CLINICAL REVIEW FOR
New Drug Applications
19-537/S-049, 20-780/S-013, 19-847/S-027, and 19-857/S-031

Drug: Cipro® tablet (ciprofloxacin hydrochloride) and oral suspension

Applicant's Proposed Indication: None proposed. Safety and efficacy information from two clinical trials in pediatric patients to be added to the Pediatric Use subsection of the Precautions section of the label.

Indication Granted:

Pediatric patients (1 to 17 years of age):
Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli*.
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS, Pediatric Use, ADVERSE REACTIONS,** and **CLINICAL STUDIES**.) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY**.)

General Information:

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Submission/Review Dates:

Dates of Submission:	September 23, 2003, September 24, 2003, December 18, 2003, January 26, 2004, January 30, 2004, February 12, 2004, March 12, 2004, March 17, 2004, March 18, 2004, and March 24, 2004
Date Review Begun:	November 12, 2003
Date Review Completed:	March 25, 2004

Drug Identification:

Generic Name:	ciprofloxacin hydrochloride
Pharmacologic Category:	fluoroquinolone antibiotic
Trade Name:	Cipro®
Molecular Formula:	$C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$
Molecular Weight:	385.8 daltons
Dosage Form:	Tablets and Suspension
Route of Administration:	Oral

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ALT	alanine transaminase (or SGPT)
AST	aspartate transaminase (or SGOT)
AUP	Acute Uncomplicated Pyleonephritis
CFR	Case report form
CFU	colony forming units
CRO	contract research organization
cUTI	complicated urinary tract infection
ECG	electrocardiogram
EEG	electrencephalography
ICD-9	International Classification of Diseases, 9th revision
IPSC	Independent Pediatric Safety Committee
IRB	Institutional Review Board
IV	intravenous
MSU	mid-stream urine
PK	pharmacokinetics
PO	oral
R	right
RDE	remote data entry
ROM	range of motion
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase (or AST)
SGPT	serum glutamic pyruvic transaminase (or ALT)
SOP	standard operating procedure
TMP/SMX	trimethoprim/sulfamethoxazole
TPD	Therapeutic Products Directorate (Canada)
TPP	Therapeutic Products Programme (Canada)
US	United States
UTI	urinary tract infection
VACTERL	acronym for vertebral, anal, cardiac, tracheal, esophageal, renal, and limb pattern of congenital anomalies.
VUR	vesicoureteral reflux

1. EXECUTIVE SUMMARY

1.1 Recommendations on Approvability

Until now, no member of the quinolone class of antibacterial drugs has been approved for use in pediatric patients, with the single exception of the use of ciprofloxacin for inhalational anthrax (post-exposure). Currently, ciprofloxacin, like other quinolone drug products, carries a WARNING, printed in all capital letters, in the labeling that states: *"Safety and effectiveness of ciprofloxacin in pediatric patients and adolescents (less than 18 years of age), except for use in inhalational anthrax (post-exposure)…have not been established."* This statement is included because the quinolones cause arthropathy in most animal species tested. The ciprofloxacin labeling further states: *"The oral administration of ciprofloxacin caused lameness in immature dogs. Histological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage."*

As a result of these preclinical findings, the Agency has brought the issue of quinolone drug development in pediatrics to the Anti-Infective Advisory Committee on three occasions (November 1989, July 1993, and November 1997). Over the years the Committee recommended that pediatric studies should be undertaken, but only in serious infections where the products potentially offer a significant treatment advantage based on efficacy and/or safety.

The current supplemental applications (dated September 23, 2003) were submitted in response to a Written Request Letter originally issued May 12, 1999, amended October 1, 2001, and a final amendment was dated September 23, 2003. The applications consist of two clinical trials in pediatric patients, a population pharmacokinetic analysis, and an animal toxicology study. The applicant proposed updating the Precautions, Pediatric Use and Animal Pharmacology sections of the labeling to reflect the results of these studies. The two clinical trials (Study 100169 and 100201) will be discussed in this review. The primary of objective of both studies was to assess musculoskeletal adverse events in pediatrics for up to 1 year post drug exposure. Musculoskeletal adverse events included those events effecting joints, cartilage, tendons, and ligaments.

Study 100169 is a prospective, randomized, double-blind, active-controlled, parallel group, multinational, multi-center pediatric clinical trial which enrolled patients from 1 year to 17 years of age with complicated UTI (cUTI) or pyelonephritis. Complicated urinary tract infections and pyelonephritis are considered serious infections in children due to the risk of recurrence (in the absence of effective treatment), which can lead to permanent renal damage.

Musculoskeletal adverse events in Study 100169 were reported more frequently in the ciprofloxacin-treated patients versus comparator-treated patients at six weeks and at one year of follow-up. At both evaluations, the 95% confidence interval of the treatment difference indicated that the arthropathy rate in the ciprofloxacin group was greater than that of the comparator group. The majority of musculoskeletal adverse events were mild or moderate and resolved by one year of follow-up. The events included arthralgia, abnormal gait, abnormal joint exam, joint disorder (i.e., sprains), leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain and decreased range of motion in a joint. The affected joints included: knee, elbow, ankle, hip,

wrist, and shoulder. Most of those events occurred by six weeks and the average duration of signs and symptoms was 30 days following the end of treatment. Resolution of signs and symptoms was determined clinically. Radiological evaluations were not routinely used to confirm resolution of the events. The events occurred more frequently in the ciprofloxacin treated patients than the control patients, regardless of whether they received IV or oral therapy. Ciprofloxacin patients were more likely to report more than one event and on more than one occasion compared to the control patients. These events occurred in all age groups and the rates were consistently higher in the ciprofloxacin group compared to the control group.

Study 100201 is an ongoing prospective, five-year, non-randomized, open label, multi-center pediatric observational study in patients 2 months through 16 years of age with various infections. Results from the first year of follow-up were reported in the current supplemental applications. Arthropathy was also reported in ciprofloxacin-treated patients and was seen in all age groups. Although this study was not randomized and the patient population was not the same as in Study 100169, the incidence of arthropathy in the ciprofloxacin-treated patients is supportive of the results seen in Study 100169. Of note, an adolescent female in the ciprofloxacin treatment group discontinued study drug after 7 days for wrist pain that developed after 3 days of treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.

Ciprofloxacin was shown to have similar efficacy to the comparator antimicrobial drugs for the treatment of complicated urinary tract infection and pyelonephritis in Study 100169. The clinical success and bacterial eradication rates at the test of cure visit (5 to 9 days following the end of therapy) indicated that ciprofloxacin was non-inferior to the comparators in the treatment of pediatric patients with cUTI or pyelonephritis.

In summary, ciprofloxacin was shown to be effective for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli* in pediatric patients. However, an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues was reported in both the randomized and observational studies. Therefore, ciprofloxacin should not be used as a drug of first choice for the treatment of complicated urinary tract infections and pyelonephritis in pediatrics and should be reserved for use when other therapy is not appropriate or effective.

A risk management program is being put in place that will track promotion, usage, and adverse reactions of ciprofloxacin in the pediatric population for a period of at least three years.

The wording in the **INDICATIONS AND USAGE** section of the label will read:

Pediatric patients (1 to 17 years of age):
Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli.*
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared

to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS, Pediatric Use, ADVERSE REACTIONS,** and **CLINICAL TRIALS**.) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY**.)

1.2 Recommendations on Post-Marketing Actions

1.2.1 Risk Management Activity

The applicant proposed a risk management plan, which includes the components listed as "Other Phase 4 Commitments."

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

- The applicant will voluntarily provide to DSPIDP any promotional materials (4 weeks in advance) and press releases (1 week in advance) prior to distribution relating to the use of ciprofloxacin for complicated urinary tract infections and/or pyelonephritis in the pediatric population for three years following the approval of this supplemental application.

- The applicant will provide biannual updates on Ciprofloxacin® usage patterns in the pediatric population, with the submission dates being no later than October 31, 2004, April 30, 2005, October 31, 2005, April 30, 2006, October 31, 2006, and April 30, 2007 respectively.

- The applicant will provide expedited (15 day) reporting to DSPIDP and the Office of Drug Safety of all spontaneous adverse events (including listed events considered serious) in patients 17 years of age or younger until April 30, 2007.

- The applicant will complete the 5 year observational study (Protocol 100201) for patients receiving ciprofloxacin treatment and will submit the final research report by March 2008. Patients in the control arm (i.e., non quinolone comparator) can be discontinued from the follow-up portion of the study. The requirement for 5 year safety data in patients who do not experience any musculoskeletal adverse events may be reassessed as additional information regarding pediatric quinolone safety becomes available.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of the Clinical Program

Two clinical trials were performed in pediatric patients to evaluate the long-term musculoskeletal and neurologic safety of ciprofloxacin through one year of follow-up.

Study 100169
This was a prospective, randomized, double-blind, active-controlled, parallel group, multinational, multicenter pediatric clinical protocol. Patients aged greater than or equal to1 year and less than 17 years, diagnosed with complicated UTI (cUTI) or pyelonephritis were enrolled. 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 ciprofloxacin or control antibiotics according to a 1:1 randomization. In the first stratum (PO therapy), ciprofloxacin oral suspension was compared to control regimens (cefixime and TMP/SMX oral suspension [in Canada only]) and in the second stratum, IV ciprofloxacin and IV ciprofloxacin followed by ciprofloxacin oral suspension were compared to control regimens (IV ceftazidime, sequential IV ceftazidime→ followed by PO cefixime and sequential IV ceftazidime→PO TMP/SMX [in Canada only]).

The primary objective of this study was to determine the musculoskeletal safety (i.e., joint, articular cartilage, tendon and ligament) of IV, sequential (IV→ PO), and oral ciprofloxacin in comparison to IV ceftazidime, sequential (IV ceftazidime → PO cefixime or IV ceftazidime → PO TMP/SMX [in Canada only]), and purely PO cefixime or PO TMP/SMX (in Canada only) therapy among pediatric patients with cUTI or pyelonephritis. A secondary objective of this trial was to assess the neurological safety of these dosage regimens among patients with cUTI or pyelonephritis.

Clinical and microbiological response data from pediatric patients with cUTI or pyelonephritis receiving ciprofloxacin or control regimens, evaluated at the Test-of-Cure visit (Day +5 to +9) and also at the first follow-up evaluation (Day +28 to +42), were additional secondary objectives of this trial.

The daily dose of ciprofloxacin administered as therapy in this trial was adjusted according to the child's body weight and conformed to a detailed set of dosing guidelines. The total duration of therapy, could vary according to the investigator's discretion but ranged between 10 and 21 days, inclusive. Investigators were to consider the patient's age, age-adjusted renal function, and extent and severity of documented structural/anatomic or functional genitourinary tract abnormalities when projecting an intended duration of study drug therapy required to achieve clinical cure and bacteriological eradication.

A total of 689 patients ranging in age from greater than or equal to 1 year to < 17 years were enrolled in this study. Of these, 684 (99.3%; 335 ciprofloxacin, 349 comparator) received at least 1 dose of study drug and were valid for the analysis of safety. A total of 442 patients (64%; 211 ciprofloxacin, 231 comparator) were considered valid for per-protocol efficacy analyses. Of these, 256 (58%) had pyelonephritis and 186 (42%) had complicated UTI.

Study 100201 - Interim Analysis
This was a prospective, non-randomized, open label, multicenter North American pediatric clinical observational study to assess long-term musculoskeletal and neurological system health in infants and younger children (i.e., ≤6 years of age at study entry) for up to 5 years post-exposure to ciprofloxacin or a non-

quinolone antibiotic for prepubescent and pubescent children and for 1 year post-exposure to ciprofloxacin or non-quinolone antibiotic for post-pubescent children.

Patients in the age range of 2 months through 16 years of age were eligible for enrollment in the study. Low-risk febrile patients with neutropenia during cancer chemotherapy could be enrolled provided their neutropenia was expected to resolve (≥500 cells per mm^3) within 10 days after the onset of fever.

The decision to treat with ciprofloxacin or a non-quinolone antibiotic was made prior to enrollment in the study and was based on the particular infection, medical history and the clinical evaluation by the prescribing physician. After the investigator determined that a particular infant or child with an eligible infection was suitable for treatment with ciprofloxacin or a non-quinolone antibiotic, the selection of study unit dose, total daily dose, duration of therapy, route of administration, and formulation (i.e., IV, oral suspension, or oral tablets) was left to the discretion of the investigator. In general, ciprofloxacin or non-quinolone antibiotic therapy was to be administered for a minimum duration of 7 days and a maximum duration of 21 days.

Interim safety results from the first year post-treatment are provided for 487 ciprofloxacin-treated patients and 507 non-quinolone control patients valid for safety analysis.

1.3.2 Efficacy

Study 100169
The Per Protocol population was defined as patients with a diagnosis of cUTI or pyelonephritis, a causative organism(s) at baseline, no inclusion or exclusion criteria or other protocol violation, and no premature discontinuation or loss to follow-up (among other criteria).

The clinical success and bacteriologic eradication rates in the Per Protocol population at 5 to 9 days following the end of therapy (i.e., the Test of Cure visit) were similar between ciprofloxacin and the comparator group as shown in Table 4. The treatment group comparisons for clinical success and bacteriologic eradication were also consistent between Stratum I and II (the oral and IV therapy groups, respectively) for ciprofloxacin and the comparator.

TABLE 4
Clinical Success and Bacteriologic Eradication at Test of Cure (5 to 9 Days Post-Therapy)

	Ciprofloxacin	Comparator
Randomized Patients	337	352
Per Protocol Patients	211 (63%)	231 (66%)
Clinical Response at 5 to 9 Days Post-Treatment*	95.7% (202/211)	92.6% (214/231)
	95% CI [-1.3%, 7.3%]**	
Stratum I (oral)	96.0% (188/196)	93.4% (197/211)
	97.5% CI [-2.8%, 8.0%]***	
Stratum II (IV)	93.3% (14/15)	85.0% (17/20)
	97.5% CI [-21.7%, 34.5%]***	
Bacteriologic Eradication by Patient at 5 to 9 Days Post-Treatment*	84.4% (178/211)	78.3% (181/231)
	95% CI [-1.3%, 13.1%]**	
Stratum I (oral)	86.4% (165/191)	80.8% (168/208)
	97.5% CI [-2.8%, 14.0%]***	
Stratum II (IV)	86.7% (13/15)	81.3% (13/16)
	97.5% CI [-28.5%, 38.5%]***	
Bacteriologic Eradication of the Baseline Pathogen at 5 to 9 Days Post-Treatment		
Escherichia coli	156/178 (88%)	161/179 (90%)

* Patients with baseline pathogen(s) eradicated and no new infections or superinfections/total number of patients. There were 5.5% (6/211) ciprofloxacin and 9.5% (22/231) comparator patients with superinfections or new infections.
** Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by strata).
*** 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.

Clinical cure rates and bacteriological eradication rates were not substantially impacted by age, race, or sex of the patient.

Study 100201
This was a safety study and therefore did not have any clinical or microbiological efficacy criteria.

1.3.3 Safety

Study 100169
The primary endpoint of the study was the evaluation of arthropathy at six weeks of follow-up (i.e., occurring by Day +42). An Independent Pediatric Safety Committee (IPSC) reviewed patient records of all cases of musculoskeletal system events, abnormal gait or joint appearance (baseline and treatment emergent), and selected other events. All cases were reviewed in a blinded fashion, and were judged as either having no evidence of clinically diagnosed arthropathy, or as having at least possible evidence of arthropathy. Arthropathy was broadly defined as any condition affecting a joint or periarticular tissue that

may have been temporary or permanent. This definition included events such as bursitis, enthesitis (inflammation of the muscular or tendinous attachment to the bone) and tendonitis.

Arthropathy occurred more frequently in patients who received ciprofloxacin than the comparator and was defined as any condition affecting a joint or periarticular tissue that may have been temporary or permanent (including bursitis, inflammation of the muscular or tendinous attachment to the bone, and tendonitis). The affected joints included: knee, elbow, ankle, hip, wrist, and shoulder. Arthropathy, as shown in Table 1, was seen in 9.3% (31/335) of ciprofloxacin patients versus 6% (21/349) of comparator patients at 6 weeks. All musculoskeletal events occurring by 6 weeks resolved, usually within 30 days of end of treatment. The rates were 13.7% and 9.5%, respectively, at 1 year. Arthropathy occurred more frequently in patients treated with ciprofloxacin than control, regardless of whether they received IV or oral drug. Ciprofloxacin patients were more likely to report more than one event and on more than one occasion compared to control patients (37% [17/46] versus 24% [8/33]).

Of the 46 patients with arthropathy in the ciprofloxacin arm, radiological testing of the affected joint was reported for 9 patients. Eight patients had X-rays and two patients had an MRI (one patient had both an X-ray and MRI). X-ray results were negative in 6 patients and included: hip for abnormal gait (Patient 301213), lumbosacral area for lumbar pain (302026), hips and spinal cord for back pain and thoracic spine pain (307004), leg (i.e., ankle, knee, and feet) for growing pains (309014), ankle for swelling (307006), and knee (3 different X-rays at 3 different times) for pyogenic arthritis secondary to a nail puncture wound (306054). One patient had an X-ray of both knees (307015) for pain and swelling and the findings were “bilateral genu valgum”, which was a pre-existing condition for that patient. Another patient (16001) had an ankle X-ray for pain which showed “lateral soft tissue swelling, no radiological evidence of definite osseous abnormality.” This patient (16001) also had an MRI performed of the ankle, which was normal. One other patient (2015) had an MRI performed for ballotable fluid on the knee discovered on joint exam (no complaints of pain or history of trauma). MRI was performed the following day. The MRI was normal with a small amount of fluid present. Two days later the joint examination was normal.

Of the 33 comparator patients, one patient (37001) had an X-ray for ankle pain and the results were negative. Another patient (401047) had an X-ray of both knees performed for oligoarthralgia, which was also negative.

TABLE 1
Arthropathy Rate up to 1 Year of Follow-up in Patients Valid for Safety

	Ciprofloxacin (N=335)	Comparator (N=349)
Arthropathy rate at 6 weeks of follow-up	**31 (9.3%)**	**21 (6.0%)**
95% Confidence Interval*	(-0.8%, +7.2%)	
Cumulative Arthropathy rate at one year of follow-up	**46 (13.7%)**	**33 (9.5%)**
95% Confidence Interval*	(-0.6, +9.1%)	
Selected Musculoskeletal Adverse Events in Patients with Arthropathy at One Year of Follow-up**	**Ciprofloxacin N=46 patients*** **	**Comparator N=33 patients*** **
Arthralgia	35	20
Abnormal Joint and/or Gait Exam	11	8
Accidental Injury	6	1
Leg Pain	5	1
Back pain	4	0
Arthrosis	4	1
Bone Pain	3	0
Joint Disorder	2	0
Pain	2	2
Myalgia	1	4
Arm Pain	0	2
Movement Disorder	1	1

*The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the comparator group by more than +6.0%. At both evaluations, the 95% confidence interval indicated that it could not be concluded that ciprofloxacin had findings comparable to the comparator.
**events occurring in more than one patient
***a patient with arthropathy may have had more than one event

Arthropathy occurred in all age groups and the rates in the ciprofloxacin arm were consistently higher than in the control arm, as shown in Table 2. The majority of musculoskeletal adverse events (i.e., joints and/or surrounding tissues) were mild or moderate and resolved by the 1 year follow up.

TABLE 2
Rate of Arthropathy at 6 Weeks of Follow-Up in Patients Valid for Safety

Arthropathy	Ciprofloxacin	Comparator
All Patients	31/335 (9.3%)	21/349 (6.0%)
Age Group		
≥ 12 months < 24 months	1/36 (2.8%)	0/41
≥ 2 years < 6 years	5/124 (4.0%)	3/118 (2.5%)
≥ 6 years < 12 years	18/143 (12.6%)	12/153 (7.8%)
≥ 12 years to 17 years	7/32 (21.9%)	6/37 (16.2 %)

The arthropathy rates in patients treated with oral versus those treated with IV (IV alone or sequential IV to oral therapy) at six weeks were different. The arthropathy rates in the oral stratum were 9.1% (27/296) for ciprofloxacin and 6.9% (21/304) for the comparator groups. The arthropathy rates in the IV stratum were 10.3% (4/39) for ciprofloxacin and 0% (0/45) for the comparator groups.

The arthropathy rates were similar between males and females and consistent between treatment groups. The rates were 13.9% (38/273) and 10.6% (30/284) in females compared to 12.9% (8/62) and 4.6% (3/65) in males for ciprofloxacin and comparator, respectively.

Arthropathy rates in patients with cUTI were 12.2% (20/164) for ciprofloxacin versus 9.6% (16/166) for comparator, and in patients with pyelonephritis the rates were 6.4% (11/171) for ciprofloxacin versus 2.7% (5/183) for the comparator.

Arthropathy rates were lower than the overall study rates in Mexico (0% for both ciprofloxacin [0/56] and comparator [0/60], respectively) and Peru (2.3% [2/87] for ciprofloxacin versus 3.4% [3/88] for comparator). There was a bigger difference between treatment group arthropathy rates in the United States (21.0% [13/62] for ciprofloxacin versus 11.3% [8/71] for comparator) than in the overall rates. The arthropathy rate was higher than the overall rate in Caucasians (13.8% [18/130] for ciprofloxacin versus 9.7% [13/134] comparator) and lower than the overall rate in Hispanics (7.8% [8/102] for ciprofloxacin versus 2.8% [3/109] for comparator) and “other” race group (5.3% [5/95] ciprofloxacin versus 3.2% [3/93] comparator).

Neurological Events

The incidence of neurological events from initial dosing through 6 weeks up follow-up was 2.7% (9/335) in the ciprofloxacin group and 2.0% (7/349) in the comparator group. All events were reported in less than 1% of patients in either treatment group, as shown in Table 3.

TABLE 3
Neurological Adverse Events Occurring Through 6 Weeks of Follow-Up
Patients Valid for Safety

Neurological Adverse Events	Ciprofloxacin N=335	Comparator N=349
Any Event	9 (3%)	7 (2%)
Dizziness	3 (<1%)	1 (<1%)
Nervousness	3 (<1%)	1 (<1%)
Insomnia	2 (<1%)	0 (0%)
Somnolence	2 (<1%)	0 (0%)
Abnormal Dreams	0 (0%)	2 (<1%)
Convulsion	0 (0%)	2 (<1%)
Hypertonia	0 (0%)	1 (<1%)
Abnormal Gait	0 (0%)	1 (<1%)

The overall incidence of adverse events at six weeks was 41% (138/335) in the ciprofloxacin arm compared to 31% (109/349) in the control arm. The most frequently reported events were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of control patients. Serious adverse events were seen in 7.5% (25/335) of ciprofloxacin patients compared to 5.7% (20/349) of the control patients and discontinuation of drug due to adverse events was seen in 3% (10/335) of ciprofloxacin patients and 1.4% (5/349) of control patients.

Adverse events, other than those affecting the musculoskeletal or neurologic systems, that occurred in at least 1% of patients treated with ciprofloxacin by six weeks included: diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%, accidental injury 3.0%, rhinitis 3.0%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8%, and rash 1.8%.

Study 100201

Patients were treated for various infections, most commonly otitis media (29% [143/487]) and urinary tract infection (22% [105/487]). They had a variety of underlying diseases, including malignancies, and were receiving multiple concomitant medications.

As in Study 100169, the IPSC evaluated each case for any possible evidence of arthropathy. The incidence rate of arthropathy by six-weeks of follow-up (i.e., Day +42) and at the end of one year of follow-up, as assessed by the IPSC, was 8% (37/487) and 11% (56/487), respectively.

The incidence of arthropathy at 1-year of follow-up was 12.3% (33/269) in females and 10.5% (23/218) in males. As in Study 100169, the arthropathy rate was seen in all age groups.

Of note, an adolescent female in the ciprofloxacin treatment arm discontinued study drug after 7 days for wrist pain that developed after 3 days of treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.

The incidence of any investigator-reported musculoskeletal adverse event by the 1-year post-treatment follow-up in 487 ciprofloxacin-treated patients was 13% (64 patients). The only musculoskeletal event occurring in > 1% of patients was arthralgia (9.4%; 46 patients). Arthrosis was reported in 3 patients (0.6%) and myalgia in 2 patients (0.4%). Tendon disorder was reported in one patient (0.3%).

The incidence of any neurologic event by 6 weeks of follow-up in ciprofloxacin-treated patients was 7.2 % (28/487). Insomnia (3.5%) was the only event occurring in ≥ 1% of patients.

1.3.4 Dosing Regimen and Administration

The dosing recommendations for IV and oral ciprofloxacin administered to pediatric patients in Study 100169 were based upon the systemic exposure to ciprofloxacin obtained in: (1) adults using the recommended treatment doses for severe/complicated UTI; (2) non-cystic fibrosis pediatric patients treated for a variety of infections (following administration of the oral formulation); and (3) pediatric patients with cystic fibrosis and lower respiratory tract infections (following administration of the IV formulation). The applicant assumed the relative bioavailability of oral ciprofloxacin to be 80% and concluded that an oral ciprofloxacin dose of 30 to 45 mg/kg/day (approximately 10 to 20 mg/kg every 12 hours) and an IV ciprofloxacin dose of 24 to 30 mg/kg/day (approximately 6 to 10 mg/kg every 8 hours) should be suitable to treat severe infections in pediatric patients.

Children with cUTI or pyelonephritis are acutely infected and represent a group where the risk versus benefit balance of pediatric fluoroquinolone administration may be favorable. Oral treatment with ciprofloxacin provides advantages over established oral antibiotic therapies such as trimethoprim/sulfamethoxazole (TMP/SMX) and amoxicillin with regard to both spectrum of activity and resistance patterns and may provide adequate therapeutic substitution for some IV antibiotic regimens as well. In this indication, ciprofloxacin may provide effective antibacterial treatment for some infants and children with cUTI and pyelonephritis without the complications and inconveniences associated with prolonged courses of IV therapies. Earlier hospital discharge or avoidance of hospital admission could become options for more patients, which in turn holds the potential to improve their quality of life.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

Generic Name:	ciprofloxacin hydrochloride
Pharmacologic Category:	fluoroquinolone antibiotic
Trade Name:	Cipro®
Molecular Formula:	$C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$
Molecular Weight:	385.8 daltons
Dosage Form:	Tablets and Suspension
Route of Administration:	Oral

2.2 State of Armamentarium for Indication(s)

Approved antimicrobials listed in the electronic Physicians Desk Reference (PDR) for the treatment of urinary tract infections (UTIs) in pediatric patients (less than 12 years old) are as follows: amoxicillin/clavulanate*, ceftazidime*, and trimethoprim/sulfamethoxazole.

