%)	28 (70.0%)
97.5% C. I. for Diff. in Prop.[3]	(-21.7%, 34.5%)		(-35.1%, 13.5%)	

1. Success, by protocol definition, includes subjects who were ranked as cured or improved. One Cipro subject in the PO stratum was ranked improved. No other subjects in either treatment group were ranked improved for this endpoint at the TOC time point.
2. Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (by strata).
3. Within-strata 97.5% confidence intervals for the differences in proportions were calculated using the normal approximation, unless the product of the sample size and observed proportion was not sufficiently large, in which case an exact test was used.

The bacteriologic response at the test-of-cure visit in the overall group and in each of the strata is summarized in Table 4 for both the "microbiologically valid" and mITT analysis groups. The 95% confidence intervals for the by-treatment difference in the proportions of subjects with eradication at the TOC visit (Cipro - comparator) in the "microbiologically valid" and mITT analysis groups indicate that Cipro is also non-inferior to the comparator in terms of this endpoint. Interaction by strata was not detected in either analysis group.

Table 4				
Bacteriologic Eradication at the Test-of-Cure Time Point				
	Microbiologically Valid Analysis Group		**mITT Analysis Group**	
	Cipro	**Comp.**	**Cipro**	**Comp.**
All Patients	**N=206**	**N=224**	**N=291**	**N=313**
Eradication	178 (86.4%)	181 (80.8%)	189 (64.9%)	191 (61.0%)
95% C. I. for Diff. in Prop. (weighted by strata)[1]	(-1.4%, 12.6%)		(-3.9%, 11.4%)	

PO Stratum	N=191	N=208	N=257	N=273
Eradication	165 (86.4%)	168 (80.8%)	173 (67.3%)	173 (63.4%)
97.5% C. I. for Diff. in Prop. [2]	(-2.8%, 14.0%)		(-5.3%, 13.1%)	
IV Stratum	**N=15**	**N=16**	**N=34**	**N=40**
Eradication	13 (86.7%)	13 (81.3%)	16 (47.1%)	18 (45.0%)
97.5% C. I. for Diff. in Prop. [2]	(-28.5%, 38.5%)		(-23.2%, 27.2%)	

1. Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (by strata).
2. Within-strata 97.5% confidence intervals for the differences in proportions were calculated using the normal approximation, unless the product of the sample size and observed proportion was not sufficiently large, in which case an exact test was used.

Trends observed with the clinical success and bacteriologic eradication endpoints at the follow-up visit are consistent with those of the TOC visit and are displayed in Table 5 for both strata combined.

Table 5

Clinical Success at the Follow-up Time Point				
	Clinically Valid Analysis Group		mITT Analysis Group	
	Cipro	Comp.	Cipro	Comp.
All Patients	**N=211**	**N=231**	**N=291**	**N=313**
Success[1]	175 (82.9%)	179 (77.5%)	210 (72.2%)	215 (68.7%)
Bacteriologic Eradication at the Follow-up Time Point				
	Microbiologically Valid Analysis Group		mITT Analysis Group	
	Cipro	Comp.	Cipro	Comp.
All Patients	**N=206**	**N=224**	**N=291**	**N=313**
Eradication	149 (72.3%)	147 (65.6%)	229 (78.7%)	229 (73.2%)

1. Success, by protocol definition, includes subjects who were ranked as cured or improved. One Cipro subject in the PO stratum was ranked improved. No other subjects in either treatment group were ranked improved for this endpoint at the TOC time point.

The study report included the results of these efficacy analyses in the valid for safety analysis group. These results were qualitatively consistent with those presented above for the clinically/microbiologically valid and mITT analysis groups.

3.2 Evaluation of Safety

Results for Arthropathy (Primary Objective, Study #1)

The arthropathy rates by day +42 and by one-year in the overall valid for safety group and in each of the strata are summarized in Tables 6 and 7, respectively. For a description of the type or severity of the arthropathies reported, please refer to the FDA medical review.