* dosing in pediatrics is not specific to UTI (i.e., for severe infections), but UTI is listed as an indication for this drug.

Cefipime and cefixime are not listed in the current PDR, but were approved for urinary tract infections in pediatrics.

2.3 Availability of Proposed Product in the U.S.

Ciprofloxacin oral tablets and suspension have been approved in the US for various adult indications since 1987 and 1997, respectively; and for inhalational anthrax (post-exposure) in pediatrics since 2000.

2.4 Important Issues with Pharmacologically Related Products

An important safety concern regarding the use of fluoroquinolone antimicrobial agents in children is the potential for arthropathy and tendinopathy. Myalgia is less frequently reported, but also found in a few case reports in the published literature. These safety concerns and the subsequent restriction of the use of fluoroquinolones in pediatric patients emanated from findings of cartilage damage in the weight-bearing joints of juvenile experimental animals. To date, there is little evidence that fluoroquinolone-associated arthropathy as described in experimental animals correlates with the same phenomenon in humans.[1] Fluoroquinolone-associated arthropathy in children has been described in the literature as a separate clinical phenomenon, distinct from that observed in laboratory animals and without damage to cartilage. The arthropathy is usually benign and heals without sequelae.[2]

The available clinical information describing joint toxicity in humans comes largely from case reports, compassionate-use protocols, and worldwide clinical safety databases.[3-6] Data from a recently conducted prospective study showed an incidence of 3.8% for musculoskeletal events (arthralgias of large joints or myalgias).[7] A large proportion of the patients included in these studies and reports had cystic fibrosis, which may itself be associated with arthropathy.[8]

Myalgia is a less well-documented phenomenon associated with fluoroquinolone use, although a few case reports have been published.[9-11] Tendinopathy appears to be a more significant adverse event associated with fluoroquinolone therapy that can result in tendon rupture.[12] The incidence of this adverse event is difficult to estimate.[13] Fluoroquinolone-associated tendinopathy appears to be more common in patients with tendons under high stress, and may pose a risk to those who participate in sports or exercise.[13,14] Other risk factors also have been identified, including age, concomitant steroid therapy, and renal disease.[15]

Fluoroquinolones can cause convulsions in adults with a history of seizures or as a result of drug interactions with theophylline or NSAIDS.[16] The incidence of neurological side effects such as seizures, hallucinations, tremor, restlessness, dizziness, and headache was reported as approximately 0.4% to 4.4% in patients treated with quinolones.[17] Severe central nervous system adverse events such as psychotic reactions, hallucinations, depressions and grand mal convulsions occur at an incidence of less than 0.5% in fluoroquinolone-treated patients, appearing within days of the start of therapy and often resolving with the discontinuation of the drug.[18]

2.5 Pre-Submission Regulatory Activity

The applicant was issued a Written Request Letter on May 12, 1999. The document was amended October 1, 2001 and September 23, 2003. Each amendment superceded the previous version. The primary objective of the studies included in the Written Request was to evaluate the long-term musculoskeletal and neurologic adverse events in pediatric patients (1 to 17 years) who received ciprofloxacin therapy.

The current application was submitted in response to the Written Request issued September 23, 2003. It consists of two clinical trials in pediatric patients, a population pharmacokinetic analysis, and an animal toxicology study.

As a result of the two clinical studies conducted to fulfill the Written Request, the applicant proposed labeling changes to add to and replace (in part) the Precautions, Pediatric Use labeling that was approved as part of NDA 19-537/S-027, originally submitted as an efficacy supplement, to add pulmonary exacerbations of cystic fibrosis, on April 3, 1998. Results from the animal toxicology study were proposed by the applicant to be added to the Animal Pharmacology section of the label that has been unchanged since the original NDA approval in 1987.

2.6 Other Relevant Background Information

When complicated urinary tract infection (cUTI) occurs in pediatrics, the term implies the occurrence of appropriate signs and symptoms consistent with acute infection (which may differ between infants versus older children and adolescents, or between boys versus girls) in the setting of a pre-existing anomaly, either structural/anatomic or functional, affecting the lower urinary tract.

Children with varying types and degrees of voiding dysfunction may be predisposed to recurrent UTIs. Underlying conditions may include a small-capacity, unstable bladder characterized by frequency, urgency, daytime enuresis, and posturing to

infrequent voiding with a large capacity bladder that empties poorly. Both obstruction and vesicoureteral reflux (VUR), especially high-grade reflux, result in an increase in the residual volume of urine in the bladder or dilated urinary tract, permitting multiplication of bacteria in the urine. Effective therapeutic intervention for children presenting with pyelonephritis is necessary because there may be a correlation between the degree of scarring and renal damage resulting from an infection when it is inappropriately treated. Although a number of patients are treated with long-term antibiotic prophylaxis, appropriate bowel management and a timed voiding schedule, recurrent infections often occur. Illnesses and factors outside of the urinary tract may also trigger an infection in a child predisposed to experiencing a UTI. In particular, illnesses such as nasal congestion, pharyngitis, anorexia or vomiting which alter fluid intake may make voiding less frequent and not forceful enough to clear away any bacteria that has made its way to the urethra and an infection may develop.

Complicated UTIs and pyelonephritis in children are most commonly due to *Escherichia coli*. Patients that experience more chronic infections or develop breakthrough infections while receiving antimicrobial prophylaxis often have isolates of enterococci, *Proteus* species, *Pseudomonas* species or *Candida* species.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Chemistry (and Product Microbiology, if applicable)

No chemistry or microbiology reviews were performed for this application.

3.2 Animal Pharmacology/Toxicology

This application can be approved from the pharmacology/toxicology perspective.

As a class, fluoroquinolones produce arthrotoxicity in juvenile dogs following 7 to 14 days of oral dosing. Juvenile dog studies with ciprofloxacin were in the original NDA 19-537 submission and provided clinical and pathological evidence of arthrotoxicity at an oral dose level of 90 mg/kg/day. Pathological evidence of arthrotoxicity was observed at an oral dose level of 30 mg/kg/day. DSPIDP concluded that juvenile dog arthrotoxicity needed additional evaluation as the sponsor conducted clinical trials in pediatric patients (b) (4)

The Written Request Letter for ciprofloxacin contained a study request to examine arthrotoxicity in juvenile dogs (males and females) and specifically to address the issues of post-dose recovery and the potential for latent arthrotoxicity as the musculoskeletal system matured. The study conducted by the sponsor examined multiple weight bearing joints during two weeks of dosing with ciprofloxacin at oral dose levels of 10, 30, and 90 mg/kg/day. Recovery and latent arthrotoxicity potential were examined in the recovery groups which were maintained for a period of five dose-free months; a period that covered complete musculoskeletal development.

No evidence (clinical and histopathological) of arthrotoxicity was observed in male and female juvenile dogs dosed for 14 days at the 10 mg/kg/day dose level at the 24-hour post-dosing terminal sacrifice and in male and female dogs held for the 5-month dose-free recovery period. The 30 mg/kg/day dose level did not result in clinical evidence of arthrotoxicity at any time during the study. Half of the juvenile dogs at the terminal sacrifice exhibited gross pathological and/or histopathological evidence of articular cartilage arthrotoxicity. The incidence and severity of the pathological and histopathological observations were reduced but still present in the 5-month post-dose recovery animals. Clinical evidence of arthrotoxicity was observed in 10 of 12 juvenile dogs at the 90 mg/kg/day dose level. These symptoms were resolved by Week 8 (six weeks into the post-dose recovery phase). All juvenile dogs exhibited articular cartilage lesions based upon gross pathology and histopathology at the terminal sacrifice (24 hours following the final dose). Similarly, all animals at the 5-month post-dose recovery sacrifice from the 2-week, 90 mg/kg/day dosing routine exhibited both gross pathological and histopathological evidence of articular cartilage lesions.

These results indicated that at 30 mg/kg/day, subclinical evidence of arthrotoxicity resulted from 14 days of dosing and that these effects, although diminished, were not completely resolved following a 5-month dose-free recovery period. Plasma area under the concentration vs. time curve (AUC) data for ciprofloxacin at the 30 mg/kg/day oral dose level to juvenile dogs (32 µg*hr/ml) was similar to the range of ciprofloxacin AUC values generated from pediatric patients at the proposed therapeutic dose level (approximately 20 to 40 µg*hr/ml). The average AUC values

resulted in an animal to human dose equivalent ratio of approximately 1.3 (32 µg*hr/ml / 24 µg*hr/ml). The ratio for the 90 mg/kg/day dose level was approximately 3.5 (85 µg*hr/ml / 24 µg*hr/ml) while the 10 mg/kg/day ratio was approximately 0.6 (14 µg*hr/ml / 24 µg*hr/ml).

The safety issue that appears to be more of a concern for pediatric patients than adult patients is subclinical or clinical arthrotoxicity. Ciprofloxacin plasma AUC levels in juvenile dogs at a dose level that resulted in arthrotoxicity were similar to plasma levels generated in pediatric patients at proposed therapeutic doses of ciprofloxacin.

See review by Steven Hundley, Ph.D., Pharmacology/Toxicology Reviewer, in HFD-590 (DSPIDP) filed with this NDA.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Sources of Clinical Data

Material Submitted	Electronic Data, including SAS transport files \\Cdsesub1\n19537\S_049\2003-09-23
Material Reviewed	Electronic Data, including SAS transport files \\Cdsesub1\n19537\S_049\2003-09-23

4.1 Tables of Clinical Studies

Protocol # Countries[a]	Objective(s) of the Study	Study Design and Patient Population	Test Product(s); Route of Administration	Number of Subjects Enrolled (Valid for Safety)	Duration of Treatment	Mean Age (Range) in Years	%M/F[b] %B/W/H/O	Study Status; Type of Report
100169 US, AR, CA, CR, DE, MX, PE, ZA	Safety; specifically musculoskeletal and neurological; clinical and microbiological responses were secondary outcomes	Prospective, randomized, double-blind, active-controlled, parallel group Patients 1 year to < 17 years of age with the indication of Complicated UTI or pyelonephritis	Ciprofloxacin IV, suspension Ceftazidime (IV), Cefixime (oral) or Trimethoprim/ Sulfamethoxazole (in Canada only)	337 (335) 352 (349)	10-21 days	6.3 (1-16) 6.2 (1-17)	19/81 1/39/30/30 19/81 2/38/31/29	Complete; Full Report
100201 (100225 is the interim analysis) US, CA	Long-term follow-up of safety; specifically the potential incidence of arthropathy	Prospective, non-randomized, open-label, observational Patients ≥ 2 months to < 17 years of age; various infectious conditions	Ciprofloxacin IV, tablets, suspension Non-quinolone antibiotic (as per investigator judgment)	510 (487) 519 (507)	7-21 days (as per investigator judgment)	6.2 (1-16) 5.3 (1-16)	45/55 7/60/28/5 52/48 5/65/25/5	Ongoing; Interim Analysis Report (100225)

[a] Countries: US = United States, CA = Canada, AR = Argentina, CR = Costa Rica, DE = Germany, MX = Mexico, PE = Peru, ZA = South Africa
[b] % M/F = % Male/% Female; % B/W/H/O = % Black/White/Hispanic/Other

4.2 Review Strategy

The two clinical trials contained in this submission (Study 100169 and Study 100201, interim Report 100225) were reviewed separately. Study 100169 had safety and efficacy endpoints and Study 100201 had only a safety endpoint. The safety results for the two studies were not pooled into an Integrated Safety Summary due to the

differences in study design (randomized versus non-randomized) and the population studied (cUTI and pyelonephritis versus various infections).

Validation of the data for Study 100201 was performed by obtaining the patient Case Report Forms for 10% of all randomized patients. The patients were randomly selected (blinded to treatment) and independently reviewed. Study 100169 used electronic CRFs, which were not felt by the reviewer to require validation.

4.3 Data Quality and Integrity

Study 100169
DSI audit was performed on March 8, 2004. Form 483 not available at the time of this review.

Study 100201
DSI audit was performed February 17, 2004. Form 483 was issued March 18, 2004. During the FDA inspection of Site 25 (Dr. Corazon Oca; Irvine, California), the following was noted by the inspector on the form:

> Failure to report Adverse Events:
> Subject #33 developed right wrist pain three days after starting the study drug. An MRI of the right wrist performed (b) (6) to evaluate this complaint demonstrated an intrasubstance tear of the right ulnar fibrocartilage. The subject was seen for follow up on February 28, 2001, with this visit recorded as a Module 2 visit. However, the MRI findings were not reported in any case report forms for this subject. The case report forms listed only right and left wrist pain and left lower back pain.

Clinical Reviewer's Comment: The Division requested the applicant include a description of the patient with fibrocartilage tear in the Adverse Reactions section of the package insert.

The following is a narrative of the patient cited on Form 483:

Patient 250033 was a 13 year old female who was enrolled in the observational study on November 6, 2000 and prescribed ciprofloxacin for "sinus problems" (sinusitis and cervical adenitis). Patient history is significant for back pain. She was active in gymnastics in the summer of 2000, but quit because of the back pain. At that time an MRI showed swollen discs. She was also active in volleyball from September to November 2000.

The patient reported mild right wrist pain on the third day of taking ciprofloxacin (November 9, 2000). Study drug was discontinued due to the adverse event on November 13, 2000, after 7 days of treatment. The wrist pain improved, but did not completely resolve. An MRI performed (b) (6) showed an intrasubstance tear of the triangular fibrocartilage in the right wrist ((b) (6) following treatment with ciprofloxacin). The patient was referred for physical therapy and prescribed anti-inflammatory medication (prescribed Relafen®, but subsequent note says that she only took acetaminophen) and braces (both wrists) by an orthopedic surgeon. Patient was lost to follow-up for about 2 months. She did not respond to two telephone messages asking her to come back for a follow-up visit. On February 28, 2001 the patient was seen by a

rheumatologist and had complaints of pain in the left wrist and left lower back. No pain in the right wrist. The rheumatologist diagnosed the patient with "probable tenosynovitis versus overuse syndrome secondary to gymnastics" and "no evidence of inflammatory arthritis." The patient was advised to take NSAIDs (ibuprofen) as needed. On (b) (6) *the patient returned to the clinic. She complained of a pain in her tail bone. X-ray showed inflamed tissue near the spinal cord. The patient was told to discontinue (or take time off) from gymnastics. No mention of wrist pain at this visit.*

4.4 Compliance with Good Clinical Practices

(b) (4) monitored both Study 100169 and 100201 in accordance with GCP guidelines and Standard Operating Procedures (SOP) for Bayer (b) (4). Monitoring visits were performed to ensure compliance with the protocol, to review source documents and case report forms (CRFs), and to assess drug accountability.

4.5 Financial Disclosures

The applicant obtained certification from each investigator and sub-investigator who enrolled patients in Study 100169. No investigator had any disclosable information to reveal, except for 3 investigators for whom the applicant did not obtain financial disclosure. The reasons for not obtaining disclosure prior to the initial of the study were unknown. (b) (6)
Of the sub-investigators listed on the FDA Form 1572, no information was obtained from 74. Reasons why financial disclosures were not obtained included: did not meet the FDA's definition of an investigator or sub-investigator (69), not obtained prior to initiation of study; reasons unknown (4), and terminated employment at facility, no forwarding address (1).

Clinical Reviewer's Comment: The reviewer feels that the any potential bias arising in this study as a result of not obtaining financial disclosure from a minority of investigators and/or sub-investigators does not affect the overall integrity of the study.

Financial disclosure was not required for Study 100201 since it was a large safety study (i.e., enrolled over 1000 patients).

5. CLINICAL PHAMACOLOGY

5.1 Pharmacokinetics

Data from a total of 6 studies were used to conduct a population pharmacokinetic (POPPK) analysis. These 6 studies included Study 100169 along with 5 other studies performed in patients with varied disease diagnoses. Patients with a variety of infections were included in the studies, including urinary tract infection, lower respiratory tract infection (in patients with cystic fibrosis), skin and soft tissue infection, severe sepsis, and acute invasive diarrhea. The POPPK was conducted with the following objectives:

- To estimate typical population pharmacokinetic parameters for ciprofloxacin in pediatric patients.
- To identify covariate, demographic and clinical factors that are significant predictors of variability in ciprofloxacin pharmacokinetic parameters.
- To provide a dosing recommendation for pediatric patients

Plasma ciprofloxacin concentration-time data were available in 357 pediatric patients. The age of these patients ranged from 0.27 to 16.9 years. The body weight of these patients ranged from 4.2 to 73.5 kg. One hundred and five patients were male and 252 patients were female. Twenty-eight out of 357 patients had a history of cystic fibrosis and 207 out of 357 patients were being treated for complicated urinary tract infection/pyelonephritis. Population pharmacokinetic analyses were performed with the NONMEM software using the First-Order Conditional Estimation (FOCE) method.

The pharmacokinetics of ciprofloxacin was described by a two-compartment model with first order absorption and absorption lag time. The POPPK analysis identified cystic fibrosis, body weight and creatinine clearance as the significant covariates. In addition, the effect of cystic fibrosis on the absorption rate constant was also found to be a significant covariate.

The following dosing recommendation for ciprofloxacin in pediatric patients for use in complicated urinary tract infections and pyelonephritis, as used in Study 100169, is proposed:

(a) oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day) or (b) intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) OR intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) followed by oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day).

See complete review by Dakshina Chilukuri, PhD, Clinical Pharmacology/Biopharmaceutics Reviewer, in HFD-590 (DSPIDP) filed with this NDA (19-537).

6. INTEGRATED REVIEW OF EFFICACY

6.1 Efficacy Findings

Study 100169

Of the 689 patients randomized, 442 patients (211 in the ciprofloxacin group and 231 in the comparator group) were considered valid for efficacy. Overall, 58% (256/442) had pyelonephritis (56% [119/211] in the ciprofloxacin arm and 59% [137/231] in the comparator arm) 42% (186/442) had cUTI (44% [92/211] in the ciprofloxacin arm and 41% [94/231] in the comparator arm). *Escherichia coli* was the most frequently isolated pre-therapy infection-causing organism. Patients less than or equal to 5 years comprised 51% (108/211) of patients in the ciprofloxacin group and 43% (99/231) of patients in the comparator group. No substantial differences in demographics or baseline disease characteristics were noted between the treatment groups.

The mean (± standard deviation) total treatment duration (comprised of oral and IV duration) in the valid for efficacy population was 11.9 ± 2.6 days (range 3 to 22 days) in the ciprofloxacin group and 11.8 ± 2.5 days (range 5 to 22 days) in the comparator group.

The treatment group comparisons for clinical cure at the TOC visit (5 to 9 days following the end of therapy) were consistent between Stratum I and II (the oral and IV therapy groups, respectively) for ciprofloxacin and the comparator. The p-value from the Breslow-Day test for treatment by disease stratum/treatment type interaction was 0.761, indicating that the treatment group differences across treatment types were not significantly inconsistent.

The clinical success and bacteriologic eradication rates in the Per Protocol population at 5 to 9 days following the end of therapy (i.e., the Test of Cure visit) were similar between ciprofloxacin and the comparator group as shown in Table 4. The treatment group comparisons for clinical success and bacteriologic eradication were also consistent between Stratum I and II (the oral and IV therapy groups, respectively) for ciprofloxacin and the comparator.

TABLE 4
Clinical Success and Bacteriologic Eradication at Test of Cure (5 to 9 Days Post-Therapy)

	Ciprofloxacin	Comparator
Randomized Patients	337	352
Per Protocol Patients	211 (63%)	231 (66%)
Clinical Response at 5 to 9 Days Post-Treatment*	95.7% (202/211)	92.6% (214/231)
95% CI [-1.3%, 7.3%]**		
Stratum I (oral)	96.0% (188/196)	93.4% (197/211)
	97.5% CI [-2.8%, 8.0%]***	
Stratum II (IV)	93.3% (14/15)	85.0% (17/20)
	97.5% CI [-21.7%, 34.5%]***	
Bacteriologic Eradication by Patient at 5 to 9 Days Post-Treatment*	84.4% (178/211)	78.3% (181/231)
95% CI [-1.3%, 13.1%]**		
Stratum I (oral)	86.4% (165/191)	80.8% (168/208)
	97.5% CI [-2.8%, 14.0%]***	
Stratum II (IV)	86.7% (13/15)	81.3% (13/16)
	97.5% CI [-28.5%, 38.5%]***	
Bacteriologic Eradication of the Baseline Pathogen at 5 to 9 Days Post-Treatment		
Escherichia coli	156/178 (88%)	161/179 (90%)

* Patients with baseline pathogen(s) eradicated and no new infections or superinfections/total number of patients. There were 5.5% (6/211) ciprofloxacin and 9.5% (22/231) comparator patients with superinfections or new infections.
** Weighted 95% confidence intervals for the differences in proportions were calculated using Mantel-Haenszel weights (weighting by strata).
*** 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 95% confidence interval for the treatment difference in clinical cure (-1.3%, 7.3%) and bacteriologic eradication (-1.3%, 13.1%) indicated that ciprofloxacin in the treatment of pediatric patients with cUTI or pyelonephritis, is non-inferior to the comparator.

Clinical cure rates and bacteriological eradication rates were not substantially impacted by age, race, or sex.

Study 100201
This was a safety study and therefore did not have any clinical or microbiological efficacy criteria.

6.2 Efficacy Conclusions

Both the clinical success and bacteriologic eradication rates at the TOC visit in Study 100169 in patients valid for efficacy indicated that ciprofloxacin is non-inferior to the comparator in the treatment of pediatric patients with cUTI or pyelonephritis.

Clinical success rates and bacteriological eradication rates were not substantially impacted by age, race, or sex of the patient.

Study 100201 did not have any clinical or microbiological efficacy criteria.

7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Study 100169
One ciprofloxacin patient (306-056) died on Day +14. The cause of death was infanticide. One comparator patient (204-016) died on Day +661. He died of complications of retroviral (HIV) disease. In both cases the cause of death was judged by the investigator to be unrelated to study drug.

Study 100201
One patient death was reported during the study. Patient 490055 died 17 days after receiving the last dose of ciprofloxacin. The patient was a 5-month-old male who had multiple congenital anomalies and had been hospitalized since birth. He developed a right atrium thrombus and died of cardiac arrest. The events were not considered related to study drug by the investigator and the reviewer is in agreement.

7.1.2 Other Serious Adverse Events

Study 100169
All serious adverse events reported in the ciprofloxacin group were judged by the investigators to be unlikely or not related to study drug. One patient (301100) had a musculoskeletal serious adverse event (myopathy; Duchenne's disease). The most common adverse events leading to premature discontinuation of ciprofloxacin therapy were vomiting (3 patients), nausea (2 patients), and moniliasis (2 patients). No patient discontinued due to a musculoskeletal event.

Study 100201
In the ciprofloxacin group, 22 patients (5%) had a serious adverse event. Two ciprofloxacin patients had serious adverse events considered at least possibly related to study drug. Patient 270024 had acute gastroenteritis and *Clostridium difficile* colitis considered possibly related to study drug. Patient 500011 had *Clostridium difficile* colitis considered probably related to study drug. All other serious adverse events reported in the ciprofloxacin group were judged by the investigators to be unlikely or not related to study drug. Two ciprofloxacin patients had musculoskeletal serious adverse events. Patient 310019 had severe osteomyelitis, which resolved and was considered unlikely related to study drug. Patient 760005 had severe hip pain, which resolved and was not considered related to study drug. In the control arm, there were 5 patients (2 patients with acute asthma exacerbations and one patient each with abscess, vertigo and pleural effusion) with serious adverse events.

7.1.3 Dropouts and Other Significant Adverse Events

Study 100169
In the ciprofloxacin group, 12/335 (3.6%) patients experienced adverse events with an action taken of study drug permanently discontinued, and 25/335 (7.5%)

patients experienced adverse events that fulfilled the definition of serious. The incidence of premature discontinuation due to an adverse event and serious adverse events was similar in the comparator group (6 [1.7%] and 20 [5.7%], respectively).

Study 100201
In the ciprofloxacin group, 14 patients (2.9%) had an adverse event with the action of study drug permanently discontinued. The most common adverse events leading to discontinuation of study drug were arthralgia (4 patients), vomiting (2 patients), and rash or urticaria (2 patients). No other events causing discontinuation of treatment occurred in more than 1 patient. Adverse events caused discontinuation of study drug in 3 control patients. One patient discontinued therapy due to vomiting, one due to rash, and one due to abdominal pain.

7.1.4 Musculoskeletal and Neurologic System Adverse Events

Study 100169
This protocol was specifically designed to evaluate musculoskeletal and neurological events during the treatment phase and up to 1-year post-treatment follow-up. The incidence of musculoskeletal adverse events any time up to 1 year was 11% (36/335) in the ciprofloxacin group and 7% (25/349) in the comparator group. Arthralgia was the most frequently reported musculoskeletal event in either group and was reported in 7% (25/330) of the ciprofloxacin patients and 5% (16/349) of the comparator patients. Arthrosis occurred in 1% (4/335) of ciprofloxacin and 0.3% (1/349) of the comparator patients. Myalgia occurred in 0.9% (3/335) of the ciprofloxacin patients and in 2% (8/349) of the comparator patients. Tendon disorder was reported in only 1 (0.3%) of the comparator patients and was not observed in the ciprofloxacin group. All other musculoskeletal events occurred in <1% of either treatment group.

The majority of musculoskeletal adverse events at 1 year follow-up were mild or moderate. Only two ciprofloxacin patients had a severe musculoskeletal adverse event. One patient had severe knee pain (no relationship to study drug, per the investigator) and severe hip pain (unlikely related to study drug, per the investigator). Another patient had myopathy diagnosed as Duchenne's disease (no relationship to study drug, per the investigator). One comparator patient had severe myalgia (fibromyalgia; not considered related to study drug, as per the investigator).

The majority of musculoskeletal adverse events resolved by the end of the study. One ciprofloxacin patient with arthralgia and 2 ciprofloxacin patients with myalgia were "improved" at the end of the study. These events were not considered by the investigators to be related to study drug. The outcome of two ciprofloxacin patients with arthralgia was unknown due to insufficient follow-up. The events were not considered by the investigators to be related to study drug. One comparator patient with arthralgia also had an unknown outcome due to insufficient follow-up. In the comparator group, 3 patients with arthralgia and one patient with myalgia had outcomes of "unchanged" at the end of the study.

To further evaluate any possible musculoskeletal events, the IPSC reviewed all cases with an adverse event that coded to the musculoskeletal system, all patients with an abnormal joint appearance (baseline and treatment-emergent), and all patients with an abnormal gait (baseline and treatment-emergent). Additionally, all cases of adverse events of leg pain, hand pain, arm pain, movement disorder, abnormal gait, peripheral edema, and selected accidental injury (related to joints or extremities) were reviewed. All cases were evaluated in a blinded fashion by the IPSC. Cases were evaluated as no evidence of arthropathy or at least possible evidence of arthropathy (arthropathy defined 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; this definition was seen as inclusive of such phenomena as bursitis, enthesitis and tendonitis).

Of the 141 patients reviewed by the IPSC, 4 were excluded from the statistical analyses, 57 were deemed not to have arthropathy, and an additional 2 patients were excluded from the applicant's statistical analyses because their events occurred pre-treatment (i.e., were pre-existing). The reviewer agrees with the removal of these patients. In total, 79 patients were deemed by the IPSC to have possible, probable, or definite arthropathy. There were 46 cases of arthropathy in the ciprofloxacin arm and 33 in the comparator arm by one year of follow-up.

The primary safety endpoint was the arthropathy rate, as assessed by the IPSC, by the follow-up visit (Day +28 to +42). The results of the IPSC assessment revealed arthropathy in 9.3% (31/335) of ciprofloxacin patients and 6.0% (21/349) of comparator patients by Day +42. The 95% confidence interval for the treatment difference in arthropathy (-0.8%, 7.2%) indicated inferiority of ciprofloxacin to comparator, using the protocol defined definition of non-inferiority of an upper bound of the 95% confidence interval of not more than 6%.

Arthropathy rates were slightly lower than the overall rates in Mexico (0% both treatment groups) and Peru (2% [2/87] ciprofloxacin versus 3% [3/88] comparator). The arthropathy rate was higher than the overall rate in Caucasians (14% [18/130] ciprofloxacin versus 10% [13/134] comparator) and lower than the overall rate in Hispanics (8% [8/102] ciprofloxacin versus 3% [3/109] comparator) and the group of patients whose race was not able to be coded (5% [5/95] ciprofloxacin versus 3% [3/93] comparator). The arthropathy rates were quite similar between males and females and consistent between treatment groups. Route of administration of study drug appeared to have little effect. The incidence of arthropathy did increase with increasing age, in both groups. The highest arthropathy rate was seen in the $\geq$12 year to <17 year age group, where the rate was 22% 7/32] for ciprofloxacin patients and 14% [5/35] for comparator patients. Arthropathy rates were higher than the overall rates in both treatment groups for patients with cUTI (12% [20/164] ciprofloxacin versus 10% [16/166] comparator), and lower than the overall rates in both treatment groups for patients with pyelonephritis (6% [11/171] ciprofloxacin versus 3% [5/183] comparator).

By the 1-year follow-up, 13.7% (46/335) of ciprofloxacin patients and 9.5% (33/349) of comparator patients had arthropathy at any point during the trial (treatment phase through the 1-year post-treatment follow-up phase).

No substantial differences between treatment groups were observed in mean change from baseline in the range of motion examination for any joint at any timepoint.

On joint examinations, more ciprofloxacin patients (28 patients; 8.4%) than comparator patients (15 patients; 4.3%) had an abnormal appearance. Most abnormalities were pain or tenderness, redness, swelling, or warmth. Of these, 10 ciprofloxacin and 7 comparator patients had these abnormalities at baseline. Most abnormalities were seen in the knees or ankles. All cases of joint appearance abnormalities, regardless of whether it was a baseline finding or treatment-emergent, were reviewed by the IPSC for possible arthropathy. Of the 26 patients with treatment-emergent joint appearance abnormalities, 25 were assessed by the IPSC as having arthropathy.

On gait assessments, more ciprofloxacin patients (35 patients; 10.4%) than comparator patients (18 patients; 5.2%) had an abnormal finding. Of these, 28 ciprofloxacin patients and 12 comparator patients had the abnormalities at baseline. All cases of gait abnormality, whether it was a baseline finding or treatment-emergent, were assessed by the IPSC for possible arthropathy. Of the 13 patients with treatment-emergent gait abnormalities, 6 were assessed by the IPSC as having arthropathy.

Most patients in both groups had some abnormal baseline findings on the Caregiver Questionnaire and had improvement or no change in these items on subsequent timepoints. For the questions on stiffness or swelling of the joints, both groups were comparable except for a slightly higher incidence in the comparator group for stiffness of the knees, stiffness of the shoulders, and swelling around the ankles at the 1 year timepoint.

Study 100201
The protocol was designed to specifically examine any musculoskeletal or neurological events. The overall rate of any musculoskeletal or CNS event through the 1-year follow-up period for ciprofloxacin was 21% (104/487) [95% CI: 18%, 25%] and 5% (25/507) [95% CI: 3%, 7%] for control. The incidence of any musculoskeletal adverse event alone by the 1-year post-treatment follow-up was 13% (64/487) [95% CI: 10%, 16%] and 3% (14/507) [95% CI: 1%, 5%] in the ciprofloxacin and control groups, respectively.

All patients who had a musculoskeletal adverse event, an abnormal joint appearance (at baseline or any time during the trial), or an abnormal gait assessment (at baseline or any time during the trial), were reviewed by an IPSC, without regards to treatment group. The IPSC evaluated each case for any possible evidence of arthropathy.

The incidence rate of arthropathy, as assessed by the IPSC, for ciprofloxacin was 11% (56/487) [95% CI: 9%, 15%] and 3% (13/507) [95% CI: 1.4%, 4.3%] for control at the end of one year of follow-up.

The incidence rates of arthropathy increased with increasing age. Among ciprofloxacin patients less than 6 years old, the incidence rate of arthropathy was

5% (12/235); for patients ages 6 to 11 years, the incidence rate was 15% (29/194); for patients ages 12 to 16, the incidence rate was 26% (15/58). Among control patients less than 6 years old, the incidence rate of arthropathy was 1.5% (4/265); for patients ages 6 to 11 years, the incidence rate was 4% (8/223); for patients ages 12 to 16, the incidence rate was 5% (1/19).

Of note, an adolescent female in the ciprofloxacin treatment group discontinued study drug after 7 days for wrist pain that developed after 3 days of treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.

Thirty-seven ciprofloxacin patients had joint appearance abnormalities compared to 11 control patients. Of these, 23 ciprofloxacin and 9 control patients had these abnormalities at baseline. Most abnormalities were seen in the knees or ankles. All cases of joint appearance abnormalities, regardless of whether it was a baseline finding or treatment-emergent, were reviewed by the IPSC for possible arthropathy. Of the 14 ciprofloxacin patients with treatment-emergent joint appearance abnormalities, 13 were assessed by the IPSC as having arthropathy. Of the 2 control patients with treatment-emergent joint appearance abnormalities, 1 was assessed by the IPSC as having arthropathy.

Forty-six ciprofloxacin patients had stance/swing abnormalities compared to 8 control patients. Of these, 36 ciprofloxacin patients and 4 control patients had the abnormalities at baseline. All cases of gait abnormality, whether it was a baseline finding or treatment-emergent, were assessed by the IPSC for possible arthropathy. Of the 10 ciprofloxacin patients with treatment-emergent gait abnormalities, 5 were assessed by the IPSC as having arthropathy. Of the 4 control patients with treatment-emergent gait abnormalities, 2 were assessed by the IPSC as having arthropathy.

Of the 10 ciprofloxacin patients with treatment-emergent gait abnormalities, 5 were assessed by the IPSC as having arthropathy. Of the 4 control patients with treatment-emergent gait abnormalities, 2 were assessed by the IPSC as having arthropathy.

7.1.5 Neurologic System Adverse Events

Study 100169

The incidence of neurological events, up to 1-year post-treatment, follow-up was 5.1% (17/335) n the ciprofloxacin group and 3.7% (13/349) in the comparator group. Convulsion occurred in 0.9% (3/335) of ciprofloxacin patients and 1.1% (4/349) of comparator patients. Neuropathy and hypesthesia were reported at the same incidence in both groups (one patient in each group for each event; 0.3% incidence). Due to coding conventions, an investigator term of “tethered cord” coded to neuropathy; this accounted for both cases of neuropathy. Both cases of hypesthesia were not considered drug-related and resolved within 5 days. All other neurological events were reported in <1% of patients in either group. No clear evidence of neurological sequelae was observed in this study.

Study 100201
The incidence of any neurologic event by the 1-year post-treatment follow-up was 11% (56/487) [95% CI: 9%, 15%] and 2% (11/507) [95% CI: 1%, 4%] in the ciprofloxacin and control groups, respectively. The only neurologic events occurring in at least 2% of patients were insomnia (4.3% [21/487] versus 0.6% [4/507]) and dizziness (1.8% [9/487] versus 0.8% [1/507]). The incidence of convulsions was the same in both treatment arms (3 patients each, 0.6%).

7.1.6 Common Adverse Events

Study 100201
The overall 1-year event rate in both treatment groups increased by approximately 5% when compared to the Day +42 event rate. The overall incidence rate of adverse events by 1 year was 45% (151/335) for ciprofloxacin and 36% (124/349) for comparator. The most common adverse events in both treatment groups were those occurring in the Body as a Whole (17% [58/335] and 9% [31/349], respectively), digestive (15% [50/335] for ciprofloxacin and 9% [31/349] for comparator), musculoskeletal (11% [36/335] and 7% [25/349], respectively), respiratory (7% [23/335] and 8% [28/349], respectively), and urogenital (8% [27/335] and 6% [22/349], respectively) body systems. The investigator(s) assessed most adverse events as mild or moderate in intensity for both treatment groups.

Adverse events, other than those affecting the musculoskeletal and central nervous systems, that occurred in > 1% of the 335 ciprofloxacin treated patients, up to 1-year post-treatment were: accidental injury 5% (17); abdominal pain 4% (12); diarrhea 5% (16); vomiting 5% (16); dyspepsia 3% (9); nausea 3% (9); rhinitis 3% (10); fever 2% (7); headache 2% (6); asthma 2% (6); rash 2% (6); and pyelonephritis 2% (7).

Study 100201
Incidence rates of adverse events, other than musculoskeletal and CNS) were accidental injury (7%; 34/487), otitis media, pharyngitis, and headache (6% each [28/487], 27/487], and [27/487], respectively). The most common events for control (other than musculoskeletal events) were pharyngitis and accidental injury (4% each; [22/507] and [21/507]).

7.1.7 Laboratory Findings

Study 100169
The incidence of laboratory test abnormalities was comparable between the 2 treatment groups. No trends that appear to be uniquely associated with ciprofloxacin treatment were identified. The most common clinically significant changes (as defined by the applicant) were $\leq$ 0.75 times the lower limit of normal for hemoglobin (4% [13/316] for the ciprofloxacin group, 3% 11/328] for the comparator group), and $\geq$ 1.8 times the upper limit of normal for SGPT (3% in each group, [8/308] and [8/318], respectively).

Study 100201
Not collected routinely.

7.1.8 Vital Signs

Study 100169
No clinically meaningful (as defined by the applicant) treatment differences were observed in mean diastolic blood pressure, systolic blood pressure, or heart rate. Of note, 4 ciprofloxacin patients had the adverse event of hypertension. All 4 patients had a medical history of hypertension. None of these events were considered by the investigators to be related to study drug. No comparator patients had an adverse event of hypertension. One comparator patient (and no ciprofloxacin patients) had the adverse event of tachycardia. No adverse event of bradycardia was reported.

Study 100201
Not collected routinely.

7.2 Safety Conclusions

Both Study 100169 and Study 100201 were designed to evaluate musculoskeletal and neurologic adverse events though at least one year of follow-up.

In the randomized, controlled trial (Study 100169), the results of the arthropathy assessment by the IPSC through six weeks (i.e., Day +42) and one year of follow-up showed that ciprofloxacin was not comparable to the control regimen. The rate of arthropathy in the ciprofloxacin group exceeded that of the comparator group by more than 6% (i.e., the upper bound of the 95% confidence interval was 7.2% at six weeks and 9.1% through one year).

In the ciprofloxacin group, the majority of musculoskeletal adverse events were mild or moderate and resolved by one year of follow-up. The events included arthralgia, abnormal gait, abnormal joint exam, joint disorder (i.e., sprain), leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain and decreased range of motion in a joint. The affected joints included: knee, elbow, ankle, hip, wrist, and shoulder. All events occurring by six weeks resolved, the majority within 30 days of the end of treatment. The events occurred more frequently in the ciprofloxacin treated patients than the control patients, regardless of whether they received IV or oral therapy. Ciprofloxacin patients were more likely to report more than one event and on more than one occasion compared to the control patients. These events occurred in all age groups and the rates were consistently higher in the ciprofloxacin group compared to the comparator group.

Of note, an adolescent female in the ciprofloxacin treatment group discontinued study drug after 7 days for wrist pain that developed after 3 days of treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.

The incidence of neurologic events within six weeks of treatment were similar between the ciprofloxacin and comparator groups (2.7% versus 2.0%, respectively)

and included dizziness, nervousness, insomnia, somnolence. Convulsions occurred in 0.9% of ciprofloxacin patients in 1.1% of comparator patients.

The overall incidence rates of adverse events regardless of relationship to study drug and within 6 weeks of treatment initiation were 41% (138/335) in the ciprofloxacin group versus 31% (109/349) in the comparator group. The most frequent events were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of comparator patients. Serious adverse events were seen in 7.5% (25/335) of ciprofloxacin patients compared to 5.7% (20/349) of comparator patients. Discontinuation of drug due to an adverse event was observed in 3% (10/335) of ciprofloxacin-treated patients versus 1.4% (5/349) of comparator patients. Other adverse events that occurred in at least 1% of ciprofloxacin patients were diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%

In Study 100201, patients were enrolled with a variety of underlying diseases, including malignancies, and were receiving multiple concomitant medications. Although this study was not randomized and the patient population was not the same as in Study 100169, the incidence of arthropathy in the ciprofloxacin-treated patients is supportive of the results seen in Study 100169. The incidence rate of IPSC assessed arthropathy in the ciprofloxacin group was 8% (37/487) by 6 weeks and 11% (56/487) by 1 year follow-up. As in Study 100169, the incidence rates of these adverse events were reported in all age groups. The incidence of any neurological event by 6 weeks was 7.2% (28/487). Insomnia (3.5%) was the only event occurring in > 1% of patients.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In adults, the recommended doses of ciprofloxacin for the therapy of severe/complicated UTI are 400 mg IV and 500 mg orally every 12 hours. At steady-state following multiple IV doses, 400 mg IV every 12 hours in adults produces an AUC_{0-12} of 12.7 μg*h/mL and C_{max} of 4.56 μg/mL. Following dosing of 500 mg every 12 hours orally to steady state, the resulting AUC_{0-12} is 13.7 μg*h/mL and C_{max} is 2.97 μg/mL. The steady-state AUC over 24 hours (i.e., AUC_{0-8} x 3) and C_{max} following 400 mg every 8 hours of ciprofloxacin IV (a regimen approved for lower respiratory tract infections, but not specifically for UTI) are 32.9 μg*h/mL and 4.07 μg/mL, respectively.

Three studies were conducted in non-cystic fibrosis patients to evaluate the pharmacokinetics of oral ciprofloxacin in various pediatric age groupings, including a limited number of neonates 5-14 weeks of age.[19-21] Following multiple-dose ciprofloxacin regimens, AUC values were 5.3 μg*h/mL in 1- to 5-year-old patients who received 15 mg/kg every 12 hours, 10.3 μg*h/mL in <1-year-old patients who received 10 mg/kg every 8 hours; and 9.3 μg*h/mL in 1- to 2-year-old patients who received 10 mg/kg every 8 hours. Corresponding C_{max} values in these studies were 2.1 μg/mL, 2.8 μg/mL, and 3.6 μg/mL, respectively. The pharmacokinetics of IV ciprofloxacin have not been investigated in non-cystic fibrosis pediatric patients. However, an AUC_{0-8} of 12.8 μg*h/mL and a C_{max} of 5.3 μg/mL in children 5 to 12 years has been reported in the literature from 13 patients with cystic fibrosis following a regimen of ciprofloxacin 10 mg/kg IV every 8 hours.[22]

Peltola and colleagues concluded that an oral ciprofloxacin dose of 30 to 45 mg/kg/day (approximately 10 to 20 mg/kg every 12 hours) should be suitable to treat severe infections in pediatric patients.[19-22] Assuming the relative bioavailability of oral ciprofloxacin is 80%, the recommended oral dose would translate to an IV ciprofloxacin dose of 24 to 30 mg/kg/day (approximately 6 to 10 mg/kg every 8 hours) to treat severe pediatric infections.

The majority of the published studies with ciprofloxacin in pediatrics have been conducted in severe infections, including acute respiratory exacerbations of cystic fibrosis where the potential treatment benefit outweighed the potential risk. Children with cUTI or pyelonephritis are acutely infected and represent another group where the risk versus benefit balance of pediatric fluoroquinolone administration may be favorable. Oral treatment with ciprofloxacin provides advantages over established oral antibiotic therapies such as trimethoprim/sulfamethoxazole (TMP/SMX) and amoxicillin with regard to both spectrum of activity and resistance patterns and may provide adequate therapeutic substitution for some IV antibiotic regimens as well. In this indication, ciprofloxacin may provide effective antibacterial treatment for some infants and children with complicated UTI and pyelonephritis without the complications and inconveniences associated with prolonged courses of IV therapies. Earlier hospital discharge or avoidance of hospital admission could become options for more patients, which in turn holds the potential to improve their quality of life.

9. OVERALL ASSESSMENT

9.1 Conclusions on Available Data

Efficacy

Both the clinical success and bacteriologic eradication rates at the TOC visit in Study 100169 in patients valid for efficacy indicated that ciprofloxacin is non-inferior to the comparator in the treatment of pediatric patients with cUTI or pyelonephritis.

Clinical success rates and bacteriological eradication rates were not substantially impacted by age, race, or sex of the patient.

Safety

Both Study 100169 and Study 100201 were designed to evaluate musculoskeletal and neurologic adverse events though at least one year of follow-up.

In the randomized, controlled trial (Study 100169), the results of the arthropathy assessment by the IPSC through six weeks (i.e., Day +42) and one year of follow-up showed that ciprofloxacin was not comparable to the control regimen. The rate of arthropathy in the ciprofloxacin group exceeded that of the comparator group by more than 6% (i.e., the upper bound of the 95% confidence interval was 7.2% at six weeks and 9.1% through one year).

The incidence of neurologic events within six weeks of treatment was similar between the ciprofloxacin and comparator groups.

Although Study 100201 was not randomized and the patient population was not the same as in Study 100169, the incidence of arthropathy in the ciprofloxacin-treated patients is supportive of the results seen in Study 100169. The incidence rate of IPSC assessed arthropathy in the ciprofloxacin group was 8% (37/487) by 6 weeks and 11% (56/487) by 1 year follow-up. As in Study 100169, the incidence rates of these adverse events were reported in all age groups. The incidence of any neurological event by 6 weeks was 7.2% (28/487). Insomnia (3.5%) was the only event occurring in > 1% of patients.

9.2 Recommendations on Regulatory Action

Ciprofloxacin is safe and effective for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli*, but is not a drug of first choice for these infections because of an increased incidence of arthropathy and other adverse reactions reported in randomized and observational studies. Based on the results of an efficacy study, the appropriate dosing regimen for the treatment of complicated urinary tract infection and pyelonephritis is:

- Oral ciprofloxacin 10 to 20 mg/kg every 12 hours (maximum of 1500 mg per day);
- Intravenous (IV) ciprofloxacin 6 to 10 mg/kg every 8 hours (maximum of 1200 mg per day); or
- IV ciprofloxacin 6 to 10 mg/kg every 8 hours (maximum of 1200 mg per day) and then converted to oral ciprofloxacin at a dose of 10 to 20 mg/kg every 12 hours (maximum of 1500 mg per day).

9.3 Recommendation on Post-Marketing Actions

9.3.1 Risk Management Activity

The applicant proposed a risk management plan, which includes the components listed as "Other Phase 4 Commitments."

9.3.2 Required Phase 4 Commitments

None

9.3.3 Other Phase 4 Requests

- The applicant will voluntarily provide to DSPIDP any promotional materials (4 weeks in advance) and press releases (1 week in advance) prior to distribution relating to the use of ciprofloxacin for complicated urinary tract infections and/or pyelonephritis in the pediatric population for three years following the approval of this supplemental application.

- The applicant will provide biannual updates on Ciprofloxacin® usage patterns in the pediatric population, with the submission dates being no later than October 31, 2004, April 30, 2005, October 31, 2005, April 30, 2006, October 31, 2006, and April 30, 2007 respectively.

- The applicant will provide expedited (15 day) reporting to DSPIDP and the Office of Drug Safety of all spontaneous adverse events (including listed events considered serious) in patients 17 years of age or younger until April 30, 2007.

- The applicant will complete the 5 year observational study (Protocol 100201) for patients receiving ciprofloxacin treatment and will submit the final research report by March 2008. Patients in the control arm (i.e., non quinolone comparator) can be discontinued from the follow-up portion of the study. The requirement for 5 year safety data in patients who do not experience any musculoskeletal adverse events may be reassessed as additional information regarding pediatric quinolone safety becomes available.

9.4 Labeling Review

The applicant did not propose a pediatric indication, but that information of the results of Studies 100169 and 100201 be added to the Pediatric Use subsection of the Precautions section of the label.

The clinical success and bacteriologic eradication results of Study 100169 indicate that ciprofloxacin is effective for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli*. Children with varying types and degrees of voiding dysfunction may be predisposed to recurrent infections and effective therapeutic intervention for is necessary to prevent scarring and renal damage. Although, cUTI and pyelonephritis in children is most commonly due to *Escherichia coli, p*atients that experience chronic infections often are infected with enterococci,

Proteus species, and *Pseudomonas* species. Although ciprofloxacin was shown in Study 100169 to be effective drug to treat cUTI and pyelonephritis in children, there was an increased incidence of arthropathy in patients treated with ciprofloxacin compared to the control patients treated primarily with cefixime through Day +42 of follow-up, which was the primary endpoint of the study.

Therefore, DSPIDP felt that in order to ensure appropriate, but limited, use in pediatric patients in whom the benefit of treatment outweighs the risk of arthropathy, it was appropriate to grant an indication for pediatric patients (1 to 17 years) for the treatment of complicated urinary tract infections and pyelonephritis, but to also include a warning that ciprofloxacin should only be used in pediatric patients for whom other treatments are not appropriate or effective, due to the increased incidence of arthropathy and other adverse reactions reported in randomized and observational studies. The entire indication, as agreed upon by the applicant and the Division is:

Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli*. NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS, Pediatric Use, ADVERSE REACTIONS,** and **CLINICAL STUDIES**.) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY**.)

In addition, DSPIDP added wording to other sections of the label:

- *Clinical Pharmacology:* added the pharmacokinetic parameters in pediatric patients.

- *Warnings:* added a statement that ciprofloxacin should only be used in patients less than 18 years of age for the treatment of cUTI and pyelonephritis and inhalational anthrax (diseases for which the drug has a pediatric indication) due to the increased incidence of arthropathy and other adverse reactions.

- *Precautions:* added a bullet to the Information for Patients subsection which alerts parents that they should inform their child's physician if the child has a history of joint-related problems before taking ciprofloxacin and also to notify the physician if any joint-related problems occur during use. In the Pediatric Use subsection wording similar to what appears in the Indications and Usage section was added along with the rate of arthropathy observed through six weeks (Day +42) and one year of follow-up in Study 100169.

- *Adverse Reactions:* added a description of the musculoskeletal and neurologic safety results obtained at six weeks and one year of follow-up from Study 100169 in more detail, including the most commonly affected joints, the rate of arthropathy in various age groups, and a description of the types of events (i.e., mostly mild, resolved, less than 30 days duration; although radiological confirmation was not available in most patients). In addition, a description was added of the other adverse events experienced by patients treated with

ciprofloxacin in Study 100169, including the overall incidence of adverse events at six weeks of follow-up, most commonly reported events (gastrointestinal), the rate of serious events compared to the control arm, and the rate of discontinuation of drug due to adverse events compared to the control arm. A sentence was added describing the fibrocartilage tear that was discovered upon DSI inspection and reported on Form 483 (see Section on Data Quality and Integrity). The incidence of arthropathy and neurologic adverse events in Study 100169, along with other adverse events occurring in at least 1% of patients, at six weeks was also added.

- *Dosage and Administration:* added a separate pediatric dosing section, including a table of dosing guidelines for cUTI and pyelonephritis based on Study 100169. Patients with moderate and severe renal insufficiency were not included in Study 100169, therefore, no information was provided on dosing adjustments necessary for pediatric patients with a creatinine clearance of < 60 mL/min/1.73m^2. The arthropathy warning statement was also repeated in this section.

- *Clinical Studies:* added a description of the efficacy results in terms of clinical success and bacteriologic eradication at the test of cure visit (5 to 9 days post-therapy) and also the arthropathy warning statement.

- *Patient Package Insert:* added a statement which alerts parents that they should only use ciprofloxacin in children with a complicated urinary tract infection or are taking ciprofloxacin for post inhalational anthrax exposure. Also parents should inform their child's physician if the child has a history of joint-related problems before taking ciprofloxacin and also to notify the physician if any joint-related problems occur during use.

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11. APPENDIX 1 - REVIEW OF STUDY 100169

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 [TMP/SMX] 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

All of the tables in this review are a reproduction of the applicant's original tables in their submission, except where noted otherwise.

Study Number	100169
Study Dates	September 9, 1999 to June 26, 2003
Date of Study Report	September 11, 2003

Study Sites

This study was conducted at 27 study sites in the United States, 4 in Canada, 5 in South Africa, 9 in Argentina, 3 in Peru, 6 in Germany, 1 in Costa Rica, and 6 in Mexico.

11.1 Objectives

The primary objective of this study was to determine the musculoskeletal safety (i.e., joint, articular cartilage, tendon and ligament) of IV, sequential (IV→ PO) and oral ciprofloxacin in comparison to IV ceftazidime, sequential (IV ceftazidime → PO cefixime or IV ceftazidime → PO TMP/SMX [in Canada only]), and oral cefixime or oral trimethoprim/sulfamethoxazole (TMP/SMX) [in Canada only] therapy among pediatric patients with complicated urinary tract infection (cUTI) or acute uncomplicated pyelonephritis (AUP).