The 95% confidence interval for the by-treatment difference in the proportions of subjects with arthropathy by day +42 (Cipro – comparator) does not exclude the protocol specified non-inferiority margin of 6%, indicating that Cipro is not non-inferior to the comparator in terms of

the rate of arthropathy. In fact Cipro appears to be worse than the comparator for the arthropathy endpoint at day +42 (as evidenced by the confidence interval for the by-treatment group difference being primarily above zero). It should also be noted that there is a marginally statistically significant treatment-by-strata interaction (according to the protocol specified Breslow-Day test for interaction p-value = 0.065) indicating that the results of the treatment group comparisons between strata were not completely consistent. The arthropathy rates for the subjects who were determined by the investigators to warrant PO therapy were numerically higher in the Cipro group (9.1%) than in the comparator group (6.9%). The arthropathy rates for the subjects who were determined by the investigators to warrant IV therapy were also numerically higher in the Cipro group (10.3%) than in the comparator group (0.0%) but the magnitude of this difference was much larger in this stratum. This type of interaction where there is a difference in magnitude but not direction is often referred to as a quantitative interaction and is typically of less clinical importance.[2]

Protection of the Type I error rate is maintained in the analysis presented in Table 6 by utilizing 97.5% confidence intervals within the strata; however, since this is an analysis of a safety endpoint, from a regulatory perspective, concern regarding inflation of the Type I error may not be paramount. Therefore, it is worth noting that without a correction for multiple comparisons, the by-treatment group comparison of arthropathy rates in the IV statum would have been considered statistically significant at a significance level of 0.05 (p=0.0291).

Table 6

Arthropathy (as determined by IPSC) by Day +42 in Valid for Safety Analysis Group

	Cipro	Comp.
All Patients	**N=335**	**N=349**
Arthropathy Observed	31 (9.3%)	21 (6.0%)
95% C. I. for Diff. in Prop. (weighted by strata)[1]	(-0.8%, 7.2%)	
PO Stratum	**N=296**	**N=304**
Arthropathy Observed	27 (9.1%)	21 (6.9%)
97.5% C. I. for Diff. in Prop.[2]	(-2.8%, 7.4%)	
IV Stratum	**N=39**	**N=45**
Arthropathy Observed	4 (10.3%)	0 (0.0%)
97.5% C. I. for Diff. in Prop.[2]	(-0.4%, 26.3%)	
Breslow-Day Treatment-by-Strata Interaction Test: p=0.065		

1. Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by strata).
2. Within-strata 97.5% confidence intervals for the differences in proportions were calculated using the normal approximation, unless the product of the sample size and observed proportion was not sufficiently large, in which case an exact test was used.

Results of the analyses of the arthropathy rates at one-year were similar to the day +42 results for the overall group and are given in Table 7. The 95% confidence interval for the by-treatment difference in the proportions of subjects with arthropathy by one year (Cipro – comparator) indicates that the risk of arthropathy may be higher for those receiving Cipro than

[2] Gail M, Simon R. Testing for Qualitative Interactions Between Treatment Effects and Patient Subsets. *Biometrics*. 1985;41:361-372.

those in the comparator group (as evidenced by the confidence interval for the by-treatment group difference being primarily above zero). Unlike the day+42 results, however, analyses at one year do not indicate that there is a treatment-by-strata interaction.

Table 7		
Arthropathy (as determined by IPSC) by One Year in Valid for Safety Analysis Group		
	Cipro	**Comp.**
All Patients	**N=335**	**N=349**
Arthropathy Observed	46 (13.7%)	33 (9.5%)
95% C. I. for Diff. in Prop. (weighted by strata) [1]	(-0.6%, 9.1%)	
PO Stratum	**N=296**	**N=304**
Arthropathy Observed	40 (13.5%)	29 (9.5%)
97.5% C. I. for Diff. in Prop. [2]	(-1.9%, 10.0%)	
IV Stratum	**N=39**	**N=45**
Arthropathy Observed	6 (15.4%)	4 (8.9%)
97.5% C. I. for Diff. in Prop. [2]	(-10.5%, 25.4%)	
Breslow-Day Treatment-by-Strata Interaction Test: p=0.7544		

1. Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by strata).
2. Within-strata 97.5% confidence intervals for the differences in proportions were calculated using the normal approximation, unless the product of the sample size and observed proportion was not sufficiently large, in which case an exact test was used.

Results for Neurologic Safety (Secondary Objective, Study #1)

The incidence of neurologic adverse events observed by one year post-treatment is given in Table 8. No statistically significant difference between treatment groups were observed for this endpoint.

Table 8		
Neurologic Adverse Events by One Year in Valid for Safety Analysis Group		
	Cipro	**Comp.**
All Patients	**N=335**	**N=349**
Neurologic Adverse Event Observed	17 (5.1%)	13 (3.7%)
95% C. I. for Diff. in Prop. [1]	(-1.8%, 4.7%)	

1. Calculated using the normal approximation.

Results for Arthropathy (Primary Objective, Study #3 Interim Analysis)

As patients were not randomly assigned to their study treatment, numerous differences between treatment groups at baseline were identified. For example, there were differences between treatment groups in terms of baseline infection type, previous antimicrobial use, patient medical history, and use of concomitant antimicrobial therapy. In the opinion of this reviewer, it is likely that other significant differences between the treatment groups in terms of unobserved covariates also exist. **The sponsor states in the study report that due to the differences between treatment groups at baseline and because the study was not blinded or randomized, the population of Cipro patients is not comparable to the population of**

control patients. This reviewer is in agreement with this statement and therefore within this document, little emphasis will be place on the results of this study. The incidences (and 95% confidence intervals for the incidences) of arthropathy (as determined by the IPSC) and any CNS event by day +42 and one-year post-treatment are provided in Tables 9 and 10, respectively.

Table 9		
Arthropathy (as determined by IPSC) in Valid for Safety Analysis Group		
	Cipro	**Comp.**
By Day +42 Post-Treatment		
Arthropathy Observed	37/487 (8%)	9/507 (2%)
95% C. I. for Proportion[1]	(5.4%, 10.3%)	(0.8%, 3.3%)
By One Year Post-Treatment		
Arthropathy Observed	56/487 (11%)	13/507 (3%)
95% C. I. for Proportion[1]	(8.8%, 14.7%)	(1.4%, 4.3%)

1. 95% confidence intervals for the proportions were calculated using Exact methods.

Table 10		
Any CNS Event in Valid for Safety Analysis Group		
	Cipro	**Comp.**
By Day +42 Post-Treatment		
CNS Event Observed	28/487 (6%)	9/507 (2%)
95% C. I. For Proportion[1]	(3.9%, 8.2%)	(0.8%, 3.3%)
By One Year Post-Treatment		
CNS Event Observed	56/487 (11%)	11/507 (2%)
95% C. I. For Proportion[1]	(8.8%, 14.7%)	(1.1%, 3.9%)

1. 95% confidence intervals for the proportions were calculated using Exact methods.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Study #1

The sponsor examined arthropathy rates by Day +42 subgrouped according to baseline characteristics. The results of these analyses are contained in Table 11. Arthropathy rates were slightly lower than the overall rates in Mexico (0.0% in both treatment groups) and Peru (2.3% Cipro versus 3.4% comparator). There was a much bigger difference between treatment group arthropathy rates in the United States (21.0% Cipro versus 11.3% comparator) than in the overall rates. The arthropathy rate was higher than the overall rate in Caucasians (13.8% Cipro versus 9.7% comparator) and lower than the overall rate in Hispanics (7.8% Cipro versus 2.8% comparator) and the uncodable race group (5.3% Cipro versus 3.2% comparator). The arthropathy rates were quite similar between males and females and consistent between treatment groups. Differences between treatment groups in the arthropathy rate by Day +42 were fairly consistent with the overall rate in the different age groups, and the arthropathy rate in both treatment groups increased with age. The highest arthropathy rate was seen in the $\geq$ 12

year to <17 year age group, where the rate was 21.9% for Cipro patients and 14.3% for comparator patients. Arthropathy rates were higher than the overall rates in both treatment groups for patients with cUTI (12.2% Cipro versus 9.6% comparator), and lower than the overall rates in both treatment groups for patients with pyelonephritis (6.4% Cipro versus 2.7% comparator). The largest difference between treatment groups in arthropathy rates was observed in the subjects receiving IV therapy (18.2% Cipro versus 0.0% comparator).

Table 11		
Arthropathy (as determined by IPSC) by Day +42 in Valid for Safety Analysis Group		
	Cipro	**Comp.**
All Patients	31 / 335 (9.3%)	21 / 349 (6.0%)
By Country		
Argentina	8 / 77 (10.4%)	7 / 79 (8.9%)
Canada	1 / 8 (12.5%)	1 / 11 (9.1%)
Costa Rica	4 / 21 (19.0%)	0 / 20 (0.0%)
Germany	1 / 13 (7.7%)	1 / 11 (9.1%)
Mexico	0 / 56 (0.0%)	0 / 60 (0.0%)
Peru	2 / 87 (2.3%)	3 / 88 (3.4%)
United States	13 / 62 (21.0%)	8 / 71 (11.3%)
South Africa	2 / 11 (18.2%)	1 / 9 (11.1%)
Race		
Caucasian	18 / 130 (13.8%)	13 / 134 (9.7%)
Black	0 / 5 (0.0%)	1 / 7 (14.3%)
Asian	0 / 3 (0.0%)	1 / 6 (16.7%)
Hispanic	8 / 102 (7.8%)	3 / 109 (2.8%)
Uncoded*	5 / 95 (5.3%)	3 / 93 (3.2%)
Gender		
Male	6 / 62 (9.7%)	4 / 65 (6.2%)
Female	25 / 273 (9.2%)	17 / 284 (6.0%)
Age Group		
≥ 12 months and < 24 months	1 / 36 (2.8%)	0 / 41 (0.0%)
≥ 2 years and < 6 years	5 / 124 (4.0%)	3 / 118 (2.5%)
≥ 6 years and < 12 years	18 / 143 (12.6%)	12 / 153 (7.8%)
≥ 12 years and < 17 years	7 / 32 (21.9%)	5 / 35 (14.3%)
Infection Type		
Pyelonephritis	11 / 171 (6.4%)	5 / 183 (2.7%)
Complicated UTI	20 / 164 (12.2%)	16 / 166 (9.6%)
Route of Treatment		
Oral	27 / 296 (9.1%)	21 / 304 (6.9%)
IV	2 / 11 (18.2%)	0 / 13 (0.0%)
Sequential	2 / 28 (7.1%)	0 / 32 (0.0%)