The secondary objectives of this trial were:

- To assess the neurological safety of these dosage regimens among patients with cUTI or pyelonephritis.
- To collect of clinical and microbiological response data from pediatric patients with cUTI or pyelonephritis receiving ciprofloxacin or control regimens at the Test-of-Cure visit (Day +5 to +9) and also at the first follow-up evaluation (Day +28 to +42).
- Blood specimens for determination of serum ciprofloxacin concentration were also collected during this trial. Ciprofloxacin concentration data from this study were pooled with those from other studies in a pediatric population pharmacokinetic analysis.

Clinical Reviewer's Comment: See FDA Clinical Pharmacology and Biopharmaceutics Review by Dakshina Chilukuri, Ph.D. filed with this NDA.

11.2 Ethical Conduct

According to the applicant, this study was conducted in accordance with Good Clinical Practice (GCP) regulations and all applicable US FDA regulations, including the archiving of required documents. These practices included the following areas: IRB procedures; informed consent; protocol adherence; administrative documents (Form FDA-1572, etc.); drug supply accountability; data collection; subject records (source documents); adverse event recording and reporting; inspection and audit preparation; and records retention. The investigators were made aware that FDA representatives and representatives of Bayer Pharmaceuticals Corporation (West Haven, CT) could inspect the documents and patient records at any time. Routine investigator GCP compliance audits were independently conducted at 9 sites. The applicant reported that the results of the audits performed indicated that the study was performed in compliance with the ICH GCP guidelines with local regulations.

Three findings relating to the maintenance of the double-blind were noted by the applicant to possibly have a significant impact on the overall study results. These findings are summarized below.

- The oral investigational medication was being dispensed in its commercial packaging. This was a study-wide finding. Since patient or caregiver could have previously used the medication, it cannot be ensured that they were fully blinded. In response to this finding, the applicant added a question to the patient caregiver questionnaire to obtain caregiver knowledge on the medication being taken. The results obtained from the questionnaire are presented in this review.

- At Site 506, the identity of the individual responsible for dispensing the medication was not documented. During the audit performed by the applicant, conflicting information was received regarding who exactly was dispensing medication. Since the oral medication bottles were not identical, it cannot be ensured that the blind of the study had been maintained in the case of oral medication.

Clinical Reviewer's Comment: Site 506 enrolled 6 patients, 3 in each group.

- At Site 307, there were a number of issues that could have potentially caused undetectable code breaks to occur. One issue concerned the intravenous (IV) medication potentially being administered according to the package insert instructions instead of the protocol instruction. Although the investigator at this site stated to the applicant that this did not happen, it could have compromised the study blind. Following the audit, a memo was sent by the applicant's Study Team to the investigator reminding him of the importance of infusing all medication according to protocol instructions. In addition, the investigational medication was not kept in the pharmacy or a secure area during the study. The oral medication was initially kept in a box in the infectious disease department and for hospitalized patients the IV medication was kept in a refrigerator on the ward. In both instances there was potential for access by blinded study personnel.

Clinical Reviewer's Comment: Site 307 enrolled 22 patients, 11 in each group.

Clinical Reviewer's Comment: These potential breeches in the double-blind design of the trial have been noted and are not thought to compromise the overall findings of the trial due to a few number of patients affected by the second and third bullets. The potential lack of blinding to oral drug is addressed by the caregiver questionnaire and is not thought to significantly impact the overall assessment of safety and efficacy by the investigator.

11.3 Investigators and Study Administrative Structure

This study was conducted at 27 study sites in the US, 4 in Canada, 5 in South Africa, 9 in Argentine, 3 in Peru, 6 in Germany, 1 in Costa Rica, and 6 in Mexico.

(b) (4) monitored this study in accordance with GCP guidelines and Standard Operating Procedures (SOP) for Bayer (b) (4) Monitoring visits were performed to ensure compliance with the protocol, to review source documents and case report forms (CRFs), and to assess drug accountability.

Urine samples for urinalysis (including pyuria), urine/serum pregnancy tests, clean-catch (i.e., midstream urine) specimens used for pathogen culture, blood samples for hematology and blood chemistry profiles, and theophylline serum concentrations were analyzed at local laboratories. In some infants, urinary bags were used for urine collection in place of midstream urine (MSU) specimens. Per Amendment 6 to the protocol, local susceptibility data was not required to be collected on the CRF.

11.4 Protocol Amendments

There were 8 amendments to the original protocol (dated June 22, 1999).

- The first, third and fifth amendments (dated July 23, 1999; October 29, 1999; and January 6, 2000, respectively) were applicable only to Canadian sites.
- The second amendment (dated September 16, 1999) was applicable to all sites.
- The fourth amendment (October 29, 1999), filed in conjunction with the third amendment, was applicable only to US sites.
- The sixth amendment (dated May 15, 2000) was made to clarify the applicability of Amendment 4 to countries other than the US and Can.

A summary of all the amendments follows. The changes implemented by the amendments are incorporated into the appropriate sections of this review.

<u>Amendment 1 (dated July 23, 1999)</u>
This amendment was applicable to Canada only and modified the protocol to meet the administrative requirements of the Canadian regulatory authority, Therapeutic Products Directorate (TPD; formerly known as the Therapeutic Products Programme or TPP).

Information obtained included serious adverse event requirements, product monographs and comparator product procurement.

Amendment 2 (dated September 16, 1999)
This amendment was applicable to all sites and the major reasons for modification were:

- To eliminate the lowest dose regimen of ciprofloxacin oral suspension (from 5 to 20mg/kg q 12 h to 10 to 20 mg/kg q 12 h);
- To extend the minimum duration of therapy from 7 to 21 to 10 to 21 days;
- To clarify the exclusion criterion for urine specimens (i.e., urine samples should have been obtained from the catheter using sterile technique, not from the Foley bag);
- To specify procedures for intervention in infections occurring in patients with indwelling appliances; To ensure that patients with organisms resistant to both treatment regimens were discontinued and administered appropriate alternative therapy;
- To standardize the position (sitting) in which vital signs were obtained;
- To provide sites with the most recent version of the ciprofloxacin package insert;
- To change dosing of study drug in relation to infant formula;
- To add an additional safety analysis which would be performed based on hypertension status at baseline versus post-treatment.

Clinical Reviewer's Comment: The applicant stated that the additional hypertension safety analysis was not performed because only 4 patients had an adverse event of hypertension. See section on safety results.

Amendment 3 (dated October 29, 1999)
This amendment was applicable to Canadian sites only and addressed concerns raised by the Division and Canadian regulatory authority, TPD and resulted in the following changes:

- Cefixime was replaced with TMP/SMX as the oral component of the control regimen (i.e., both in the purely oral control regimen (Stratum I) and as the oral component of the sequential IV to oral control regimen (Stratum II);
- Procurement of TMP/SMX by the local pharmacy for each site;
- Clarification was provided in the language describing the performance of the required gait/joint examinations and the category of professional (i.e., evaluator) required to perform the exams;
- Clarification was provided regarding the use of intervention to evaluate cases presenting with signs and/or symptoms suggestive of arthropathy;
- Enrollment of patients in the adolescent age group was capped (no single center could enroll more than 2 patients aged 12 to < 17 years).

Amendment 4 (dated October 29, 1999)
The fourth amendment was filed in conjunction with the third amendment but was applicable only to US sites. The amendment was generated to address issues raised by the Division and to allow for the use of different comparative agents in the US and Canada. While cefixime was selected as the control regimen in the US, current labeling for the product in Canada precluded both administration for the

treatment of cUTI/pyelonephritis in pediatric patients and the use of twice daily dosing. Due to the resistance patterns within the US, cefixime was the only recommended control regimen for patients enrolled in the US. Therefore, this amendment allowed for the following changes:

- Provisions for a combined analysis of different control regimens to be used in the US and Canada. The various regimens of ciprofloxacin were compared to an overall control group comprised of patients receiving IV ceftazidime, IV ceftazidime→PO cefixime, IV ceftazidime→PO TMP/SMX, PO cefixime or PO TMP/SMX;
- Clarification was provided in the language describing the performance of the required gait/joint examinations and the category of professional (i.e., evaluator) required to perform the exams;
- Clarification was provided regarding the use of intervention to evaluate cases presenting with signs and/or symptoms suggestive of arthropathy;
- Enrollment of patients in the adolescent age group was capped (no single center could enroll more than 2 patients aged 12 to < 17 years).

Amendment 5 (dated January 6, 2000)
The fifth amendment was applicable only to Canadian sites and provided that resistance to any one of the study drugs would merit the patient's removal from the study. In addition, upon the request of the TPD, patients who developed arthropathy were discontinued from study drug immediately but were to be followed for safety.

Amendment 6 (dated May 15, 2000)
The sixth amendment was made to clarify the applicability of Amendment 4 to countries other than the United States and Canada. It provided for the following:

- Updated the introduction to include the cessation of a similar protocol in Europe;
- Extended the permissible window for a patient's pretherapy gait/joint examination from 48 hours prior to initiation of study drug therapy up to 24 hours after receipt of the first dose of study drug. This permitted study enrollment in the overnight hours when children present through the emergency department and qualified physical therapy personnel may not be available;
- Replaced Joseph Barone, MD (Bayer), as the Medical Monitor with (b) (4)
- Deleted (b) (4)
- Clarified the reporting steps of serious adverse events;
- Allowed for enrollment of children reliant on infant formula provided they were treated with IV medication only;
- Delete (b) (4)

Amendment 7 (dated March 19, 2001)
The purpose of the seventh amendment was to expand the exclusion of patients with renal insufficiency (from a calculated clearance >30 mL/min/1.73m^2 to greater than 60 mL/min/1.73m^2) due to recommendations within the package inserts for ceftazidime and cefixime. Due to the desire for investigators and study staff to remain blinded to the study regimen, it was not possible to change dosing intervals for the cephalosporin comparators in children with renal impairment as suggested in

the package inserts. This amendment also clarified the restriction put on enrollment of adolescent patients (i.e., only two patients between the ages of 12 and 16 years for the initial 10 patients enrolled) from any single site into the trial.

Amendment 8 (dated August 20, 2001)
The applicant met with the Division in August 2001 to provide an update on enrollment in the ciprofloxacin pediatric program. During this discussion it was noted that the Division was interested in more comparative (i.e., quinolone versus non-quinolone) safety data in pediatric patients. In an effort to provide these data, Amendment 8 extended patient enrollment an additional 10 months (through October 2002) and modified the sample size from 436 to 640.

11.5 Deviations in Randomization

This was a stratified study in which random codes were sent directly to a pharmacist at each study site. Patients were to be enrolled in ascending sequence, starting from the beginning of the random code numbers, for Stratum I (oral therapy), and in descending sequence, starting from the end of the random code numbers, for Stratum II (IV therapy). At 5 centers, the stratification was not implemented correctly, and the sequence of random code numbers was not followed properly for the 2 strata. However, the applicant stated that very few patients were affected by the incorrect enrollment sequence, and the overall treatment group balance within each strata was not adversely affected.

Three sites incorrectly used sample random codes provided to them for instructional purposes, rather than the actual random codes supplied to them for use in the study. The applicant stated that the sample random codes had equal balance between ciprofloxacin and comparator patients; therefore, the treatment group balance was not affected.

Clinical Reviewer's Comment: These deviations in randomization have been noted and are not thought to significantly affect the overall trial results due to the limited number of patients affected and the fact that the treatment arms are equally affected.

11.6 Study Design

This study was a prospective, double-blind, randomized, parallel-group comparison of the musculoskeletal and neurological safety of ciprofloxacin versus an active control regimen in pediatric patients with cUTI or pyelonephritis.

Patients aged at least 1 year and < 17 years, diagnosed with cUTI or pyelonephritis were enrolled. 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 ciprofloxacin or control antibiotics according to a 1:1 randomization. In the first (oral therapy) stratum, ciprofloxacin oral suspension was compared to control regimens (cefixime or TMP/SMX suspension [in Canada only]) and in the second 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]). Patients with a history of *Pseudomonas* infections or those in whom

Pseudomonas sp. 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 (i.e., IV or sequential therapy and purely PO therapy) and each dose level within the strata were pooled to perform comparisons between the control and experimental regimens.

Clinical and microbiological response data were evaluated at the Test-of-Cure visit (Day +5 to +9) and also at the first follow-up evaluation (Day +28 to +42).

Included within the safety assessments were detailed serial musculoskeletal examinations, which included full range of motion around all weight-bearing joints and the shoulder girdle, gait assessments, and patient/parent questionnaires conducted during therapy and in follow-up for 12 months following completion of the study drug regimen.

11.7 Study Population

The primary diagnosis for inclusion was cUTI and pyelonephritis in infants, children and adolescents between 2 and 17 years of age. In assessing patient eligibility, investigators were to consider the following factors in a risk/benefit assessment to determine if fluoroquinolone therapy was warranted:

- whether patients had multiple recent bouts of cUTI (i.e., >2 treated episodes within the past 6 months) and if so, what the clinical and bacteriological response patterns had been to other classes of antimicrobial agents;
- whether patients were known to have persistent or recurrent cUTI caused by resistant bacterial pathogens or whether the current infection was classified as a post-surgical infection.

11.8 Inclusion Criteria

To be eligible for enrollment, all patients were to meet the following criteria:

- Age $\geq$1 year but <17 years;

- Written informed consent provided by parent/legal guardian and patient (as appropriate);

- Positive urine culture obtained by clean-catch mid-stream urine (MSU), intermittent catheterization, indwelling catheterization or suprapubic aspiration. A positive culture was defined as the following for urine obtained by MSU: $\geq 10^5$ colony-forming units per milliliter (CFU/mL); by indwelling urethral catheter: $\geq 10^5$ CFU/mL; by clean intermittent urethral catheterization: $\geq 10^4$ CFU/mL; and by suprapubic aspiration: $\geq 10^3$ CFU/mL. Patients could be enrolled prior to the availability of culture results provided all other inclusion criteria were met.

- Current episode of cUTI as indicated by 1 or more of the following symptoms:

- For infants and younger children only (ie, ≥12 months but <24 months and ≥ 2 years through <6 years): recent weight loss, failure to thrive, abdominal pain, nausea, vomiting, diarrhea, jaundice, or fever (>38°C {100.4°F} obtained orally, >38.6°C {101.4°F} obtained rectally, >37.4°C {99.4°F} axillary temperature, or >38.5°C {101.2°F} obtained tympanically);

- For older children and adolescents only (i.e., ≥6 years through <12 years and ≥12 years through <17 years): dysuria, urgency, urinary incontinence associated with urgency, bedwetting in a previously "dry" child, abdominal pain, urinary frequency/pollakisuria or foul-smelling urine or fever (>38°C {100.4≥F} obtained orally, >38.6 ≥C {101.4≥F} obtained rectally, >37.4≥C {99.4≥F} axillary temperature, or >38.5≥C {101.2≥F} obtained tympanically);

- Patients presenting with cUTI were also to have ONE or more of the following factors:

  - Indwelling catheter or use of intermittent catheterization;

  - Obstructive uropathy due to bladder outlet obstruction;

  - Vesicoureteral reflux (VUR) or other urologic abnormalities;

  - Functional or neurogenic disturbances of micturition with significant impact on bladder emptying or pressure profile within the bladder;

  - Recurrent UTI, defined as 2 or more acute UTIs over a 6-month period;

  - Evidence the current UTI could be caused by a resistant uropathogen, including evidence that the current episode was a breakthrough infection or an older child or adolescent on chronic or intermittent antimicrobial suppression with unresolved vesicoureteral reflux;

  - Patients presenting with pyelonephritis had fever (>38°C {100.4°F} obtained orally, >38.6°C {101.4°F} obtained rectally, >37.4°C {99.4°F} axillary temperature or >38.5°C {101.2°F} obtained tympanically) AND at least ONE of the following symptoms: nausea and/or vomiting; and/or costovertebral angle tenderness and/or flank pain.

11.9 Exclusion Criteria

- Patients meeting any of the following criteria were to be excluded from enrollment:

- Known hypersensitivity to ANY of the study drug regimens or related compounds, including fluoroquinolones, cephalosporins, or a severe hypersensitivity to penicillin;

- (In Canada only), a known hypersensitivity to ANY of the study drug regimens or related compounds, including fluoroquinolones, cephalosporins, and sulfa-containing compounds, or a severe hypersensitivity to penicillin;

- Participated in any clinical study within 1 month prior to this study;

- Previous enrollment in this clinical study;

- Known significant liver impairment (alanine transaminase [ALT]/ aspartate transaminase [AST] and/or baseline bilirubin >3 times upper limit of normal);

- Known significant renal insufficiency (calculated creatinine clearance of < 60 mL/min/1.73m^2);

- Pregnant or lactating, or sexually active and using unreliable contraception. Sexually active females were to use reliable contraception or remain abstinent during exposure to study drug. Reliable contraception included barrier methods [e.g., condoms, diaphragms, intra-uterine devices, implants]).

- Reliance on infant formula for nutrition such that dosing of study medication 2 hours before or after a feeding was not possible if receiving the oral formulation of study drugs;

- Administered prior therapy with an effective antibacterial agent at a therapeutic dose within 48 hours of screening (i.e., an antimicrobial which demonstrated clinically determinable reduction of signs and symptoms of cUTI);

- Required any concomitant systemic antibacterial agent;

- Known risk of experiencing seizures, a history of any convulsive disorders or head injury trauma, currently on antiseizure medication or within 2 months poststroke;

- Acquired immunodeficiency syndrome (AIDS), defined as CD4 count <200/mm^3, when a cell count was available. Human immunodeficiency virus (HIV) testing was not required for this protocol;

- Treatment with quinolones in the previous 14 days prior to study entry;

- Known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy. Patients with conditions precluding the performance of a reliable series of musculoskeletal examinations were to be excluded from trial participation;

- Infants and children with spina bifida with total or near total paralysis of the lower extremities (i.e., motor strength of 0/1+ in the major muscle groups of both lower extremities), and/or who could ambulate only with the recruitment of the upper extremity muscle groups, and/or have associated significant congenital or acquired neuro-orthopedic structural pathology of the lower extremities (i.e., bilateral neuropathic joints, hip dysplasias or dislocations, or arthrogryposis).

Note: No single center was to enroll more than 2 patients aged 12 through 16 years within the initial group of 10 patients enrolled at the site. Should enrollment at a site exceed 10 patients, the site was allowed to enroll additional patients within the 12- to 16-year age range;

11.10 Removal of Patients from Therapy or Assessment

If the patient did not show improvement within 2 to 5 days (therapeutic failure), or if a serious allergic reaction occurred or a superinfection developed, study drug therapy was discontinued and other appropriate therapy initiated. If a uropathogen was found to be resistant to one of the study regimens, the patient was withdrawn from the study and administered appropriate alternative therapy. Before other antimicrobial agents were given, however, the patient was fully evaluated and appropriate cultures and laboratory tests performed so that the information required to evaluate study drug therapy was available and recorded in the remote data entry (RDE) system.

In Canada, as per the request of the TPD, if the patient developed arthropathy during treatment, study medications were to be stopped immediately. The patient was to remain in the study for purposes of safety analyses.

All patients who discontinued therapy prematurely (both Regimens A and B) including those who received at least 1 dose of study drug continued to undergo prospective musculoskeletal safety assessments (i.e., periodic examination of the weight-bearing joints and shoulder girdle, gait assessments and caregiver questionnaires) up to and including the 12-month safety follow-up visit.

11.11 Study Drug

Ciprofloxacin
Ciprofloxacin was supplied as an intravenous (IV) solution and as oral suspension.

Ciprofloxacin IV is a clear, almost colorless to pale yellow solution (b) (4) The batch numbers for ciprofloxacin IV were 0ECT, 0JCD and 8IEW.

Intravenous ciprofloxacin was supplied in bulk by Bayer as 20 mL (10 mg/mL) vials for subsequent dilution. Ciprofloxacin IV was to be infused over a period of 60 minutes. The ciprofloxacin IV dose was prepared by aseptically withdrawing the concentrate from the vial of ciprofloxacin IV. This was diluted with a suitable IV solution (e.g., 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP) to a final concentration of 1-2 mg/mL. The final dilution volume administered ranged between 50 mL and 400 mL, depending upon the patient's weight and unit dose selected by the investigator.

Ciprofloxacin oral suspension 5% (5 gm ciprofloxacin/100 mL) strength was used. After dilution to the final 100 mL volume following reconstitution, 1 teaspoonful (5 mL) of the 5% suspension delivered 250 mg of ciprofloxacin. The batch numbers for ciprofloxacin oral suspension 5% were GALHC1, GARAG1, IT0005A, IT002ST, IT100RG, IT1023R and IT10598.

The daily dose of ciprofloxacin administered as therapy for cUTI in this trial was adjusted according to the patient's body weight and conformed to the dosing guidelines presented in Tables 2 and 3, respectively.

Definitions for mild, mild-to-moderate, moderate-to-severe and severe cUTI and pyelonephritis that formed the basis for the dosing of ciprofloxacin IV and oral therapy were left to the judgment of the clinical investigator.

TABLE 2
Ciprofloxacin IV Dosing*
Stratum II

Pediatric dose	Dose Regimen Suitability Based Upon Severity of Infection at Presentation
6 mg/kg q8h[a] (total daily dose 18 mg/kg)	moderate cUTI or pyelonephritis
10 mg/kg q8h[b] (total daily dose 30 mg/kg)	severe cUTI or pyelonephritis

* Pediatric IV ciprofloxacin doses of 400 mg q8h (i.e., total IV daily dose 1200 mg) were maximum doses in this study and were not to be exceeded, even in children weighing over 51 kg.
[a] May be comparable, in terms of exposure profile, to an adult 200 mg q8h IV dose (not an approved adult regimen).
[b] May be comparable, in terms of exposure profile, to an adult 400 mg q8h IV dose.

TABLE 3
Ciprofloxacin Oral Suspension Dosing*
Stratum I and Stratum II

Pediatric dose	Dose Regimen Suitability Based Upon Severity of Infection at Presentation
10 mg/kg q12h (total daily dose 20 mg/kg)	Mild to moderate cUTI or pyelonephritis
15 mg/kg q12h[a] (total daily dose 30 mg/kg)	Moderate to severe cUTI or pyelonephritis
20 mg/kg q12h[b] (total daily dose 40 mg/kg)	severe cUTI or pyelonephritis

* Pediatric ciprofloxacin doses of 750 mg q12h orally (i.e., total oral daily dose 1500 mg) were maximum doses in this study and were not to be exceeded, even in children weighing over 51 kg.
[a] May be comparable, in terms of exposure profile, to an adult 500 mg q12h oral dose.
[b] May be comparable, in terms of exposure profile, to an adult 750 mg q12h oral dose.

Clinical Reviewer's Comment: The population pharmacokinetic analysis of ciprofloxacin was submitted as part of this NDA and was performed using data from 6 studies and 357 patients. A total of 1472 plasma ciprofloxacin concentrations were

available from the 357 patients, including samples from 207 patients enrolled in Study 100169. The final dosing recommendations from the applicant's analysis are below. Please see Clinical Pharmacology and Biopharmaceutics Review by Dakshina Chilukuri, Ph.D. filed with this NDA for more information.

Cefixime
Cefixime oral suspension was procured and supplied by Bayer. When reconstituted as directed, the oral suspension could be delivered at a dose of 100 mg/5 ml of cefixime. The batch numbers for cefixime were 474276, 478555, 462-336, 479660 and 481853.

The recommended dose of the suspension is 8 mg/kg/day for cUTI and pyelonephritis. This could be given in 2 divided doses of 4 mg/kg q12h as required in this protocol. Children who weighed more than 50 kg or who were older than 12 years of age were treated with the recommended adult dose of cefixime of 200 mg q12h.

Trimethoprim/sulfamethoxazole (Canada only)
Trimethoprim/sulfamethoxazole (TMP/SMX) oral suspension was supplied by the local pharmacy for each site. Each teaspoonful (5 mL) of the pediatric suspension contains 40 mg trimethoprim and 200 mg sulfamethoxazole.

The recommended dose for TMP/SMX in children with cUTI is 4 mg/kg trimethoprim and 20 mg/kg sulfamethoxazole every 12 hours. The maximum daily dose of TMP/SMX to be administered was 320 mg trimethoprim and 1600 mg sulfamethoxazole.

Ceftazidime
Ceftazidime IV was applicable to Stratum II (IV therapy) only in this clinical trial. Ceftazidime IV solution was supplied by the local pharmacy for each site. Ceftazidime was prepared and administered according to instructions in the product package insert.

For this trial, ceftazidime was to be dosed at 30 to 45 mg/kg q8h.

11.12 Duration of Treatment

The total duration of therapy in this trial for each age group (i.e., $\geq$ 12 months but < 24 months; $\geq$ 2 years, but < 6 years; $\geq$ 6 years, but < 12 years; and $\geq$ 12 years, but < 17 years) could vary according to the discretion of the investigator, but should range between 10 and 21 days, inclusive. Investigators were to consider the patient's age, normality of renal function adjusted for age, and extent and severity of documented structural/anatomic or functional genitourinary tract abnormalities when projecting an intended duration of study drug therapy required to achieve clinical cure and bacteriological eradication.

In Stratum I, study drug (i.e., ciprofloxacin, cefixime, or TMP/SMX) was given as a purely oral regimen. In Stratum II, ciprofloxacin or ceftazidime therapy was initiated using the IV formulation but could be switched thereafter (i.e., at the time the patient achieved adequate clinical and microbiological control of infection [on IV therapy]) to oral ciprofloxacin, cefixime, or TMP/SMX at the investigator's discretion.

In general, older children and those with bilateral, normally functioning kidneys were expected to receive treatment for a maximum of 14 days. Infants and children with hypofunctional kidneys and/or with significant renal structural anomalies, especially in the setting of frequent or recurrent episodes of UTI, were expected to require treatment for a maximum of 21 days. The above criteria were intended as guidelines. The clinical judgment of the treating investigator was to be considered in projecting an intended duration of study medication required to achieve the desired endpoints of clinical cure and bacteriological eradication.

Patients with a history of *Pseudomonas* infections or those in whom *Pseudomonas sp.* was isolated at the pretherapy culture were to remain on IV therapy for the entire course of study.

11.13 Method of Assigning Patients to Treatment Groups

Patients who met all enrollment criteria were to be stratified based on the clinical judgment of the investigator of the need for IV therapy. Within each stratum, patients were then randomized in a 1:1 ratio of ciprofloxacin:control as indicated in Table 4.

TABLE 4
Treatment Regimens by Stratum (based on need for IV therapy)

Stratum I (Oral Therapy)	
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.
	VERSUS
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 sulfamethoxazole every 12 hours. In older children and adolescents weighing $\geq$ 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.