* According to the study report, further inspection of uncodable races revealed these patients were of Mestizo (mixed European and native South American descent).

4.2 Other Special/Subgroup Populations

Study #1

At the request of the medical division, a subgroup analysis of clinical success and bacteriologic success at TOC by infection type was conducted. The results of this analysis are contained in Table 12. The by-treatment group differences in the proportions with clinical success or bacteriological eradication in each subgroup were similar to the results in the overall group for the clinically valid or microbiologically valid analysis group and the mITT analysis group. The rates of bacteriological eradication were lower in the cUTI stratum than in the pyelonephritis stratum for both treatment groups. This was also true for the clinical success endpoint but the difference between strata was not as large.

Table 12

Clinical Success[1] at the Test-of-Cure Time Point

	Clinically Valid Analysis Group		mITT Analysis Group	
	Cipro	**Comp.**	**Cipro**	**Comp.**
All Patients	202/211 (95.7%)	214/231 (92.6%)	225/291 (77.3%)	237/313 (75.7%)
Pyelonephritis	115/119 (96.6%)	128/137 (93.4%)	126/149 (84.6%)	143/167 (85.6%)
Complicated UTI	87/92 (94.6%)	86/94 (91.5%)	99/142 (69.7%)	94/146 (64.4%)

Bacteriologic Eradication at the Test-of-Cure Time Point

	Microbiologically Valid Analysis Group		mITT Analysis Group	
	Cipro	**Comp.**	**Cipro**	**Comp.**
All Patients	178/206 (86.4%)	181/224 (80.8%)	189/291 (64.9%)	191/313 (61.0%)
Pyelonephritis	109/117 (93.2%)	118/132 (89.4%)	115/149 (77.2%)	125/167 (74.9%)
Complicated UTI	69/89 (77.5%)	63/92 (68.5%)	74/142 (52.1%)	66/146 (45.2%)

1. Success, by protocol definition, includes subjects who were ranked as cured or improved. One Cipro subject in the PO stratum was ranked improved. No other subjects in either treatment group were ranked improved for this endpoint at the TOC time point.

Table 13 displays the bacteriological response at the TOC time point by organism. The vast majority of organisms were *Escherichia Coli*. The eradication rates were numerically similar in the two treatment groups for this organism.

Table 13: Tabulations of Bacteriologic Eradication At the TOC Time Point by Organism		
	Microbiologically Valid Analysis Group	
Eradication Rate*	**Cipro**	**Comparator**
Staphylococcus Aureus		1/1 (100%)
Staphylococcus Saprophyticus	1/1 (100%)	
Staphylococcus Hyicus		1/1 (100%)
Streptococcus Sp.	1/1 (100%)	
Streptococcus Pneumoniae		1/1 (100%)
Streptococcus Viridans Group		1/1 (100%)
Enterococcus Sp.	1/2 (50%)	
Enterococcus Faecalis	1/1 (100%)	1/3 (33%)
Gram-Positive Rods		1/1 (100%)
Gram-Negative Rods Fermentative Enterobacteriaceae	1/1 (100%)	
Escherichia Coli	156/181 (86.2%)	161/185 (87.0%)
Klebsiella Pneumoniae	9/9 (100%)	10/10 (100%)
Klebsiella Oxytoca		3/3 (100%)
Klebsiella Ozaenae	1/1 (100%)	1/1 (100%)
Proteus Mirabilis	2/2 (100%)	5/5 (100%)
Proteus Vulgaris	2/2 (100%)	2/2 (100%)
Enterobacter Cloacae	3/3 (100%)	1/2 (50%)
Serratia Sp.		1/1 (100%)
Serratia Marcescens		1/1 (100%)
Citrobacter Freundii	1/1 (100%)	
Morganella Morganii	1/1 (100%)	1/2 (50%)
Pantoea Agglomerans	4/4 (100%)	5/5 (100%)
Pseudomonas Aeruginosa		5/6 (83%)
Pseudomonas Fluorescens	1/1 (100%)	
Acinetobacter Sp.		1/1 (100%)

*Empty cells indicate that there were no organisms of that type in that treatment group.