TABLE 4 (continued)
Treatment Regimens by Stratum (based on need for IV therapy)

Stratum II (IV Therapy)	
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 1200 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.
	VERSUS
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 8 hours (maximum of 6 grams per day) followed by oral TMP/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 Can). Dosing continued for 10 to 21 days inclusive of total therapy.

11.14 Blinding

The study was designed to be double-blinded. In order to maintain the blind, a pharmacist provided study drug directly to the patient so that study site personnel would remain blinded. Labeling was done by the study site pharmacist in a manner that maintained the blind during study drug administration.

11.15 Concomitant Therapy

Efforts were made to minimize the total number of concomitant drugs (of any kind) administered to the patient during the duration of study medication administration. All concomitant medication were recorded in the RDE system. Antibacterial agents were not to be administered concomitantly with study medication.

Investigators were to avoid the use of fluoroquinolone antibiotics (including ciprofloxacin) in all study patients following termination or completion of the study drug regimen through completion of the 12-month safety follow-up visit, insofar as clinically feasible and provided that a fluoroquinolone antibiotic was not absolutely clinically indicated at any time during this 1-year follow-up.

All antibacterial agents as well as corticosteroids, anti-inflammatory agents and analgesics (which could mask musculoskeletal symptomatology) administered following completion of the study drug regimen through the 12-month (or last available) follow-up visit inclusive were recorded in the RDE system along with dose, route of administration, frequency of daily administration, duration (including calendar dates), and indication for use.

11.16 Treatment Compliance

Patient guardians were instructed to bring unused study medication with them at the Test-of-Cure visit (Day +5 to +9). All unused study drug was to be accounted for and was sent for destruction at the completion of the trial. Patients must have taken ≥80% of the scheduled doses in order to be considered compliant with the study protocol.

11.17 Bacteriological Outcomes

Based on the pretherapy and subsequent urine cultures obtained, microbiological response was determined provided the following criteria for urine culture were fulfilled on entry:

- mid stream urine (MSU): $\geq 10^5$ CFU/mL;
- urine obtained by indwelling urethral catheter: $\geq 10^5$ CFU/mL;
- urine obtained by clean intermittent urethral catheterization: $\geq 10^4$ CFU/mL; and
- suprapubic aspiration: $\geq 10^3$ CFU/mL.

11.17.1 Bacteriologic Response at Test-of-Cure

Bacteriological response was assigned on Day +5 to +9 following therapy (Test-of-Cure) and included the following categories:

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 $\geq 10^2$ CFU/mL for specimens obtained by suprapubic aspiration);

Indeterminate: the bacteriological response to the study drug was not evaluable for any reason (e.g., the pretreatment culture was negative, post-treatment culture was not performed);
Superinfection: the 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 cUTI or pyelonephritis,
- the requirement for 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. If more than 1 pathogen was identified, each was to be present at a colony count of $\geq 10^5$ CFU/mL, $\geq 10^4$ CFU/mL or $\geq 10^3$ CFU/mL, depending on the urine collection method, in order to be included in the analysis.

Patients with indwelling catheters were to have had blood cultures (2 sets from 2 different sites) obtained simultaneously with the catheterized urine specimen at the time of study enrollment. If 2 or more pathogens grew from the baseline urine culture, all isolates were considered contaminants (i.e., unevaluable), unless the same pathogen was also isolated from a simultaneously obtained blood culture. If the same pathogen grew in the urine at $>10^5$ CFU/mL and was isolated from the blood, then it was considered an evaluable pathogen.

If the method of obtaining a specimen for urine culture was switched between the baseline and the Test-of-Cure visit (e.g., from suprapubic aspiration to MSU), the bacteriologic outcome from these patients was to have been analyzed separately from the bacteriologic outcome data in patients whose method was not changed.

Clinical Reviewer's Comment: The applicant noted that because there were very few patients who switched the urine collection technique between the baseline and the Test-of-Cure visit (e.g., from suprapubic aspiration to MSU), this additional analysis was not performed. This approach is acceptable to the reviewer, since there were less than 10 patients affected.

11.17.2 Bacteriologic Response Following Therapy

Bacteriologic response determined on Day +28 to +42 following therapy (first follow-up visit) included the following categories:

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.

11.18 Clinical Outcomes

The clinical evaluation was based on serial examination to determine the effect of study drug therapy on the signs and symptoms of infection. All pertinent laboratory tests or procedures that reflected the course of the infectious disease were also assessed. Absence of or reduction of signs and symptoms was used to assess clinical response. In the event that the patient failed study drug therapy and was prescribed alternative antimicrobial therapy, continued clinical evaluation of the patient focused on their response to the alternative antimicrobial therapy at a subsequent visit.

For a course of therapy to be judged valid for evaluating the clinical efficacy of drug therapy, the following criteria had to be met:

- Infectious diagnosis was supported by signs and symptoms of cUTI or pyelonephritis;
- All inclusion/exclusion criteria were met;
- Urinary tract infection was confirmed pretreatment;
- At least 8 days (24 IV doses OR 16 oral doses OR a combination) of study drug was taken unless the patient was a treatment failure;
- Study drug was 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, was administered concomitantly with the study drug;
- A clinical evaluation was performed at the Test-of-Cure (Day +5 to +9) visit unless the patient was an early clinical failure. An indeterminate designation at Test-of-Cure invalidated the patient for efficacy evaluation.

11.18.1 Clinical Response During Therapy

Clinical response was determined on Day 2 to 5 during therapy as follows:

Improvement: clinically significant decrease in signs and symptoms of infection;
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.

11.18.2 Clinical Response at Test-of-Cure

Clinical responses determined on Day +5 to +9 following therapy (Test-of-Cure) 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.

11.18.3 Clinical Response at Follow-up

Clinical responses determined on Day +28 to +42 following therapy (first follow-up) were 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.

11.18.4 Clinical Efficacy Endpoints

In Stratum I, the clinical efficacy endpoint was considered to be the comparison between the proportion of patients treated and evaluable with sequential (IV→PO) or purely oral regimens of ciprofloxacin who experienced clinical success versus the analogous proportion of patients treated and evaluable within the control regimens (IV ceftazidime → PO cefixime or TMP/SMX or purely PO cefixime or TMP/SMX).

In Stratum II, the clinical efficacy endpoint was the comparison between the proportion of patients treated and evaluable with purely IV ciprofloxacin who experienced clinical success versus the analogous proportion of patients treated and evaluable within the control regimen (IV ceftazidime).

For the overall assessment of efficacy, which in this protocol was to be considered a secondary efficacy measure, clinical outcome was determined to be a success if it was assessed as success (i.e., resolution, at Day +5 to +9 post-therapy) AND also assessed as success (i.e., continued resolution, at Day +28 to +42 post-therapy) OR if clinical outcome was assessed as indeterminate at Day +5 to +9 post-therapy and as success at follow-up (i.e., continued resolution, at Day +28 to +42 post-therapy).

The clinical outcome was determined to be failure as soon as there was one assessment of failure at any time point.

Clinical Reviewer's Comment: The protocol included a definition for an overall clinical assessment of efficacy, which was to be a combination of the Test-of-Cure clinical response and the long-term follow-up clinical response. In the analysis, the overall clinical assessment of efficacy was not used by the applicant, since for analysis purposes; clinical response at follow-up encompassed all the components of the planned overall clinical response assessment of efficacy. This approach is acceptable to the reviewer.

11.18.5 Clinical Response for Patients on Alternative Antibiotics

Patients who failed study drug therapy or improved, but were administered alternative antibiotics, were to have a clinical assessment at Day +5 to +9 after the last dose of alternative therapy. Responses were graded according to the following:
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.

11.19 Safety Outcomes

Arthropathy was the primary outcome variable for safety in this protocol. The primary timepoint was Day +28 to +42. 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. This definition was seen as broad and inclusive of such phenomena as bursitis, enthesitis and tendonitis. The musculoskeletal safety assessments were carried out primarily through objective evaluations of joint appearance, structure and function (i.e., range of motion testing) and of gait conducted by either rheumatologists or trained physical therapists experienced in musculoskeletal examinations.

Joint assessment included formal physical examination of all joints; however, special care and attention was given to the weight-bearing joints (i.e., knees, hips, and ankles) and to the shoulder girdle. All joints were examined for pain/tenderness, evidence of inflammation (i.e., redness, warmth, deformity, swelling or ballotable fluid), loss of function (to the extent this can be assessed in younger children and infants), and any restrictions to expected active/passive range of motion. Both active and passive range of motion were always assessed. Patients with any pretreatment baseline musculoskeletal exam abnormalities were excluded from the study.

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. Infants and children with spina bifida with total or near total paralysis of the lower extremities (i.e., motor strength of 0/1+ in the major muscle groups of both lower extremities), and/or who could ambulate only with the recruitment of the upper extremity muscle groups, and/or have associated significant congenital or acquired neuro-orthopedic structural pathology of the lower extremities (i.e., bilateral neuropathic joints, hip dysplasias or dislocations, or arthrogryposis) were to have been excluded from trial participation.

Subjective complaints spontaneously volunteered by both patients and by their parents or caregivers, especially those attributable to the musculoskeletal system, were carefully recorded and followed up with additional objective clinical assessments regardless of the period on-study (i.e., during study drug regimen or during the follow-up observation period).

For shoulders, knees, hips and ankles/feet, the motions tested were the following with the patient ranges of motion recorded:

- shoulders: extension, flexion, abduction, internal and external rotation;
- hips: extension, flexion, adduction, abduction, internal and external rotation;
- knees: extension and flexion;
- ankles/feet: plantar flexion, dorsiflexion.

All joint examinations were performed by an examiner skilled in the evaluation of joint function/appearance; preferably the same individual in order to minimize inter-rater variability. Gait was evaluated in both the stance and swing phases with any abnormalities noted.

A training video on physical therapy evaluations was provided by the applicant to all sites to ensure that all patients were examined using the same instructions.

The applicant convened an Independent Pediatric Safety Committee (IPSC) of experts, including a pediatric rheumatologist, pediatric infectious disease specialist, pediatric neurologist and pediatric orthopedic surgeon, to meet and discuss musculoskeletal cases to assess for potential arthropathy.

A secondary safety objective of this study was to assess effects of ciprofloxacin and the comparators on the neurological system in pediatric patients with cUTI or pyelonephritis. Neurological system adverse events were to be captured for up to 1-year post-therapy.

Safety was also assessed by obtaining a medical history and physical examination findings (including vital signs), reports of clinical adverse events, results of blood chemistry and hematology, urinalysis, theophylline levels and prothrombin time (when applicable), and pregnancy test results.

Blood was drawn from patients for clinical laboratory assessment of the following variables:
Hematology: hemoglobin; hematocrit; white blood cell count with differential to include neutrophils, bands, lymphocytes, monocytes, eosinophils, and basophils; platelet count; and prothrombin (PT) time and partial thromboplastin time (PTT) for patients with coagulation disorders or who were receiving warfarin sodium concomitantly; blood chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), serum creatinine, uric acid, total bilirubin, AST, ALT, alkaline phosphatase, serum pregnancy test (for females of child-bearing potential), theophylline serum concentrations (for patients receiving theophylline concomitantly).

Urine was analyzed for semiquantitative and microscopic examination for appearance, specific gravity, occult blood, protein, pH, ketones, glucose, red blood cells, crystals, bacteria, epithelial cells, white blood cells, and casts.

A urinary leukocyte count (cell count by hemocytometer or the sediment examination method) was performed. Evidence of pyuria was defined as $\geq$10 WBC/mm^3 from an unspun urine sample or >5 WBC/HPF from a centrifuged urine specimen.

11.20 Study Visits

Patient screening was to be performed within 48 hours prior to onset of therapy. Patients were then examined on Day 2 to 5 during therapy, with additional on-therapy visits every 2 to 5 days during an extended treatment course. The patient was evaluated again at the Day +5 to +9 post-therapy (Test-of-Cure) 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 to assess musculoskeletal and neurological safety.

11.20.1 Screening Visit

Patient screening was performed within 48 hours prior to onset of therapy. Joint and gait assessment was done prior to initiation of study drug treatment to exclude patients with pre-existing abnormalities and to establish a baseline values. If qualified personnel were not available at the time of initial patient presentation, the patient's pretherapy gait/joint examination could be conducted from 48 hours prior to initiation of study drug therapy up to 24 hours after receipt of the first dose of study drug.

In addition, the following procedures were performed during the screening visit for all prospective candidates:

- A medical history was taken and a physical examination was performed prior to entry into the study to establish the infection diagnosis and the acceptability of the patient for enrollment;

- The general health status of the patient at the onset of therapy and accompanying diseases or conditions were determined and recorded;
- Vital signs, including blood pressure, heart rate (HR) and temperature, were obtained;
- The baseline caregiver questionnaire was completed;
- A pre-therapy clinical assessment was performed; including an assessment of severity of infection;
- Blood and urine samples were obtained for baseline hematology, serum chemistry, and urinalysis profiles;
- A urinary leukocyte count (cell count by hemacytometer or the sediment examination method) was performed;
- Appropriate pretreatment urine cultures were obtained for the isolation and identification of the organism causing the infection. Per Amendment 6, local susceptibility data was not required to be collected in the CRF;
- Patients with indwelling catheters were to have blood cultures (2 sets from 2 different sites) obtained simultaneously with the catheterized urine specimen at the time of study enrollment. In cases where bacteremia was suspected, two different sets of blood cultures were also to be drawn.

11.20.2 On-Therapy Visits

Day 2 to 5, with additional visits as needed. Patients were clinically evaluated at least once during therapy (Day 2 to 5). Patients having a protracted treatment course (14 -21 days) were to have weekly safety laboratory collection.

The following procedures were performed during the on-therapy visits:

- Vital signs including blood pressure, heart rate and temperature were obtained;
- An assessment of pyuria was done and a urine culture was obtained, with appropriate susceptibility testing of potential pathogens;
- A complete gait/joint examination was performed;
- Adverse event data were collected;
- Blood and urine samples for safety laboratory assessments were obtained;
- Repeat blood cultures were to be drawn from patients having positive blood cultures at the pre-therapy visit;
- Blood samples (1-2 mL) were to be drawn for measurement of ciprofloxacin serum concentrations.

11.20.3 Test-of-Cure and First Follow-up Visits

The patient was evaluated again at the Day +5 to +9 post-therapy (Test-of-Cure) visit and the Day +28 to +42 follow-up (first follow-up) visit. Clinical and bacteriological evaluation (urine culture and quantitative measurement of pyuria) were obtained and adverse event data were collected at each of these time points.

Vital signs, including blood pressure, HR and temperature, were obtained. In addition, a thorough safety assessment, including gait/joint examinations and safety laboratory assessments were performed. All procedures except for safety labs were to be repeated at the first follow-up visit (Day +28 to +42). In addition, a pyuria assessment was to be made and the patient's caregiver was to be asked to complete the caregiver questionnaire at this visit.

11.20.4 Post-Therapy Visits

In-office visits were conducted at the 3-month and 1-year time points. At these visits, a gait/joint examination was performed and adverse event data referable to the musculoskeletal or neurological systems was collected. The caregiver was also asked to complete the caregiver questionnaire at the 1-year follow-up visit. Interim telephone calls were conducted at the 6- and 9-month time points to assess musculoskeletal and neurological safety.

The study flowchart (Table 5) summarizes the timing of efficacy and safety measurements assessments obtained during the study.

TABLE 5
Study Flowchart

	Pre-treat-ment	During-treatment	Post--treatment					
		Day 2 to 5 (with additional visits as needed through Day 21)	Day +5 to +9 after end of treatment (Test-of-Cure visit)[a]	Day +28 to +42 after end of treatment (first follow-up visit)	Day + 88 to +100 (3 month follow-up)	Day +175 to +190 (6 month follow-up)	Day +270 to +285 (9 month follow-up)	Day +355 to +375 (1 year follow-up)
Informed consent	X							
Check of eligibility criteria	X							
Medical history	X							
Clinical assessment	X	X	X	X				
Physical examination	X	X	X	X				
Gait/joint examination	X	X[b]	X[b]	X[b]	X[b]			X[b]
Caregiver questionnaire	X			X				X
Blood chemistry/hematology	X	X	X	X[c]				
Blood cultures	X[d]	X[d]						
Urinalysis and urine culture with susceptibility testing[e]	X	X	X	X				
Pregnancy Test: urine	X[f]							
Pregnancy Test: serum	X[f]		X[f]					
Vital signs	X	X	X	X				
Adverse event monitoring		< ----------X[g]---------- >						
Serious AE monitoring		< ----------X[h]---------->						
Serious and non-serious musculoskeletal and neurological system AE monitoring		< ----------X[h]---------->						
Pharmacokinetic sampling		X						
Documentation of concomitant therapy and procedures		< ----------X---------- >						

[a] These procedures were carried out at the end of treatment in patients prematurely discontinuing study drug treatment prior to administration of alternate antimicrobial therapy.

[b] In case of complaints/abnormal findings, appropriate intervention was initiated.

[c] Only if previous values were abnormal.

[d] If bacteremia was suspected and for patients that were chronically catheterized; patient was followed as clinically indicated until resolution of bacteremia.

[e] As per Amendment 6, local susceptibility data was not to be collected on the CRF.

[f] Older female children and female adolescent patients of childbearing potential could be enrolled based upon a negative urine pregnancy test performed in the clinic. In this group, a serum pregnancy test was also performed at the pre-treatment baseline and repeated at the Test-of-Cure (Day +5 to +9).

[g] Adverse events were collected through study Day +9. Events referable to the neurological or musculoskeletal system were reported through the 1-year follow-up.

[h] Serious adverse events involving the musculoskeletal and neurological systems were reported up to and including the 1-year follow-up visit; SAEs involving all other systems were reported up to and including the late follow-up visit (+28 to +42 days after the end of study drug administration).

11.21 Statistical and Analytical Plans

11.21.1 Safety

All safety analyses were performed for the population considered valid for safety (also referred to as the Intent to Treat population by the applicant). The safety population was defined as all randomized patients who took at least one dose of study drug.

The primary objective of the study was to determine whether ciprofloxacin given for 10 to 21 days was equivalent to control regimens given for 10 to 21 days, in terms of arthropathy incidence documented up to the first follow-up visit (Day +28 to +42 after the end of therapy) in pediatric patients with cUTIs or pyelonephritis.

The primary population for analysis was to be the patients considered valid for safety. Clinical response, a secondary analysis, was performed on the subset of patients considered valid for efficacy, as well as on the subset of patients considered valid for safety. Bacteriological response, another secondary analysis, was performed on the subset of patients considered microbiologically valid as well as on the subset of patients microbiologically valid for safety (those having bacteriological response recorded). The effect of disease stratum/treatment type (as seen by assignment to either oral or sequential and purely IV therapy) was to be taken into account in the statistical analyses.

Demographic and baseline characteristics were to be summarized by treatment group, and for the population overall, using the mean and standard deviation, median, quartiles and minima/maxima (quantitative data), or frequency counts (qualitative/categorical data). Descriptive statistics were to be provided for the 4 age groups under study.

Medical conditions were to be tabulated by ICD-9 codes and concomitant medications by ATC codes (World Health Organization Drug Dictionary or WHO-DD).

The two treatment groups were to be compared using a one-way analysis of variance with treatment as the main effect for continuous variables like age and weight, or using a chi-squared test for categorical data. The primary safety variable was to be the arthropathy event rate at the first follow-up visit (Day +28 to +42). A two-sided 95% confidence interval for the weighted difference between treatment groups in arthropathy incidence rates was to be constructed using Mantel-Haenszel weights reflecting disease stratum/treatment type. The difference was to be constructed as the arthropathy incidence rate for the experimental ciprofloxacin arm minus the arthropathy incidence rate for the control therapy either cefixime, ceftazidime or ceftazidime → cefixime, or [ceftazidime → TMP/SMX or TMP/SMX as per Amendment 3]).

Clinical Reviewer's Comment: Amendment 3 changed the oral control drug in Canadian sites from cefixime to TMP/SMX. In the statistical analysis, the control drugs from U.S. and Canadian sites were combined, and the analysis the applicant presented results as ciprofloxacin versus comparator. Treatment by country (Canadian sites versus non-Canadian sites) interaction tests were to be performed for the rate of arthropathy and for the primary efficacy variables. This change to the statistical plan was detailed in Amendment 4. However, in the final analysis, this interaction test was not performed by the applicant due to low enrollment by Canadian sites. This is acceptable because the enrollment in Canadian sites was 19 patients total (8 in the ciprofloxacin group and 11 in the comparator group). Of these patients only 9 (3 in the ciprofloxacin group and 6 in the comparator group) were valid for efficacy.

Non-inferiority was to be defined statistically in this case as the upper limit of a 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. If this test of homogeneity of the odds ratios indicates a significant interaction, exploratory analyses were to be attempted to define its source.

Laboratory data was to be analyzed using descriptive statistics and identification of values outside of the normal range.

Comparison of incidence rates of all types of adverse events was to be done in a descriptive manner. Events were to be tabulated by type (according to the COSTART glossary) and frequency, for all events and for those events considered by the investigator to have a possible or probable relationship to drug treatment.

Adverse event tables were to be calculated at the first follow-up (Day +28 to +42) and the 1-year follow-up (Day +355 to +375).

Descriptive statistics were to be presented across the 4 age groups;

- $\geq$ 12 months but < 24 months;
- $\geq$ 2 years, but < 6 years;
- $\geq$ 6 years, but < 12 years; and
- $\geq$ 12 years, but < 17 years.

Age group was not to be used as a stratification factor in the final analyses and no statistical testing was to be performed within age groups.

11.21.2 Efficacy

All efficacy analyses relating to clinical success rates were to be performed for the clinically valid subset of patients (valid for efficacy or Per Protocol population) as well as for the intent to treat population (valid for safety population). Efficacy analyses relating to microbiological

success rates were to be performed for the valid subset of patients with microbiological response data as well as for the intent to treat population with microbiological response data. Missing and indeterminate data were to be treated as failures in the intent to treat population. Superinfections were treated as bacteriological failures.

Clinical Reviewer's Comment; In addition to the applicant defined populations of "valid for safety" and "valid for efficacy", the statistical reviewer defined the modified intent-to-treat (mITT) population as those patients who received at least one dose of study drug and had a baseline pathogen identified. The clinical success and bacteriologic eradication results for this population will be included in Results section of this review, since DSPIDP considers this population to be of interest, along with the Per Protocol (i.e., valid for efficacy) population.

The primary efficacy response variable was to be the clinical success (resolution) rate at the Test-of-Cure visit (Day +5 to +9 after the end of therapy). 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 disease stratum/treatment type. The difference was to be constructed as the clinical success rate for the experimental ciprofloxacin arm minus the clinical success rate for the control therapy (either cefixime, ceftazidime or ceftazidime → cefixime, or [ceftazidime → TMP/SMX or TMP/SMX as per Amendment 3]).

Non-inferiority was to be defined statistically in this case as the lower limit of a 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. If this test of homogeneity of the odds ratios indicates a significant interaction, exploratory analyses were to be attempted to define its source. Overall clinical success rates and microbiological success rates were also to be examined and weighted confidence intervals calculated with equivalence as defined above.

Age group was not to be used as a stratification factor in the final analyses and no statistical testing was to be performed within age groups.

Clinical reviewer's Comment: Stratification by cUTI and AUP was performed by the clinical and statistical reviewers. The results for these two disease groups will be reported separately (as well as combined) in the Results section of this review.

11.22 Determination of Sample Size

Based on assumed true arthropathy rates of 1.5% in both the control and experimental groups, a clinically meaningful difference (delta) of 6 percentage points for the difference between treatments and alpha=0.025 (one-sided), a total sample size of 436 patients (based on 1:1 allocation with 218 patients in each arm) would provide 99.8% power to reject the null hypothesis of inequivalence. This includes an

upward adjustment of 15% to account for added variability in a multi-center design. Note: if the incidence be as high as 4%, the study would still have minimum power of 80% for detecting a lower limit of equivalence of 6% with alpha=0.025 (one-sided) based on 436 patients.

The first secondary objective of the study was to compare the clinical success (resolution) rates at the Test-of-Cure visit (Day +5 to +9 after the end of therapy) between the patients receiving ciprofloxacin and the active control patients. Based on assumed true clinical success rates of 90% in both groups and a clinically meaningful difference (delta) of 12 percentage points, the sample size of 436 patients calculated for the safety comparison would provide 93.5% power (at alpha=0.025, one-sided) to reject the null hypothesis after accounting for an 80% patient validity rate.

Clinical Reviewer's Comment: A delta of 6% and 12% for the safety and efficacy analyses, respectively, was agreed upon by the applicant and the Division during protocol development.

11.23 Independent Pediatric Safety Committee

An Independent Pediatric Safety Committee (IPSC) was formed to review musculoskeletal and neurological adverse events. Cases were reviewed in a blinded fashion. The mission of the IPSC was to determine 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 IPSC was formed in September 1999 with two members, a pediatric infectious disease specialist and a pediatric rheumatologist. By October 2001, it consisted of 4 members, including a pediatric neurologist and a pediatric orthopedic surgeon. The IPSC members participated in 15 meetings, scheduled by Bayer, from April 2001 through September 2003.

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. This definition was seen as broad and inclusive of such phenomena as bursitis, enthesitis and tendonitis.

Evidence of arthropathy was characterized as either physical or historical evidence.

Physical evidence of arthropathy may have included but was not necessarily limited to: warmth, redness, joint effusion, tenderness, synovial thickness, abnormal gait or limp, weakness, and/or limited joint mobility/motion.

Since these objective findings may not alone have provided an adequate range of symptoms, a broader range of events to include all COSTART terms in the musculoskeletal system was added. See Table 1 in Appendix 1.

Historical evidence included joint and/or periarticular tissue pain and/or stiffness.

Diagnostic imaging demonstrating structural damage or change was also accepted as evidence of arthropathy.

Evidence of arthropathy may have been further categorized as weak or strong evidence. Historical data was considered weak evidence; joint effusion, synovial thickness, limited motion and diagnostic imaging findings were examples of strong evidence.

Relevant modifiers of evidence included severity, duration, and the presence of concurrent factors such as trauma, infection, and other confounding diseases (e.g. cerebral palsy causing abnormal gait). In addition, concurrence of parameters or change in parameters over time was given greater weight (e.g. increased joint stiffness with swelling).

Overall evidence for arthropathy was classified by the IPSC as none; possible; probable; or definite.

If a case was identified as possible, probable or definite arthropathy by the IPSC, the Committee also assessed the relationship to study drug as none; possible; probable; or definite.

In making the determination of relationship to study drug, multiple factors were considered. The 3 major considerations were any pre-existing conditions, conditions with clear alternative etiology (i.e., septic arthritis, trauma), and/or timing of the event in relationship to study drug administration. Generally, conditions that began more than 1 year after the administration of study drug were not considered related to study drug.