Because of the disproportionate exclusion (from the microbiologically valid analysis group) of subjects with a *Klebsiella Pneumoniae* or *Pseudomonas Aeruginosa* as their baseline pathogen, (see *Section 3.0* for details), the eradication results at TOC for these pathogens in the valid for safety analysis group are provided. Twelve of the 16 Cipro subjects with *Klebsiella Pneumoniae* at baseline (75%) had their baseline pathogen eradicated at TOC. All ten of the comparator subjects with *Klebsiella Pneumoniae* at baseline (100%) had their baseline pathogen eradicated at TOC. Of the eight Cipro subjects with *Pseudomonas Aeruginosa* at baseline, three (38%) had this organism eradicated at TOC. Finally, of the eight comparator subjects with *Pseudomonas Aeruginosa* at baseline, five (63%) had this organism eradicated.

5. SUMMARY AND CONCLUSIONS

The following statistical issues and their impact have been described in the context of the review. Please refer to the specified section for details.

Study #1

- Exclusions of patients from the clinically valid analysis group were made for numerous reasons. For comparison, a mITT analysis was defined and conducted for the clinical success endpoint at TOC (ref: *Sections 3.0, 3.1*)
- Protocol specified that those with missing or unavailable bacteriologic information at TOC were to be excluded from the microbiologically valid analysis group. For comparison, a mITT analysis was defined and conducted for bacteriologic eradication at TOC (ref: *Section 3.0, 3.1*)
- Increase in sample size (ref: *Section 3.0*)
- Treatment-by-strata interaction for primary safety endpoint, the incidence of arthropathy, at Day +42 (ref: *Section 3.2*)

Study #3

- Significant differences between treatment groups in terms of baseline covariates were identified. Comparisons of Cipro patients and control patients are not valid. (ref: *Section 3.2*)

5.1 Statistical Issues and Collective Evidence

This review has considered the results of one controlled clinical trial (Study #1) and one observational study (Study #3). This reviewer is in agreement with the sponsor that the baseline differences between treatment groups in Study #3 preclude legitimate by-treatment group comparisons, therefore this section will focus on the results of Study #1 only.

In Study #1, the arthropathy rates by day +42 were 9.3% (31/335) and 6.0% (21/349) for the Cipro and control groups, respectively. The 95% confidence interval for the difference between treatment groups was (-0.8%, 7.2%), indicating that Cipro is not noninferior to the comparator in terms of arthropathy at this time point (since the pre-specified noninferiority margin of 6% is not excluded from the interval). In fact, the interval suggests that Cipro is associated with a higher arthropathy rate than the comparator since the interval is primarily above zero. Similar conclusions are indicated for the one-year time point. The arthropathy rates by one-year post-treatment were 13.7% (45/335) and 9.5% (33/349) for the Cipro and control groups, respectively. The 95% confidence interval for the difference between treatment groups was (-0.6%, 9.1%), indicating that Cipro is not noninferior to the comparator in terms of arthropathy at the one-year follow-up time point. In fact, once again, the interval suggests that Cipro is associated with a higher arthropathy rate than the comparator since the interval is primarily above zero.

The efficacy (including clinical success and bacteriologic eradication endpoints) of Cipro was evaluated as secondary objectives of Study #1. Regardless of the analysis group utilized, the results consistently indicated that Cipro was noninferior to the comparator in terms of clinical success and bacteriologic eradication at both the test-of-cure and follow-up time points.

5.2 Conclusions and Recommendations

It is the opinion of this reviewer that Cipro has not been shown to be noninferior to the comparator in terms of the arthropathy endpoint at day +42 or one-year post-treatment. In fact, the data suggests that the risk of arthropathy (as defined in the protocol) is higher with the use of Cipro than with the control. It is also the opinion of this reviewer that noninferiority of the efficacy of Cipro (in terms of clinical success and bacteriologic eradication) relative to that of the comparator has been demonstrated.

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