Statistical testing was used to determine whether the ciprofloxacin treatment group was non-inferior to the control group with regard to the incidence rate of arthropathy, as determined by the IPSC. For this analysis, all classification categories of drug relatedness were combined. It should be noted that arthritis was summarized in a descriptive fashion with other adverse events.

A SAS program was developed to help identify patients with potential cases of arthropathy. Patients who met any one of 5 conditions were identified, and then reviewed by the IPSC to determine whether arthropathy was present. Before the blind was broken, the IPSC reviewed all potential cases of arthropathy as identified by the following algorithm:

- Patients with any musculoskeletal adverse events, as identified by the COSTART coding system (COSTART codes between 7000000 and 7999999).
- 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.
- Patients with abnormal gait/joint appearances, as determined by the investigators.
- Patients with abnormal stance or swing, as determined by the investigators.

- Patients with a 10 degree or greater decrease from baseline on any range of motion (ROM) exam. (Note: If ROM was the only finding, the case was not reviewed, as the IPSC did not believe that this, as an isolated finding, would warrant consideration as indicative of arthropathy.)

Prior to declaring clean database and breaking the study blind, investigator terms for adverse events were reviewed by a medical physician employed by the applicant. Those adverse events that could potentially relate to musculoskeletal events, but due to coding conventions would not code to the musculoskeletal system, were selected as additional cases for the IPSC review. In addition to the algorithm, all cases of adverse events that coded to COSTART terms of leg pain (01050030), hand pain (01100015), arm pain (01100005) and abnormal gait (08030010) were also reviewed. Additionally, due to coding conventions, decreased range of motion and movement in the hip coded to movement disorder, therefore, all events of movement disorder (08020760) were also reviewed. Due to coding conventions, ankle and hand swelling are coded to peripheral edema (02030425), so these events were added for review. Selected accidental injuries (01030015) were reviewed if they related to joints or the extremities.

Clinical Reviewer's Comment: At the end of the study, 116 patients were identified using the arthropathy algorithm. Four patients were removed due to changes or clarifications in the data, which modified the adverse events such that they no longer fit the definition of arthropathy). An additional 21 patients were identified by the applicant, who were not already identified by the algorithm. In total 141 cases were reviewed by the IPSC. See safety results section of the review.

11.24 EFFICACY RESULTS

11.24.1 Patient Enrollment by Study Center

Table 2 in Appendix 1 summarizes patient enrollment by center. Sixty-one centers from 8 countries enrolled 689 patients into the study. Of the 689 patients, 337 were in the ciprofloxacin group, and 352 were in the comparator group.

In the ciprofloxacin group, there were 297 patients (88%) in Stratum I (oral therapy) and 40 (12%) in Stratum II.

In the comparator group, there were 211 patients (91%) in Stratum I. Of the 211, all but 3 (i.e., 208) took oral cefixime. There were 20 patients (9%) in Stratum II that received IV therapy (i.e., ceftazidime IV only or IV and then were switched to oral therapy).

11.24.2 Premature Termination

Table 6 displays the reasons for premature termination from the study. As shown, 58 ciprofloxacin and 56 comparator patients did not complete study drug as planned.

TABLE 6

Reasons for Premature Discontinuation from Study Treatment

	Ciprofloxacin (N=337)	Comparator (N=352)
Any reason	58 (17%)	56 (16%)
Adverse event [a]	10 (3%)	5 (1%)
Patient non-compliance	1 (<1%)	1 (<1%)
Consent withdrawn	13 (4%)	10 (3%)
Insufficient therapeutic effect	1 (<1%)	3 (<1%)
Patient lost to follow-up	1 (<1%)	5 (1%)
Investigator decision	0 (0%)	2 (<1%)
Protocol violation	32 (9%)	30 (9%)

[a] the applicant noted that two ciprofloxacin patients and one comparator patient had adverse events with the action taken of "study drug permanently discontinued", but did not have the reason for termination of study drug listed as an adverse event on the end of study page of the CRF. These patients are included here by the applicant.

The most common reason for discontinuation was protocol violation (9% in each group). The majority of these protocol violations were absence of a causative organism (negative culture or no urine culture obtained), insufficient colony counts, and organisms resistant to study drugs. There were more ciprofloxacin patients (10) than comparator patients (5) who discontinued therapy due to adverse event. The two treatments groups had very similar rates of discontinuation due to the other reasons. Also, the numbers of patients completing 1-year follow-up were similar. Overall, 307 (92%) of ciprofloxacin patients and 314 (90%) of comparator patients completed 1-year post-treatment follow-up.

11.24.3 Patient Enrollment by Country of Enrollment

Table 7 presents the distribution of patients included in the various analyses overall, and by country. For 5 patients (2 ciprofloxacin, 3 comparator), it could not be confirmed that any study medication was taken. These patients were excluded from the population valid for safety.

TABLE 7
Patients Enrollment and Validity for Analysis Population by Country of Enrollment

	Patient Enrollment and Validity	
	Ciprofloxacin	Comparator
All Patients (all countries)	337	352
Valid for Safety	335 (99%)	349 (99%)
Valid for Efficacy	211 (63%)	231 (66%)
Argentina	78	79
Valid for Safety	77 (99%)	79 (100%)
Valid for Efficacy	61 (78%)	67 (85%)
Canada	8	11
Valid for Safety	8 (100%)	11 (100%)
Valid for Efficacy	3 (38%)	6 (55%)
Costa Rica	21	21
Valid for Safety	21 (100%)	20 (95%)
Valid for Efficacy	17 (81%)	13 (62%)
Germany	13	11
Valid for Safety	13 (100%)	11 (100%)
Valid for Efficacy	5 (38%)	4 (36%)
Mexico	57	61
Valid for Safety	56 (98%)	60 (98%)
Valid for Efficacy	36 (63%)	37 (61%)
Peru	87	89
Valid for Safety	87 (100%)	88 (99%)
Valid for Efficacy	62 (71%)	69 (78%)
United States	62	71
Valid for Safety	62 (100%)	71 (100%)
Valid for Efficacy	22 (35%)	29 (41%)
South Africa	11	9
Valid for Safety	11 (100%)	9 (100%)
Valid for Efficacy	5 (63%)	6 (67%)

The countries with the highest enrollment were Peru (176 patients), Argentina (157 patients), and the United States (133 patients). Validity rates for efficacy were high in Argentina (82%) and Peru (74%). In the United States, the validity rate for efficacy was low (38%).

Clinical Reviewer's Comment: The United States had a low validity rate compared to Argentina and Peru. There were 82 patients who were valid for safety, but not efficacy between the two arms. The reasons listed for invalidity are as follows: concomitant antimicrobial, other than pre-therapy (1), concomitant antimicrobial therapy (1), exclusion/inclusion criteria violation (14), inadequate duration of treatment (8), insufficient CFU at pre-treatment culture (13), no causative organism isolated pre-treatment (20), non-adherence to dosing regimen (1), protocol violation (24). The clinical significance of these findings is difficult to pinpoint, but may have to do with investigators not adequately screening patients prior to enrollment or following the protocol.

11.24.4 Blinding

In order to maintain the blind, a pharmacist provided study drug directly to the patient so that study site personnel would remain blinded.

The potential for patient unblinding was relevant since study drug was dispensed in commercial packages and since the study drugs have different tastes and textures and different solutions (oil-based for ciprofloxacin, water-based for the comparator). At the request of the Division, an item was added to the Caregiver Questionnaire as to whether the patient/caregiver believed they knew which study drug that they received. Overall, 29 ciprofloxacin patients and 19 comparator patients answered "yes" to this question. A follow-up question asked which study drug they thought they received. Overall, 17 ciprofloxacin patients and 11 comparator patients answered the follow-up question. Of those patients, 10 (59%) ciprofloxacin patients and 6 (55%) comparator patients correctly identified study drug.

Clinical Reviewer's Comment: Although unblinding was a potential problem, very few patients thought they knew which study drug they received and only about half of them correctly identified study drug. Therefore, patient unblinding is not considered by the reviewer to have significantly affected the study.

11.24.5 Analysis Populations

Total enrolled: Of the 689 patients enrolled into the trial, 337 were in the ciprofloxacin group, and 352 were in the comparator group.

Valid for Safety (Intent to Treat population): Two patients in the ciprofloxacin group and 3 patients in the comparator group were randomized but it could not be confirmed by the applicant that they received study medication. These patients were excluded from the analysis of safety. Therefore, there were 335 patients in the ciprofloxacin group and 349 patients in the comparator group valid for the analysis of safety.

Valid for Efficacy (Per Protocol population): One hundred twenty-six (126) patients in the ciprofloxacin group and 121 in the comparator group were excluded from the valid for efficacy population. Table 8 presents a summary of the reasons for patient exclusion. Therefore, the valid for efficacy population included 442 patients total, 211 in the ciprofloxacin group and 231 in the comparator group.

TABLE 8
Summary of Reasons for Exclusion from the Valid for Efficacy Population

	Ciprofloxacin (N=337)	Comparator (N=352)
Any reason	126 (37%)	121 (34%)
No causative organism[a]	44 (13%)	36 (10%)
Protocol violation	28 (8%)	25 (7%)
Inadequate duration of treatment	19 (6%)	10 (3%)
Insufficient CFU at Pre-Rx culture	16 (5%)	17 (5%)
Exclusion/inclusion criteria violation	12 (4%)	16 (5%)
Organism resistant to study drug	1 (0.3%)	4 (1%)
Patient never received any study medication	2 (0.6%)	3 (0.9%)
Required clinical evaluation not obtained	1 (0.3%)	3 (0.9%)
Lost to follow-up	0	3 (0.9%)
Post- therapy antibiotics	1 (0.3%)	2 (0.6%)
Concomitant antimicrobial therapy	1 (0.3%)	2 (0.6%)
Non-adherence to dosing regimen	1 (0.3%)	0

[a] No pre-therapy pathogen isolated or no urine culture specimen obtained.

Protocol violations (28 in the ciprofloxacin group and 25 in the comparator group) included the following:

- Clinical symptoms assessed outside (either too early or too late) of the Test-of-Cure visit window (Day +5 to +9) (24 ciprofloxacin group versus 21 comparator group)
- Test-of-Cure visit was actually performed during the study drug administration period (3 ciprofloxacin group versus 2 comparator group)
- Elevations in liver enzyme test pre-therapy (1 each in the ciprofloxacin group and the comparator group)
- Pre-therapy urine culture was not obtained (1 patient in the comparator group)

The following patients were inclusion/exclusion criteria violations, but the applicant allowed them to remain in the study and analysis populations:

Five patients were enrolled despite the fact they were non-ambulatory at baseline. Two ciprofloxacin patients (301-071 and 307-011) and 3 comparator patients (28-009, 307-008, and 307-022) had some degree of

paralysis. Additionally, 1 ciprofloxacin patient (301-100) had a severe baseline gait abnormality (later diagnosed as Duchenne's disease).

Patients with known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy were to be excluded from the study. Overall, 27 (8%) ciprofloxacin patients and 26 (7%) comparator patients had a medical history of any abnormal musculoskeletal or connective tissue finding.

At study entry, 28 ciprofloxacin patients and 12 comparator patients had an abnormal gait assessment at baseline and 10 ciprofloxacin patients and 7 comparator patients had an abnormal joint appearance at baseline. These baseline abnormalities and medical histories may have rendered it difficult to assess any potential drug effect on gait or joint appearance.

As per the caregiver questionnaires, 8 patients (3 ciprofloxacin [16001, 401074, 701034], 5 comparators [103015, 204035, 307008, 705010, 705017]) had a baseline history of seizures. These patients should have been excluded as they could have been placed at risk for seizures during therapy. Additionally, Patient 307-008 was receiving phenytoin concomitantly with study drug. However, none of these patients had seizures during therapy. One ciprofloxacin patient (16-001) had a convulsion (297 days after dosing). One comparator patient (307008) had a convulsion (27 days after dosing).

Clinical Reviewer's Comment: These baseline abnormalities make an assessment of the potential adverse effects of the drug on the musculoskeletal and neurologic systems difficult. However, given the small numbers and the roughly equal distribution across the two treatment groups, the overall impact on the interpretation of safety is minimal. The IPSC has taken baseline abnormalities into consideration when assessing each patient for the development of arthropathy during the study. Therefore, these patients will remain in the reviewer's valid for efficacy population and will be noted for patients assessed to have arthropathy.

11.24.6 Demographic and Other Baseline Characteristics

Valid for Efficacy Population

Descriptive statistics for some of the key demographic and baseline variables for the population of patients valid for efficacy are provided in Table 9.

The majority of patients enrolled are female (85% in the ciprofloxacin arm and 86% in the comparator arm).

Of note, three race groups contributed the vast majority of patients: Caucasian, Hispanic and "uncodable." Further inspection of uncodable

races by the applicant revealed these patients were Mestizo (i.e., of mixed European and native South American descent).

None of the differences between treatment groups was determined to be statistically significant, and in general the distribution of demographic variables was similar in the two groups, although there were more patients in the ciprofloxacin group than in the comparator group with severe infections (7% versus 3%).

For more complete information on the enrollment of patients by age group, see Table 11.

TABLE 9
Demographic and Other Baseline Characteristics
Patients Valid for Efficacy

Characteristics	Ciprofloxacin	Comparator
	N = 211	N = 231
Sex		
% Female	179 (85%)	198 (86%)
Race		
% Caucasian	79 (37%)	87 (38%)
% Black	1 (<1%)	1 (<1%)
% Asian	1 (<1%)	1 (<1%)
% Hispanic	65 (31%)	69 (30%)
% Uncodable	65 (31%)	73 (32%)
Age in Years for All Pts, Mean ± SD (range)	5.8 ± 3.6 (1 to 16)	6.3 ± 3.6 (1 to 15)
Age in Years for Pts ≥ 2 Years, Mean ± SD	6.5 ± 3.3	6.9 ± 3.2
Age in Months for Pts <24 Months, Mean ± SD	16.3 ± 3.8	15.4 ± 2.8
Infection Type		
% Pyelonephritis	119 (56%)	137 (59%)
% cUTI	92 (44%)	94 (41%)
Infection Severity		
% Mild	50 (24%)	56 (24%)
% Moderate	146 (69%)	169 (73%)
% Severe	15 (7%)	6 (3%)
Infection Duration (Days), Mean ± SD (range)	11.3 ± 2.2 (7 to 21)	11.3 ± 2.2 (10 to 21)

Valid for Safety Population

The distribution of demographic variables for the valid for safety population is shown in Table 10.

As noted for the valid for efficacy population, uncodable races were determined by the applicant to be patients of Mestizo descent.

None of the differences between treatment groups was determined to be statistically significant, and in general the distribution of demographic variables was similar in the two groups, although there were more patients in the ciprofloxacin group than in the comparator group with severe infections (7% versus 4%).

TABLE 10
Demographic and Other Baseline Characteristics
Patients Valid for Safety

Characteristics	Ciprofloxacin N = 335	Comparator N = 349
Sex		
% Female	273 (81%)	284 (81%)
Race		
% Caucasian	130 (39%)	134 (38%)
% Black	5 (1%)	7 (2%)
% Asian	3 (<1%)	6 (2%)
% Hispanic	102 (30%)	109 (31%)
% Uncodable	95 (28%)	93 (27%)
Age in Years for All Pts, Mean ± (range)	6.3 ± 3.8 (1 to 16)	6.2 ± 3.7 (1 to 17)
Age in Years for Pts ≥ 2 Years, Mean ± SD	6.9 ±3.5	6.9 ±3.4
Age in Months for Pts <24 Months, Mean ± SD	16.4 ± 3.6	16.3 ± 3.4
Infection Type		
% Pyelonephritis	171 (51%)	183 (52%)
% cUTI	164 (49%)	166 (48%)
Infection Severity		
% Mild	76 (23%)	93 (27%)
% Moderate	234 (70%)	243 (70%)
% Severe	25 (7%)	13 (4%)
Infection Duration (Days), Mean ± SD (range)	11.3 ± 2.4 (5 to 21)	11.2 ± 2.2 (7 to 21)

Medical histories involving the musculoskeletal system and central nervous system were reported with equal frequency between treatment groups (8% ciprofloxacin versus 7% comparator and 7% both treatment groups, respectively).

The distribution of patients by age group in the valid for efficacy population is shown in Table 11. Patients less than or equal to 5 years comprised 51% (108/211) of patients in the ciprofloxacin group and 43% (99/231) of patients in the comparator group.

Clinical Reviewer's Comment: Table 11 was created by the reviewer.

TABLE 11
Age Distribution of Patients Valid for Efficacy

	Ciprofloxacin N = 211	Comparator N = 231
≥1 year < 2 years	26 (12%)	24 (10%)
≥2 years < 6 years	82 (39%)	75 (33%)
≥6 years < 12 years	92 (44%)	111 (48%)
≥12 years <17 years	11 (5%)	21 (9%)

11.24.7 Microbiology Results

The most frequently isolated causative organisms at enrollment in patients valid for efficacy are shown in Table 12.

TABLE 12
Most Common Causative Organisms at Enrollment
Patients Valid for Efficacy

	Ciprofloxacin N = 211	Comparator N = 231
Escherichia coli	181	185
Klebsiella pneumoniae	9	10
Pantoea agglomerans	4	5
Proteus mirabilis	2	5

11.24.8 Concomitant Medications

Incidence rates of concomitant medication use were 30% in the ciprofloxacin group and 37% in the comparator group (data not shown). The most common treatment-emergent medications (i.e., medications started for the first time after randomization) were those with actions on the nervous system (16% in the ciprofloxacin group and 22% in the comparator group), and musculoskeletal system (10% in the ciprofloxacin group and 13% in the comparator group). The rates of use of anti-inflammatory and antirheumatic products in the musculoskeletal system were lower in the ciprofloxacin group (9% versus 12% comparator) as were the rates of use of analgesics (14% versus 19% comparator) in the nervous system. The remaining rates of use of each medication class were fairly consistent in the two groups.

Prevalence rates of medication use were 40% for the ciprofloxacin group and 45% for the comparator group. The highest prevalence rates and largest treatment group differences were seen in the nervous system (18% ciprofloxacin versus 26% comparator). This was largely due to a difference between treatment groups in analgesic prevalence (16% ciprofloxacin versus 21% comparator).

Thirteen percent of patients in each treatment group received concomitant antimicrobials. The most common antimicrobials used were TMP/SMX (25 patients) and nitrofurantoin (18 patients).

11.24.9 Compliance with Study Medication

The mean (± standard deviation) total treatment duration (comprised of oral and IV duration) in the valid for efficacy population was 11.9 ± 2.6 days (range 3 to 22 days) in the ciprofloxacin group and 11.8 ± 2.5 days (range 5 to 22 days) in the comparator group. The mean (± standard deviation) total number of doses (comprised of oral and IV doses) was 24.8 ± 10.4 doses (range 4 to 104 doses) in the ciprofloxacin group and 25.0 ± 12.8 doses (range 8 to 161 doses) in the comparator group.

Clinical Reviewer's Comment: The treatment duration was at the discretion of the investigator. The protocol specified a range of 10-21 days (as per Amendment 2), so a mean treatment course of 11 days means most patients were treated with relatively short courses of antimicrobials in both treatment groups.

The mean (± standard deviation) total treatment duration and number of doses in the valid for safety population were slightly lower than those in the valid for efficacy duration. The mean total treatment duration was 10.6 ± 3.8 days (range 1 to 22 days) in the ciprofloxacin group and 10.9 ± 3.5 days (range 1 to 23 days) in the comparator group. The mean total number of doses was 22.9 ± 14.3 doses (range 1 to 123 doses) in the ciprofloxacin group and 23.8 ± 14.9 doses (range 1 to 161 doses) in the comparator group.

11.24.10 Analysis of Efficacy

Clinical response at the Test-of-Cure Visit (+5 to+9 Days)
Clinical response 5-9 days after the end of the therapy was the primary efficacy variable (Test-Of-Cure). The overall result, along with the 95% confidence interval of the difference, is shown in Table 13A.

TABLE 13A
Clinical Response at TOC (+5 to+9 Days)
Patients Valid for Efficacy

	Ciprofloxacin N = 211	Comparator N = 231
Cure	202 (95.7%)	214 (92.6%)
Failure	9 (4.3%)	17 (7.3%)
95% Confidence Interval	(-1.3%, 7.3%)	

The protocol stated that if the lower limit of the confidence interval for the difference in cure rates lies above -12%, then non-inferiority would be

concluded. Since the lower limit of the confidence interval was -1.3%, ciprofloxacin can be considered non-inferior to the comparator.

Clinical Reviewer's Comment: The clinical cure rates for the mITT population at TOC were 77.3% (225/291) and 75.7% (237/313) for ciprofloxacin and comparator, respectively (95% CI of the difference [-5.2%, 8.2%]), which still allows the conclusion of non-inferiority.

Clinical results broken down by disease type (i.e., cUTI or pyelonephritis) are shown in Table 13B

Clinical Reviewer's Comment: Tables 14 and 15 were created by the reviewer.

TABLE 13B
Clinical Cure at TOC (+5 to+9 Days) by Infection Diagnosis
Patients Valid for Efficacy

	Ciprofloxacin	Comparator
Overall	202/211 (95.7%)	214/231 (92.6%)
cUTI	87/92 (94.6%)	86/94 (91.5%)
Pyelonephritis	115/119 (96.6%)	128/137 (93.4%)

The treatment group comparisons were consistent between Stratum I and II (the oral and IV therapy groups, respectively) for ciprofloxacin and the comparator as shown in Table 13C. The p-value from the Breslow-Day test for treatment by disease stratum/treatment type interaction was 0.761, indicating that the treatment group differences across treatment types were not significantly inconsistent.

TABLE 13C
Clinical Cure at TOC (+5 to+9 Days) by Stratum
Patients Valid for Efficacy

	Ciprofloxacin	Comparator
Overall	202/211 (95.7%)	214/231 (92.6%)
Stratum I (oral)	188/196 (96%)	197/211 (93%)
Stratum II (IV)	14/15 (93%)	17/20 (85%)

Clinical response at the Follow-Up Visit (+28 to+42 Days)
Clinical response as assessed at the follow-up visit is shown in Table 14.

Clinical Reviewer's Comment: Tables 14 was created by the reviewer.

TABLE 14
Clinical Cure at Follow-Up (+28 to +42 Days)
Patients Valid for Efficacy

Response	Ciprofloxacin N=211	Comparator N=231
Sustained Cure	175 (82.9%)	179 (77.7%)
Failure	10 (4.7%)	16 (6.9%)
Relapse	11 (5.2%)	15 (6.5%)
Indeterminate	0 (0%)	2 (0.9%)
Missing	15 (7.1%)	19 (8.2%)

Bacteriologic Response at the Test-of-Cure Visit (+5 to+9 Days)
The bacteriologic response at the Test-of-Cure visit (+5 to+9 Days) by treatment stratum is shown in Table 15.

Clinical Reviewer's Comment: Tables 15 was created by the reviewer.

TABLE 15
Bacteriologic Response at TOC (+5 to+9 Days) by Stratum
Patients Valid for Efficacy

	Ciprofloxacin	Comparator
Stratum I (oral)	N=196	N=211
Eradication	165 (84.2%)	168 (79.6%)
Persistence	21 (10.7%)	21 (10.0%)
Superinfection	2 (1.0%)	9 (4.3%)
New Infection	3 (1.5%)	10 (4.7%)
Indeterminate	4 (2.0%)	3 (1.4%)
Missing	1 (0.5%)	0 (0%)
Stratum II (IV)	N=14	N=18
Eradication	13 (86.7%)	13 (65.0%)
Persistence	1 (6.7%)	0 (0%)
Superinfection	0 (0%)	1 (5.0%)
New Infection	1 (6.7%)	2 (10.0%)
Indeterminate	0 (0%)	4 (20.0%)
Missing	0 (0%)	0 (0%)

Bacteriologic response at the Test-of-Cure visit for all routes of therapy, including the 95% confidence interval of the difference between ciprofloxacin and comparator is shown in Table 16. The protocol specified that indeterminate and missing responses would be excluded from the analysis of patients valid for efficacy; therefore, the confidence interval and overall eradication rates in this population do not include the indeterminate and missing responses.

TABLE 16
Bacteriologic Response at the Test-of-Cure Visit (+5 to+9 Days)
Patients Valid for Efficacy

	Ciprofloxacin N=211	Comparator N=231
Eradication	178 (84%)	181 (79%)
Persistence	22 (10%)	21 (9%)
Indeterminate	4 (2%)	7 (3%)
Superinfection	2 (1%)	10 (4%)
New Infection	4 (2%)	12 (5%)
Missing	1 (1%)	0 (0%)
Overall Eradication Rate*	178/206 (86%)	181/224 (81%)
95% Confidence Interval	(-1.4%, 12.6%)	

* excluding indeterminate and missing results

The protocol stated that if the lower limit of the confidence interval for the difference in eradication rates lies above -12%, then non-inferiority would be concluded. Since the lower limit of the confidence interval was -1.4%, ciprofloxacin can be considered non-inferior to the comparator.

Clinical Reviewer's Comment: The eradication rates for the mITT population at TOC were 64.9% (189/291) and 61.0% (191/313) for ciprofloxacin and comparator, respectively (95% CI of the difference [-3.9, 11.4%]), which still allows the conclusion of non-inferiority.

TABLE 17
Bacterial Eradication at TOC (+5 to+9 Days) by Infection Diagnosis
Patients Valid for Efficacy

	Ciprofloxacin	Comparator
Overall	178/206 (86.4%)	181/224 (80.8%)
cUTI	69/89 (77.5%)	63/92 (68.5%)
Pyelonephritis	109/117 (93.2%)	118/132 (89.4%)

The patients with persistence, superinfection, or new infection at the TOC visit will be discussed below in more detail in Tables 18A through 18F in an attempt to better understand the organisms involved as well as selected patient characteristics.

Clinical Reviewer's Comment: Tables 18A through 18F were created by the reviewer.

Of the patients with persistence of the baseline organism, all 22 patients in the ciprofloxacin group had *E. coli* as the organism. In the comparator group, the persistent organisms were: *E. coli* (18), *E. faecalis* (1), *E. cloacae* (1), and *Morganella morganii* (1). One patient in the comparator group (9004) had eradication of one of their baseline organisms (*E. coli*)

as well as persistence of another original organism (*M. morganii*) and was categorized as “persistence” by the applicant.

TABLE 18A
Persistent Organisms at the Test-of-Cure Visit (+5 to+9 Days) in the Ciprofloxacin Group
N=22
Patients Valid for Efficacy

Organism	Pt #/Sex/Age	Country	Race	Disease
E. coli	301095/F/6	Argentina	Caucasian	cUTI
	301303/F/7	Argentina	Caucasian	cUTI
	302026/F/9	Argentina	Caucasian	cUTI
	304004/F/5	Argentina	Caucasian	cUTI
	306018/F/3	Argentina	Caucasian	Pyelonephritis
	306052/F/11	Argentina	Caucasian	cUTI
	601005/F/9	Costa Rica	Hispanic	cUTI
	601021/F/4	Costa Rica	Hispanic	cUTI
	601057/F/3	Costa Rica	Hispanic	Pyelonephritis
	601101/F/9	Costa Rica	Hispanic	cUTI
	701015/F/3	Mexico	Hispanic	cUTI
	701021/F/7	Mexico	Hispanic	Pyelonephritis
	701040/F/13	Mexico	Hispanic	cUTI
	705018/F/4	Mexico	Hispanic	cUTI
	706032/F/2	Mexico	Hispanic	cUTI
	401091/F/16	Peru	Mestizo	Pyelonephritis
	401104/F/1	Peru	Mestizo	cUTI
	402049/F/8	Peru	Mestizo	cUTI
	403043/F/5	Peru	Mestizo	Pyelonephritis
	403050/F/9	Peru	Mestizo	Pyelonephritis
	13040/F/8	United States	Hispanic	Pyelonephritis
	15064/M2	United States	Asian	cUTI

TABLE 18B
Persistent Organisms in the Comparator Group at the Test-of-Cure Visit (+5 to+9 Days)
N=21
Patients Valid for Efficacy

Organism	Pt #/Sex/Age	Country	Race	Disease
E. coli	301089/F/7	Argentina	Caucasian	cUTI
	305024/F/7	Argentina	Caucasian	cUTI
	306044/F/5	Argentina	Caucasian	Pyelonephritis
	307009/F/14	Argentina	Caucasian	cUTI
	309015/F/8	Argentina	Hispanic	Pyelonephritis
	309017/F/9	Argentina	Hispanic	Pyelonephritis
	601048/F/6	Costa Rica	Hispanic	Pyelonephritis
	701039/F/7	Mexico	Hispanic	cUTI
	702009/F/8	Mexico	Hispanic	Pyelonephritis
	706046/F/9	Mexico	Hispanic	cUTI
	401060/F/3	Peru	Mestizo	Pyelonephritis
	401067/F/6	Peru	Mestizo	Pyelonephritis
	401116/F/1	Peru	Mestizo	Pyelonephritis
	402036/F/11	Peru	Mestizo	Pyelonephritis
	403042/F/12	Peru	Mestizo	Pyelonephritis
	27006/F9	United States	Caucasian	cUTI
	28010/F/8	United States	Caucasian	cUTI
	38018/F/6	United States	Caucasian	cUTI
E. faecalis	301090/F/7	Argentina	Caucasian	cUTI
E. cloacae	305013/M/3	Argentina	Caucasian	cUTI
Morganella morganii	9004/F/8*	United States	Caucasian	cUTI

*patient had eradication of one of their baseline organisms (*E. coli*) as well as persistence of another baseline organism (*M. morganii*) and was categorized as “persistence” by the applicant.

There were 12 patients with a superinfection, two in the ciprofloxacin group and 10 in the comparator group. Two patients in the comparator group had both a superinfecting organism and a new infecting organism (12001 and 105002). These patients were classified as having a superinfection by the applicant and are included in the 10 comparator patients with a superinfection by the applicant (Table 18).

A variety of uropathogens resulted in superinfections. Of note, 3 patients had more than one superinfecting organism: *Citrobacter freundii* and *P. aerguinosa* were found in one patient (601062), *Enterococcus* sp. And *Corynebacterium* sp. were found in another patient (016009); and *Enterococcus* sp. *E. faecalis*, and *E. faecium* were found in a third patient (16009).

TABLE 18C
Organisms Causing Superinfection in the Ciprofloxacin Group at the Test-of-Cure Visit (+5 to+9 Days)
N=2
Patients Valid for Efficacy

Organism	Pt #/Sex/Age	Country	Race	Disease
E. coli	401023/F/10	Peru	Hispanic	cUTI
Staphlyococcus sp.	701012/M/1	Mexico	Hispanic	cUTI

TABLE 18D
Organisms Causing Superinfection in the Comparator Group at the Test-of-Cure Visit (+5 to+9 Days)
N=10 patients (11 organisms)
Patients Valid for Efficacy

Organism	Pt #/Sex/Age	Country	Race	Disease
Citrobacter freundii	601062/M/1*	Costa Rica	Hispanic	cUTI
Corynebacterium sp.	15060/F/13*	United States	Hispanic	Pyelonephritis
Alcaligenes sp.	12001/F/14 $	United States	Caucasian	cUTI
E. coli	1041/F/11	United States	Caucasian	Pyelonephritis
Enterococcus sp.	15060/F/13*	United States	Hispanic	Pyelonephritis
	16009/F/14*	United States	Hispanic	cUTI
E. faecalis	9012/F/8	United States	Caucasian	cUTI
	16009/F/14*	United States	Hispanic	cUTI
E. faecium	16009/F/14*	United States	Hispanic	cUTI
E. aerogenes	701031/F/2	Mexico	Hispanic	cUTI
Morganella morganii	706051/M/12	Mexico	Hispanic	Pyelonephritis
Staphlyococcus sp.	105002/M/3 $	Canada	Caucasian	cUTI
P. aeruginosa	601062/M/1*	Costa Rica	Hispanic	cUTI
	27005/F/1	United States	Caucasian	

*patient with more than one superinfecting organism
$ patient with a superinfection and new infection. Classified by the applicant as a superinfection.

There were 18 patients with a new infecting organism, 4 in the ciprofloxacin group and 12 in the comparator group. As with the superinfections, a variety of organisms resulted in new infections. One patient in the ciprofloxacin group (505010) had two organisms causing a new infection: *C. freundii* and *P. aeruginosa*. Two patients in the comparator group had both a new infecting organism and a superinfecting organism (12001 and 105002). These patients were classified as having a superinfection by the applicant and are not included in the 12 patients with superinfections in the comparator group (Table 18F).

TABLE 18E
Patients with New Infections in the Ciprofloxacin Group at the Test-of-Cure Visit (+5 to+9 Days)
N=4 (5 organisms)
Patients Valid for Efficacy

Organism	Pt #/Sex/Age	Country	Race	Disease
C. freundii	505010/F/15*	Germany	Caucasian	cUTI
E. cloacae	704006/F/6	Mexico	Hispanic	Pyelonephritis
E. coli	307004/M/16	Argentina	Caucasian	cUTI
Staphlyococcus sp.	301245/F/5	Argentina	Caucasian	cUTI
P. aeruginosa	505010/F/15*	Germany	Caucasian	cUTI

*patient with more than one superinfecting organism

TABLE 18F
Patients with New Infections in the Comparator Group at the Test-of-Cure Visit (+5 to+9 Days)
N=14 (12 classified as new infections, and 2 as superinfections by the applicant, see footnote)
Patients Valid for Efficacy

Organism	Pt #/Sex/Age	Country	Race	Disease
E. cloacae	307008/M/10	Argentina	Caucasian	cUTI
	601039/F/8	Costa Rica	Hispanic	Costa Rica
E. coli	105024/F/9	Canada	Caucasian	cUTI
	701050/F/14	Mexico	Hispanic	Pyelonephritis
Enterococcus sp.	301045/F/5	Argentina	Caucasian	cUTI
	2001/M/14	United States	Caucasian	cUTI
E. faecalis	301150/F/6	Argentina	Caucasian	cUTI
	303001/F/9	Argentina	Caucasian	pyelonephritis
	8004/F/9	United States	Hispanic	cUTI
E. faecium	301012/F/11	Argentina	Caucasian	cUTI
	44030/F/4	United States	Caucasian	cUTI
Pantoea agglomerans	701017/M/15	Mexico	Hispanic	cUTI
P. aeruginosa	105002/M/3 $	Canada	Caucasian	cUTI
	12001/F/14* $	United States	Caucasian	cUTI
S. marcescens	12001/F/14* $	United States	Caucasian	cUTI

*patient with more than one superinfecting organism
$ patient had a new infection and superinfection. Classified by the applicant as a superinfection

The bacteriological eradication rates for all isolated organisms (excluding indeterminate and missing responses) are shown in Table 19.

TABLE 19
Eradication Rates by Organism at the Test-of-Cure Visit (+5 to +9 Days)
Patients Valid for Efficacy

	Ciprofloxacin	Comparator
Escherichia coli	156/178 (88%)	161/179 (90%)
Klebsiella pneumoniae	9/9 (100%)	10/10 (100%)
Pantoea agglomerans	4/4 (100%)	5/5 (100%)
Enterobacter cloacae	3/3 (100%)	1/2 (50%)
Proteus mirabilis	2/2 (100%)	5/5 (100%)
Proteus vulgaris	2/2 (100%)	2/2 (100%)
Enterococcus sp.	1/1 (100%)	0
Enterococcus faecalis	1/1 (100%)	1/2 (50%)
Enterobacteriaceae sp.	1/1 (100%)	0
Citrobacter freundii	1/1 (100%)	0
Klebsiella ozaenae	1/1 (100%)	1/1 (100%)
Morganella morganii	1/1 (100%)	1/2 (50%)
Pesudomonas fluorescens	1/1 (100%)	0
Staphylococcus saprophticus	1/1 (100%)	0
Streptococcus sp.	1/1 (100%)	0
Acinetobacter sp.	0	1/1 (100%)
Klebsiella oxytoca	0	3/3 (100%)
Pseudomonas aeruginosa	0	5/5 (100%)
Staphyloccocus aureus	0	1/1 (100%)
Streptococcus viridans group	0	1/1 (100%)
Serratia marcescens	0	1/1 (100%)

Clinical Reviewer's Comment: For the purposes of the analyses below, which were conducted by the reviewer, indeterminate and missing responses were counted as failures.

Although the subanalyses below present interesting results, it is difficult to make conclusions from the data due to the number of inter-related variables. For more information on individual patients with persistence, superinfection, or new infection, see Tables 18A through 18F above.

When analyzed by country of enrollment, eradication rates* were slightly lower than the overall rates in Mexico (75% [27/36] ciprofloxacin versus 81% [30/37] comparator) and Costa Rica (77% for both treatment groups [13/17] and [10/13]). Eradication rates were higher than the overall rates in Peru (90% [56/62] ciprofloxacin versus 93% [64/69] comparator). There was a larger difference between treatment group eradication rates in the United States (86% [19/22] ciprofloxacin versus 45% [13/29] comparator) than in the overall rates. This was due to the ciprofloxacin arm having no superinfections or new infections and the comparator arm having 6 superinfections and 3 new infections. Common organisms that

caused superinfection and new infection in the comparator arm were *Enterococcus faecalis* and *Enterococcus* sp.

There was also a larger difference between treatment group eradication rates* in Caucasians (86% [68/79] ciprofloxacin versus 67% [58/87] comparator) than in the overall rates. The eradication rates were lower for both treatment groups in Hispanics (75% [49/65] ciprofloxacin versus 77% [53/69] comparator) when compared to the overall rate, and higher for both treatment groups in the uncoded race subgroup (92% [60/65] ciprofloxacin versus 93% [68/73] comparator). In males, the comparator eradication rate was 79% [26/33], compared to 88% [28/32] in the ciprofloxacin group. Comparator drug performed worse than ciprofloxacin in all age groups except ≥ 2 years to < 6 years group (87% [65/75] versus 85% [70/82]. In the ≥ 12 month to <24 month age group, the comparator group had eradication rate of 83% [20/24] versus 92% [24/26] for the ciprofloxacin group. In the ≥ 6 years to <12 years group, the comparator had an eradication rate of 77% [85/111] versus 84% [77/92] for the ciprofloxacin group. In the ≥12 years, < 17 years the comparator had an eradication rate of 52% [11/21] versus 64% [7/11] for the ciprofloxacin group.

Eradication rates* were lower than the overall rates in both treatment groups for patients with cUTI (75% [69/92] ciprofloxacin versus 67% [63/94] comparator), and higher than the overall rates in both treatment groups for patients with pyelonephritis (92% [109/119] ciprofloxacin versus 86% [118/137] comparator). Ciprofloxacin had higher eradication rates as infection severity increased (76% [38/50] mild, 86% [126/146] moderate and 93% [14/15] severe) whereas comparator drug had similar rates for all infection severities (77% [43/56], 79% [134/169], and 67% [4/6] respectively).

As indicated by an asterisk (*) indeterminate and missing responses were counted as failures by the FDA Clinical Reviewer.

Bacteriologic Response at the Follow-up Visit

The bacteriological response at follow-up among patients valid for efficacy is shown in Table 20

Clinical Reviewer's Comment: Table 20 was created by the reviewer.

TABLE 20
Bacteriologic Response at the Follow-Up Visit (+28 to+42 Days)
Patients Valid for Efficacy

	Ciprofloxacin N=211	Comparator N=231
Continued Eradication	149 (70.6%)	147 (63.6%)
Eradication with Recurrence	11 (5.2%)	26 (11.3%)
Indeterminate	14 (6.6%)	18 (7.8%)
Superinfection	2 (0.9%)	9 (3.9%)
New Infection	12 (5.7%)	10 (4.3%)
Missing	1 (0.5%)	0 (0%)
Overall Eradication Rate*	149/196 (76%)	147/213 (69%)

* excluding indeterminate and missing results

The rate of eradication with recurrence was lower in the ciprofloxacin group (5.2%) than in the comparator group (11.3%) as was the rate of superinfection rates (0.9% for ciprofloxacin versus 3.9% for comparator). The new infection rate was similar in both treatment groups, with 5.7% of ciprofloxacin patients having new infections and 4.3% of comparator patients.

Twenty-three percent (23%; 49/211) of ciprofloxacin patients used post-therapy antimicrobials compared to 29% (66/231) of comparator patients. The two most common antimicrobials used were cephalexin (5% [10/211] ciprofloxacin versus 8% [18/231] comparator) and nitrofurantoin (6% [13/211] ciprofloxacin versus 8% [17/231] comparator).

11.25 Summary of Efficacy

Of the 689 patients randomized, 442 patients (211 in the ciprofloxacin group and 231 in the comparator group) were considered valid for efficacy. Overall, 58% (256/442) had pyelonephritis (56% [119/211] in the ciprofloxacin arm and 59% [137/231] in the comparator arm) 42% (186/442) had cUTI (44% [92/211] in the ciprofloxacin arm and 41% [94/231] in the comparator arm). *Escherichia coli* was the most frequently isolated pre-therapy infection-causing organism. Patients less than or equal to 5 years comprised 51% (108/211) of patients in the ciprofloxacin group and 43% (99/231) of patients in the comparator group. No substantial differences in demographics or baseline disease characteristics were noted between the treatment groups.

The mean (± standard deviation) total treatment duration (comprised of oral and IV duration) in the valid for efficacy population was 11.9 ± 2.6 days (range 3 to 22 days) in the ciprofloxacin group and 11.8 ± 2.5 days (range 5 to 22 days) in the comparator group.

The clinical cure rate at the Test-of-Cure (TOC) visit (5 to 9 days after the end of therapy) was the primary endpoint. Clinical cure in patients valid for efficacy was 96% [202/211] in the ciprofloxacin group and 93% [214/231] in the comparator group. The 95% confidence interval for the treatment difference in clinical cure rate

(-1.3%, 7.3%) indicated that ciprofloxacin in the treatment of pediatric patients with cUTI or pyelonephritis, is non-inferior to the comparator.

The treatment group comparisons for clinical cure at the TOC visit were consistent between Stratum I and II (the oral and IV therapy groups, respectively) for ciprofloxacin and the comparator. The p-value from the Breslow-Day test for treatment by disease stratum/treatment type interaction was 0.761, indicating that the treatment group differences across treatment types were not significantly inconsistent.

The bacteriological eradication rate at the test of cure visit in patients valid for efficacy was 84% [178/211] in the ciprofloxacin group and 78% [181/231] in the comparator group. The 95% confidence interval for the treatment difference in eradication rate (-1.3%, 13.1%) indicated that ciprofloxacin is non-inferior to the comparator in the treatment of pediatric patients with cUTI or pyelonephritis.

Clinical cure rates and bacteriological eradication rates were not substantially impacted by age, race, or sex.

11.26 SAFETY RESULTS

Of the 689 patients enrolled into the study, 684 received at least one dose of study drug. For 5 patients (2 in the ciprofloxacin group and 3 in the comparator group), it could not be confirmed whether study drug was taken.

The distribution of patients by age group is shown in Table 21. Patients less than or equal to 5 years comprised 48% (160/335) of patients in the ciprofloxacin group and 46% (159/349) of patients in the comparator group.

TABLE 21
Age Distribution of Patients Valid for Safety

	Ciprofloxacin N = 335	Comparator N = 349
≥1 year < 2 years	36 (10.7%)	41 (11.7%)
≥2 years < 6 years	124 (37.0%)	118 (33.9%)
≥6 years < 12 years	143 (42.7%)	153 (43.8%)
≥12 years <17 years	32 (9.6%)	35 (10.0%)
17 years	0	2 (0.6%)

Tables 22A and 22B summarize treatment duration and dosing information, respectively, for patients valid for safety. The mean duration and number of doses were similar in both treatment groups.

Clinical Reviewer's Comment: Tables 22A and 22B were created by the reviewer.

TABLE 22A
Treatment Duration
All Patients Valid for Safety

	Days ± Std Dev (Range)	
	Ciprofloxacin N=335	Comparator N=349
Total Treatment Duration	10.6 ± 3.8 (1.0 to 22.0) N=335	10.9 ± 3.5 (1.0 to 23.0) N=345
Duration of Oral Therapy	10.3 ± 3.7 (1.0 to 22.0) N=323	10.7 ± 3.3 (1.0 to 22.0) N=332
Duration of IV Therapy	5.3 ± 3.0 (2.0 to 14.0) N=40	5.0 ± 3.4 (1.0 to 15.0) N=45

TABLE 22B
Dosing Information
All Patients Valid for Safety

	Days ± Std Dev (Range)	
	Ciprofloxacin N=335	Comparator N=349
Total Number of Doses	22.9 ± 14.3 (1.0 to 123.0) N=335	23.8 ± 14.9 (1.0 to 161.0) N=345
Number of Capsules	22.1 ± 12.5 (1.0 to 111.0) N=323	23.1 ± 13.5 (1.0 to 158.0) N=332
Number of IV Doses	13.5 ± 10.0 (3.0 to 42.0) N=40	12.1 ± 10.2 (1.0 to 43.0) N=45

Clinical Reviewer's Comment: The applicant was asked to provide additional information on the 40 patients who were switched from IV to oral ciprofloxacin. The following table was compiled by the applicant using information recorded in the pharmacy log at each investigator site. The doses for IV ciprofloxacin are within the range specified by the protocol (i.e., 6 to 10 mg/kg). No guidance was provided to investigators in the protocol on how to switch patients from IV to oral dosing, but the oral doses selected are also within the range specified by the protocol (i.e., 10 to 20 mg/kg).

Patient Number	*Body Weight (kg)*	*Dose/Regimen IV as Recorded in Pharmacy Log*	*IV Dose in mg/kg (calculated by Bayer)*	*Dose/Regimen PO as Recorded in Pharmacy Log*	*PO Dose in mg/kg (calculated by Bayer)*	*Comments*
2032	*14.3*	*143mg*	*10*	*none prescribed*		
8015	*48.5*	*400 mg q 8h*	*8.25*	*none prescribed*		
11002	*17.2*	*160mg TID*	*9.3*	*225mg BID*	*13.1*	
11005	*22.1*	*130mg*	*5.9*	*250 mg BID*	*11.3*	
12008	*9.7*	*58.2 mg q 8h*	*6*	*100 mg q 12h*	*10.3*	
13016	*22.7*	*220 mg IV q 8 hr*	*9.7*	*300 mg q 12*	*13.2*	
13018	*46.5*	*400 mg IV q 8 hr*	*8.6*	*13.5 ml q 12*	*14.5*	
13025	*14.8*	*100 mg IV q8*	*6.8*	*225 mg q12*	*15.2*	
13038	*40.5*					*Info missing*
13040	*31.6*	*190 mg q 8*	*6*	*9ml (BID x 20 doses)*	*14.2*	
13047	*38.2*	*380mg q 8*	*9.9*	*600mg q 12 x 10 days*	*15.7*	
15028	*27.3*	*273 mg q 8*	*10*	*558mg q 12h*	*20.4*	
15047	*14.5*	*145 mg q 8h*	*10*	*290mg q 12*	*20*	
16001	*45.8*	*400mg q 8 h*	*8.7*	*none prescribed*		
26018	*22*	*220mg x 2*	*10*	*none prescribed*		
32017	*19.7*					*Info missing*
38006	*20.9*	*209mg*	*10*			*oral dose not provided*
40001	*18.3*	*183mg q 8 h*	*10*	*none prescribed*		
44004	*31.9*	*250mg q 8h*	*7.8*	*none prescribed*		
44060	*34.5*	*300mg/300ml q 8 h*	*8.7*	*none prescribed*		
102003	*47.1*	*165 mg q8*	*3.5*			*oral dose not provided*
102006	*19.5*	*140 mg q 8 h*	*7.2*	*none prescribed*		
105021	*29*	*232 mg q 8 h*	*8*	*435 mg q 12h*	*15*	
201004	*21.6*	*21.6 ml in 100ml saline q 8hr*		*4.3 ml BD for 10 days*	*10*	
303010	*8.9*	*6 mg/Kg - 53 mg/8hr*	*6*	*10 mg/kg - 95 mg/12 hr*	*10.7*	
303026	*22.2*	*10 mg/Kg - 220 mg/8hr*	*10*	*15 mg/Kg - 330 mg/12 hr*	*14.9*	
304001	*28.5*	*Total dose 280 mg/8 hr*	*9.8*	*Total dose 500 mg/12 hr*	*17.5*	
305007	*12.6*	*9.5 mg/Kg - 120 mg/8hr*	*9.5*	*10 mg/kg - 125 mg/12 hr*	*9.9*	
307002	*20.5*	*6 mg/Kg*	*6*	*none prescribed*		
401011	*35*	*10 mg/Kg - 350 mg/8hr*	*10*	*15 mg/Kg - 500 mg/12 hr*	*14.3*	
401018	*15.5*	*10mg/kg - 155 mg/8hr*	*10*	*15 mg / Kg - 240 mg/12hr*	*15.5*	

Patient Number	*Body Weight (kg)*	*Dose/Regimen IV as Recorded in Pharmacy Log*	*IV Dose in mg/kg (calculated by Bayer)*	*Dose/Regimen PO as Recorded in Pharmacy Log*	*PO Dose in mg/kg (calculated by Bayer)*	*Comments*
401039	*8.4*	*10 mg/Kg - 84 mg/8hr*	*10*	*15 mg / Kg - 126 mg/12 hr*	*15*	
401050	*9.9*	*10 mg /Kg - 99 mg/8hr*	*10*	*15 mg / Kg - 148.5 mg/12 hr*	*15*	
501001	*23.5*	*141mg*	*6*			*oral dose not provided*
502003	*51.9*	*100mg dose (=60ml) q 8 hr*	*1.9*	*500mg =10ml dose q12h*	*19*	
505010	*53*	*22.2 mg/kg/d*		*28 mg/kg/d*		
506014	*61*					*Info missing*
601022	*21*					*Info missing*
601079	*40*					*Info missing*
705007	*8.7*					*Info missing*

11.26.1 Analysis of Adverse Event Rates

A brief overview of patients who experienced adverse events through the 1-year follow-up are shown in Table 23.

TABLE 23
Overview of Adverse Events
Patients Valid for Safety

	Ciprofloxacin N = 335	Comparator N = 349
Died	1 (0.3%)	1 (0.3%)
Any Adverse Event Up to 1 Year	151 (45%)	124 (36%)
Any Drug-Related Adverse Event Up to 1 Year	53 (16%)	44 (13%)
Any Serious Adverse Event	25 (8%)	20 (6%)
Discontinuation due to an Adverse Event[a]	10 (3%)	5 (1%)

[a] two ciprofloxacin patients and one comparator patient had adverse events with the action taken of "study drug permanently discontinued", but did not have the reason for termination of study drug as an adverse event on the end of study page of the CRF

Rates of adverse events, drug-related events, serious adverse events, and premature discontinuations due to adverse events were all slightly higher in the ciprofloxacin group than the comparator group.

11.26.2 Overview of Arthropathy Adverse Events

At the end of the study (i.e., through one year of follow-up) there were 116 patients identified using the arthropathy algorithm. Four patients were initially identified by the algorithm and were reviewed by the IPSC. Due to changes and clarifications of patient data, these patients were removed by the applicant. The patient data that changed was the following:

- Patient 307206 initially had an adverse event (AE) of arthralgia that was later clarified to dorsolumbar pain.
- Patient 309018 and Patient 402018 initially had AEs of elbow pain and knee pain, respectively. These AEs were later removed by the investigators as the conditions were considered pre-existing medical history.
- Patient 504009 had a joint examination considered abnormal with "other" as a finding. The "other" was queried and was determined to be related to placement of an IV in the hand. The appearance of the joint was normal and the CRF was clarified.

Clinical Reviewer's Comment: The reviewer agrees with the applicant's removal of these 4 patients from the arthropathy algorithm, as they do not appear to be true arthropathies, as defined by the protocol.

An additional 21 patients were identified by the applicant that had not already been identified by the algorithm at the end of the study (i.e., patients with adverse events potentially related to musculoskeletal events).

In total, 141 cases were reviewed by the IPSC. There were 70 patients from the algorithm and 12 patients from the additional cases that were considered by the IPSC to have at least possible arthropathy.

Clinical Reviewer's Comment: Of the 141 patients reviewed by the IPSC, 4 were excluded from the statistical analyses, 57 were deemed not to have arthropathy, and an additional 2 patients (90002 and 37002) were excluded from the applicant's statistical analyses because their events occurred pre-treatment (i.e., were pre-existing). The reviewer agrees with the removal of these patients. In total, 79 patients were deemed by the IPSC to have possible, probable, or definite arthropathy. The committee was blinded to study treatment. A break down of cases by treatment received can be found in Tables 20 and 21 in Appendix 1. There were 46 cases of arthropathy in the ciprofloxacin arm and 33 in the comparator arm by one year of follow-up.

11.26.3 Arthropathy Adverse Events Occurring by Day +42 of Follow-up

The primary analysis variable was arthropathy rate by the follow-up visit (Day +28 to +42), as assessed by the IPSC.

The arthropathy event rates occurring by Day +42 within oral treatment type/disease stratum were 9% (27/296) ciprofloxacin versus 7% (21/304) comparator [95% CI of the difference -2.8%, 7.4%] and within IV treatment type/disease stratum 10% (4/39) ciprofloxacin versus 0% (0/45) comparator [95% CI of the difference -0.4%, 26.3%]. The p-value from the Breslow-Day test for treatment by treatment route interaction was marginally statistically significant at 0.065, indicating that the treatment

group differences across treatment routes were not completely consistent.

Clinical Reviewer's Comment: The one year arthropathy rates by treatment type/disease stratum do not show a statistically significant result (p-value 0.7544). Systemic exposure to ciprofloxacin was similar between the patients receiving IV and oral drug. In addition, only 11 of the 39 patients received IV ciprofloxacin for the entire duration of treatment. The others were stepped down to oral therapy after a mean of 5 days. Therefore, the clinical significance of this statistical result is felt to be minimal by the reviewer.

A summary of the combined oral and IV results for ciprofloxacin and comparator is shown in Table 23 along with the 95% confidence interval of the difference.

TABLE 23
Arthropathy Rate by Day +42 Follow-Up
Patients Valid for Safety

Arthropathy	Ciprofloxacin (N=335)	Comparator (N=349)
Yes	31 (9.3%)	21 (6%)
No	304 (91%)	328 (94%)
95% Confidence Interval	(-0.8%, 7.2%)	

The protocol stated that if the upper limit of the confidence interval for the difference in arthropathy rates was less than 6%, then non-inferiority would be concluded. Since the upper limit of the confidence interval was greater than 6% (i.e., 7.2%), it cannot be concluded that ciprofloxacin is non-inferior to the comparator.

Tables 24 and 25 in Appendix 1 detail the ciprofloxacin and comparator cases of arthropathy, respectively, that occurred by Day +42 of follow-up.

Clinical Reviewer's Comment: Tables 24 and 25 in Appendix 1 were created by the reviewer. In the reviewer's assessment, there were 30 patients who experienced adverse events by Day +42. Of these patients, 5 also experienced events after Day +42. The reviewer moved one ciprofloxacin patient from the Day +42 to one year grouping based on a reassessment of when the event occurred. In the comparator arm, 21 patients experienced events before Day +42 and 1 also experienced another event after Day +42.

Table 26 summarizes arthropathy by Day +42 follow-up by selected baseline characteristics in patients valid for safety.

Clinical Reviewer's Comment: Table 26 was created by the reviewer.

Arthropathy rates were slightly lower than the overall rates in Mexico (0% both treatment groups) and Peru (2% ciprofloxacin versus 3% comparator). There was a much bigger difference between treatment group arthropathy rates in the United States (21% ciprofloxacin versus 11% comparator) than in the overall rates. The arthropathy rate was higher than the overall rate in Caucasians (14% ciprofloxacin versus 10% comparator) and lower than the overall rate in Hispanics (8% ciprofloxacin versus 3% comparator) and the "uncodable" race group (5% ciprofloxacin versus 3% 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 ≥12 year to <17 year age group, where the rate was 22% for ciprofloxacin patients and 14% for comparator patients. Theoretical reasons for this difference posed by the applicant for explaining the higher rate in the older patients are: greater physical activity, more accurate ability to report pain, and greater weight across weight-bearing joints of adolescents versus younger children.

Arthropathy was also more common in cUTI patients (12.2% ciprofloxacin; 9.6% comparator) than pyelonephritis patients (6.4% ciprofloxacin; 2.7% comparator). Theoretical reasons proposed by the applicant for these differences could be differences in concomitant medications, in age, in pre-existing joint problems, in infection-associated arthropathy and in duration of infection.

Clinical Reviewer's Comment: The applicant has proposed multiple reasons for the differences between older and younger children and between cUTI and pyelonephritis patients. All proposed reasons are potentially valid, but it is not possible to identify the true cause of the differences, due to the nature of the data collection and because many of the variables are correlated with each other.

TABLE 26
Rate of Arthropathy at Day +42 Follow-Up by Selected Baseline Characteristics
Patients Valid for Safety

Arthropathy -Yes	Ciprofloxacin (N=335)	Comparator (N=349)
All Patients	31 (9.3%) N=335	21 (6.0%) N=349
Country		
Argentina	8 (10.4%) N=77	7 (8.9%) N=79
Canada	1 (12.5%) N=8	1 (9.1%) N=11
Costa Rica	4 (19.0%)	0

Arthropathy -Yes	Ciprofloxacin (N=335)	Comparator (N=349)
	N=21	N=20
Germany	1 (7.7%) N=13	1 (9.1%) N=11
Mexico	0 N=56	0 N=60
Peru	2 (2.3%) N=87	3 (3.4%) N=88
United States	13 (21.0%) N=62	8 (11.3%) N=71
South Africa	2 (18.2%) N=11	1 (11.1%) N=9
Race		
Caucasian	18 (13.8%) N=130	13 (9.7%) N=134
Black	0 N=5	1 (14.3%) N=7
Asian	0 N=3	1 (16.7%) N=6
Hispanic	8 (7.8%) N=102	3 (2.8%) N=109
Uncoded	5 (5.3%) N=95	3 (3.2%) N=93
Sex		
Male	6 (9.7%) N=62	4(6.2%) N=65
Female	25 (9.2%) N=273	17 (6.0%) N=284
Age Group		
≥ 12 months < 24 months	1 (2.8%) N=36	0 N=41
≥ 2 years <6 years	5 (4.0%) N=124	3 (2.5%) N=118
≥ 6 years < 12 years	18 (12.6%) N=143	12 (7.8%) N=153
≥ 12 years <17 years	7 (21.9%) N=32	5 (14.3%) N=35
≥ 17 years	0 N=0	1 N=2
Infection Type		
cUTI	20 (12.2%) N=164	16 (9.6%) N=166
Pyelonephritis	11 (6.4%) N=171	5 (2.7%) N=183
Route of Treatment		
Oral	27 (9.1%) N=296	21 (6.9%) N=304
IV	2 (18.2%)	0

Arthropathy -Yes	Ciprofloxacin (N=335)	Comparator (N=349)
	N=11	N=13
Sequential	2 (7.1%) N=28	0 N=32

11.26.4 Arthropathy Adverse Events Occurring Through One Year of Follow-up

The arthropathy rate for all data available (approximately 1 year after study drug) was 13.7% (46/335) in the ciprofloxacin group and 9.5% (33/349) in the comparator group. In the patients on oral drug, the rates were 13.5% (40/296) for ciprofloxacin and 9.5% (29/304) for comparator. In the IV stratum, the rates were 15.4% (6/39) for ciprofloxacin and 8.9% (4/41) for comparator.

Clinical Reviewer's Comment: Tables 27 and 28 in Appendix 1 were created by the reviewer and list the 21 ciprofloxacin and 13 comparator patients, respectively, with arthropathy occurring between Day +42 and one year of follow-up, as assessed by the IPSC. Of these, 5/21 ciprofloxacin patients and 1/13 comparator patients had an event(s) occurring by Day +42 as well as an event(s) occurring between Day +42 and one year.

In order to understand the arthropathy cases further, additional analyses were performed by the FDA Clinical Reviewer.

Clinical Reviewer's Comment: Tables 29 through 38 were created by the reviewer.

Table 29 shows the musculoskeletal findings which were experienced by patients with arthropathy, as determined by the IPSC.

TABLE 29
Arthropathy Rate in Patients Valid for Safety

	Ciprofloxacin (N=335)	Comparator (N=349)
Cumulative Arthropathy rate at one year of follow-up	**46 (13.7%)**	**33 (9.5%)**
95% Confidence Interval*	(-0.6, 9.1%)	

TABLE 29 (continued)
Arthropathy Rate in Patients Valid for Safety

Musculoskeletal Findings Reported by 1 year of Follow-up**		
Arthralgia	**35**	**20**
Knee	11 (3/11 AT)	5 (1/5 PE)
Elbow	6	0
Ankle	5 (2/5 AT)	5 (1/5 AT)
Wrist	4	1 (PE)
Hip	4	2
Unspecified	3 (1/3 AT)	3
Shoulder	2	2
Knee and Ankle	0	2
Accidental Injury	**6 (6/6 AT)**	**1**
Knee bruise	1	0
Articular hypermotility	1 (worsening of PE)	1 (worsening of PE)
Joint hypermobility	1	0
Knee ligaments pulled/strained	1	0
Sprained ankle	1	0
Foot trauma	1	0
Lateral-collateral ligament injury	1	0
Ankle injury	1	0
Leg Pain	**5**	**1**
Unspecified	3	1
Arch collapse	1 (AT)	0
Plantar surface heel pain	1 (AT)	0
Back pain	**4**	**0**
Lumbar pain	1	0
Thoracic spine pain	1	0
Unspecified	2	0
Arthrosis	**4**	**1**
Ankle effusion or swelling	3	1 (AT)
Knee swelling	1	0
Bone Pain	**3**	**0**
Cervical spine pain	1	0
Thoracic spine pain	1	0
Coccyx pain	1	0
Joint Disorder	**2**	**0**
Ankle warmth or stiffness	2 (1/2 discounted by IPSC)	0
Pain	**2**	**2**
Growing pains	1	1 (worsening of PE)
Foot pain	1	1

TABLE 29 (continued)
Arthropathy Rate in Patients Valid for Safety

Myalgia	**1**	**4**
Fibromyalgia	1	1
Quadriceps pain	0	1
Rib pain	0	1
Coxalgia	0	1
Unspecified	0	1
Arm Pain	**0**	**2 (1/2 AT)**
Pyogenic arthritis	**1 (AT)**	**0**
Viral Infection (i.e., fever, rash, ankle arthralgia and swelling)	**1**	**0**
Myasthenia	**1**	**0**
Hand pain	**1**	**0**
Musculoskeletal Congenital Anomaly	**1**	**0**
Hypotonia	**1**	**0**
Leg cramps (i.e., stiff knees)	**1**	**0**
Rash (i.e., knee redness)	**1 (AT)**	**0**
Movement Disorder (i.e., hip movement or rotation reduced)	**1**	**1**
Peripheral Edema (i.e., ankle swelling)	**1 (AT)**	**0**
Abnormal Gait	**0**	**1**
Tendon Disorder (i.e., Achilles tendon ache)	**0**	**1**
Abnormal Gait Exam	**1**	**2**
Knees ± ankles and feet	0	2
Unspecified	1	0
Abnormal Joint Exam	**10**	**6**
Pain/tenderness	3	5
Knee	1	0
Hip and ankle	1 (PE)	0
Ankle ± foot	1	1
Shoulder	0	1 (AT)
Pubic	0	1 (worsening of PE)
Elbow	0	1 (PE)
Hip	0	1
Redness and/or warmth	5	1
Ankle	2	1 (discounted by IPSC)
Hip	1	0
Knee	2	0
Swelling (i.e., ankle and/or foot)	2	0

Footnote to Table 29 (Arthropathy Rate in Patients Valid for Safety)
* 95% Confidence Interval for the difference between treatment groups (ciprofloxacin minus comparator) in the proportion of patients with arthropathy weighted by initial route of administration. Patients treated with ciprofloxacin were found to have an increased rate of arthropathy compared to patients treated with the non-quinolone comparator. The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the comparator group by more than 6.0%. Since the 95% confidence interval indicated that the arthropathy rate in the ciprofloxacin group could be up to 7.2% higher than that of the comparator group, the safety objective was not met.
** a patient with arthropathy may have had more than one finding
PE = pre-existing
AT = accidental trauma

Table 30 shows the arthropathy rates by country of enrollment. The highest rate of arthropathy for both treatment arms is in the United States. The US was one of the top enrolling countries, but when calculated as a percentage of the population enrolled, the US still has the highest rate of arthropathy for ciprofloxacin.

TABLE 30
Arthropathy Rates by Country of Enrollment

	Number of Events out of the Safety Population by Country for Each Study Arm (%)	
Country	Ciprofloxacin N=46	Comparator N=33
Argentina	12/77 (16%)	9/79 (11%)
Canada	1/8 (13%)	2/11 (18%)
Costa Rica	4/21 (19%)	0
Germany	1/13 (8%)	3/11 (27%)
Mexico	2/56 (4%)	0
Peru	3/87 (3%)	5/88 (6%)
United States	20/62 (32%)	13/71 (18%)
South Africa	2/11 (18%)	1/9 (11%)

Table 31 shows the arthropathy rates by sex of the patient. The high percentage of females in both groups is reflective of the fact that the approximately 85% of the entire study population in is female.

TABLE 31
Sex Distribution of Patients with Arthropathy

	Ciprofloxacin N=46	Comparator N=33
Females	38 (83%)	30 (91%)
Males	8 (17%)	3 (9%)

Table 32 shows the age distribution of patients with arthropathy out of all patients enrolled into the study.

TABLE 32
Rate of Arthropathy Through 1 Year of Follow-Up in Patients Valid for Safety

Arthropathy	Ciprofloxacin	Comparator
All Patients	46/335 (13.7%)	33/349 (9.5%)
Age Group		
≥ 12 months < 24 months	2/36 (5.6%)	0/41
≥ 2 years <6 years	9/124 (7.3%)	6/118 (5.1%)
≥ 6 years < 12 years	28/143 (19.6%)	18/153 (11.8%)
≥ 12 years to 17 years	7/32 (21.9%)	9/35 (25.7 %)

There were 6 cases of arthropathy (13%; 6/46) occurring in ciprofloxacin patients in Stratum II (i.e., those who received IV or sequential therapy) by the end of one year of follow-up. Four of the 6 patients had an event(s) occurring by Day +42.

Four cases of arthropathy (12%; 4/33) occurred in comparator patients in Stratum II by the end of one year of follow-up. All 4 events occurred between Day +42 and one year. No cases occurred by Day +42.

Of note, there were few patients enrolled into Stratum II in the overall study population (39 in the ciprofloxacin arm and 45 in the comparator arm).

Of the 46 patients with arthropathy in the ciprofloxacin arm, radiological testing of the affected joint was reported for 9 patients. Eight patients had X-rays and two patients had an MRI (one patient had both an X-ray and MRI). X-ray results were negative in 6 patients and included: hip for abnormal gait (Patient 301213), lumbosacral area for lumbar pain (302026), hips and spinal cord for back pain and thoracic spine pain (307004), leg (i.e., ankle, knee, and feet) for growing pains (309014), ankle for swelling (307006), and knee (3 different X-rays at 3 different times) for pyogenic arthritis secondary to a nail puncture wound (306054). One patient had an X-ray of both knees (307015) for pain and swelling and the findings were “bilateral genu valgum”, which was a pre-existing condition for that patient. Another patient (16001) had an ankle X-ray for pain which showed “lateral soft tissue swelling, no radiological evidence of definite osseous abnormality.” This patient (16001) also had an MRI performed of the ankle, which was normal. One other patient (2015) had an MRI performed for ballotable fluid on the knee. The MRI was normal with a small amount of fluid present.

Of the 33 comparator patients, one patient (37001) had an X-ray for ankle pain and the results were negative. Another patient (401047) had an X-ray of both knees performed for oligoarthralgia, which was also negative.

The breakdown of the arthropathy assessment by the IPSC (i.e., definite, probable, or possible arthropathy) is shown in Table 33A for ciprofloxacin and comparator. In addition, for each arthropathy classification, it is noted the number of cases which were probably, possibly, or not related to study drug. The arthropathy cases in the ciprofloxacin group were nearly equally divided between definite and possible, with a minority of probable cases. In contrast, most cases in the comparator group were possible arthropathies.

TABLE 33A
Arthropathy Classification and Corresponding Relationship to Study Drug (as determined by IPSC)

Classification	Ciprofloxacin N=46	Comparator N=33
Definite	21 (46%) 4 were probably related to study drug; 9 possibly related, and 8 not related	9 (27%) none were probably related to study drug; 4 were possibly related; 5 were not related
Probable	5 (11%) 2 were probably related to study drug; 2 were possibly related; and 1 was not related	4 (12%) 2 were probably related to study drug; 1 was possibly related; and 1 was not related
Possible	20 (43%) 1 was probably related to study drug; 13 were possibly related; and 6 were not related	20 (61%) 1 was probably related to study drug; 12 were possibly related to study drug; and 7 were not related

Table 33B shows the reverse relationship as shown in Table 33A. In Table 33B the cases for ciprofloxacin and comparator are grouped by relationship to study drug (i.e., probably, possibly, or not related) and then the corresponding arthropathy classification is given (i.e., definite, probable, or possible arthropathy). The majority of cases in each treatment group were possibly related to study drug.

TABLE 33B
Relationship to Study Drug and Corresponding Arthropathy Classification
(as determined by IPSC)

Relationship	Ciprofloxacin N=46	Comparator N=33
Probable	7 (15%) 4 were definite arthropathies; 2 were probable; and 1 was possible	3 (9%) none were definite arthropathies; 2 were probable; and 1 was possible
Possible	24 (52%) 9 were definite arthropathies; 2 were probable; and 13 were possible	17 (52%) 4 were definite arthropathies; 1 was probable; and 12 were possible
None	15 (33%) 8 were definite arthropathies; 1 was probable; and 6 were possible	13 (39%) 5 were definite arthropathies 1 was probable; and 7 were possible

The severity of arthropathy events is shown in Table 34. Since many patients had more than one event, they were classified by the reviewer based upon the most severe event.

TABLE 34
Severity of Arthropathy Events

Severity of Event	Ciprofloxacin N=46 patients*	Comparator N=33 patients
Mild	35	22
Moderate	3	2
Severe	3 2 patients with 3 events Pt 2015: L hip arthralgia and bilateral knee pain (definite arthropathy; possibly related to study drug) Pt 14001: R knee ligaments pulled/strained due accidental trauma, skiing accident (definite arthropathy; possibly related to study drug)	1 Patient 2012: myalgias and was diagnosed by a rheumatologist as having fibromyalgia (definite arthropathy; no relation to study drug)
No information	5	8

There were only two serious arthropathy events (in one patient each) which occurred during the study and both patients were in the ciprofloxacin group as shown in Table 35. Both events were classified by the IPSC as definite arthropathy. Of note, both patients had other events which were not serious. The IPSC assessment was based on the totality of the events.

TABLE 35
Serious Arthropathy Adverse Events

Ciprofloxacin N=46 patients	Comparator N=33 patients
Pyogenic arthritis of R knee secondary to nail wound (definite arthropathy, probably related to study drug) [Pt. 306054]	None
Viral syndrome with arthralgia possibly related to Rubeola (definite arthropathy, not related to study drug) [Pt. 307006]	

In the ciprofloxacin group, there were no tendon disorders noted. There was one ligament injury (Pt. 16014) which occurred secondary to a soccer injury. In the comparator group, there was one tendon disorder noted. Patient 301089 had a right Achilles tendon ache, no history of trauma (possible arthropathy; possibly related to study drug).

The relative start of an arthropathy event in relation to the last dose of medication was calculated for all events. As each patient may have had more than one event, the numbers reflect the total number of events, and not patients. In the ciprofloxacin group the mean relative start of an arthropathy event was 102 days (range -12 to 404) and 81 days (range -11 to 363) for comparator.

Table 36 shows the arthropathy events which developed while the patient was still receiving study medication. Of the patients with arthropathy, similar percentages (26% for ciprofloxacin and 30% for comparator) developed arthropathy before the end of treatment with study drug.

TABLE 36
Patients with Arthropathy Developing During Study Drug Administration

Ciprofloxacin N=46 patients		Comparator N=33 patients	
12/46 (26%)		10/33 (30%)	
Pt. Number	Description	Pt. Number	Description
307006	Viral syndrome with arthralgia	1041	Arthralgia in knees while squatting
309007	Bilateral hip warmth	1051	Arthralgia/abnormal gait, difficulty walking
601052	Arthralgia	15059	Arm pain and R elbow pain
601091	L hip pain	23007	Bilateral shoulder tenderness
601104	L leg pain	26001	L ankle swelling (soccer injury)
1003	R ankle warmth and R ankle effusion	40003	Ankle pain, guarding in foot
1040	L ankle and foot redness	102002	Bilateral ankle redness
16001*	R ankle pain	204016	L shoulder warmth, pain, tenderness, bruising (pt fell off a chair)
16010	Bilateral ankle swelling	307020	Wrist pain
19004	Bilateral ankle stiffness	402027	myalgia
27001	Bilateral swelling of ankles/feet		
40001*	Knee swelling		

*Patient in Stratum II (IV or sequential therapy)

The reviewer noted that there were many arthropathy events which occurred as a result of “accidental trauma”, which for the purposes of this review is defined as a specific traumatic event which caused the patient injury. Of the patients with arthropathy, twice as many ciprofloxacin patients as comparator patients (i.e., 24% versus 12%) developed an arthropathy event as a result of a traumatic injury, as shown in Table 37.

TABLE 37
Arthropathy Events Associated with "Accidental Trauma"

Ciprofloxacin N=46 patients					Comparator N=33 patients				
11/46 (24%)					4/33 (12%)				
Pt. #/Age (yrs)/Country			Description	Rel Start to End of Tx	Pt. #/Age (yrs) /Country			Description	Rel Start to End of Tx
309001	13	ARG	Bruised knee (pt. hit knee on bed)	24	1041	12	US	R ankle pain (pt. hit ankle on a metal bar while swinging)	1
309019*	7	ARG	Arthralgia (pt. hit while playing)	5	13011#	7	US	Elbow pain (pt. fell)	363
601043	6	CR	Arthralgia in knees (pt. fell down)	28	26001*	12	US	R ankle swelling (pre-existing soccer injury)	-6
1031	10	US	R foot arch collapse (pt. twisted ankle)	87	204016	2	SA	R shoulder warmth, pain, tenderness, bruising (pt. fell from a chair)	-9
8001	5	US	L ankle swelling (pt. tripped and rolled ankle)	125					
13038#	12	US	R knee redness (pt. fell)	6					
13047#	9	US	Bilateral knee pain (pt. fell off bike)	199					
14001	15	US	R knee and ankle sprained (pt. fell while skiing)	29					
16001#	12	US	R ankle pain (pt. fell)	27					
16014**	12	US	L foot trauma, R knee pain, heel pain (horse stepped on pt.'s foot and multiple soccer injuries)	102 74 23					
206001	1	SA	R ankle swelling (pt. sprained ankle)	10					
Mean of Relative Start to End of Treatment 59 days					Mean of Relative Start to End of Treatment 87 days				

Ciprofloxacin N=46 patients			Comparator N=33 patients		
11/46 (24%)			4/33 (12%)		
Pt. #/Age (yrs)/Country	Description	Rel Start to End of Tx	Pt. #/Age (yrs) /Country	Description	Rel Start to End of Tx
(range 5 to 199) MEDIAN 28.5 days			(range -9 to 363) MEDIAN 2.5 days		

* patient also had an event related to physical exercise
** patient also had two other events which occurred >365 days after the end of the study and are not included here
#Patient in Stratum II (IV or sequential therapy)

In addition to the events related to traumatic injury, the reviewer also noted that events were associated with strenuous physical activity (PA) or physical exercise (PE). Table 38 shows the cases for ciprofloxacin and comparator. Of the patients with arthropathy, there was approximately an equal distribution of events associated with PA or PE in both groups (i.e., 13% vs. 15%).

TABLE 38
Arthropathy Events Associated with Physical Activity (PA) or Exercise (PE)

Ciprofloxacin N=46 patients				Comparator N=33 patients			
6/46 (13%)				5/33 (15%)			
Pt. #/Age (yrs)/Country			Description	Pt. #/Age (yrs) /Country			Description
309019*	13	ARG	Elbow pain (pt. doing PE the day prior)	26001*	12	US	R ankle pain (sports activity)
402049	8	PERU	Coxalgia (playing basketball and martial arts the day prior)	37001	4	US	L ankle pain (running)
1001	5	US	Generalized joint pain (increased PA)	40003	6	US	Bilateral hip pain (running)
1021	10	US	Bilateral wrist tenderness/discomfort (playing volleyball)	309015	8	ARG	Quadriceps pain (excessive playing)
27001	6	US	Bilateral swelling of ankle/foot (gymnastics)	502008#	9	GER	R ankle pain (pt. playing soccer the day prior)
27003	8	US	Bilateral elbow pain (“sports activities’”)				

* patient also had an event related to accidental trauma
#Patient in Stratum II (IV or sequential therapy)

11.26.5 All Adverse Events Occurring by Day +42

All adverse events grouped by body system occurring by Day +42 and those experienced by at least 2% of patients in at least one treatment group are shown in Tables 39 and Table 43, respectively.

TABLE 39
Adverse Events by Day +42 by Body System
Patients Valid for Safety

Body System	Ciprofloxacin (N=335)		Comparator (N=349)	
Any body system	138	(41%)	109	(31%)
Body as a Whole	46	(14%)	36	(10%)
Cardiovascular	7	(2%)	3	(<1%)
Digestive	50	(15%)	31	(9%)
Hemic and lymphatic	9	(3%)	8	(2%)
Metabolic & nutritional	2	(<1%)	2	(<1%)
Musculoskeletal	24	(7%)	14	(4%)
Nervous	9	(3%)	7	(2%)
Respiratory	23	(7%)	28	(8%)
Skin and appendages	10	(3%)	14	(4%)
Special senses	3	(<1%)	1	(<1%)
Urogenital	27	(8%)	21	(6%)

The overall adverse event rate by Day +42 was 41% (138/335) in the ciprofloxacin group versus 31% (109/349) in the comparator group. Under Body as a Whole, the Day +42 event rates were 14% (46/335) in the ciprofloxacin group versus 10% (36/349) in the comparator group. The largest difference between treatment groups (data not shown) in the Body as a Whole, Day +42 event rates, was for abdominal pain, which was seen in 3% of ciprofloxacin patients versus <1% of comparator patients. The rate of digestive system events by Day +42 was higher in the ciprofloxacin group than in the comparator group (15% [50/335] ciprofloxacin versus 9% [31/349] comparator). The events primarily responsible for this difference (data not shown) were nausea (3% ciprofloxacin versus <1% comparator) and vomiting (5% ciprofloxacin versus 1% comparator). Musculoskeletal events were also higher in the ciprofloxacin group than the comparator group (7% [20/335] vs. 4% [14/349]). Otherwise, the event rates were generally similar between treatment groups.

11.26.6 Musculoskeletal Adverse Events Occurring by Day +42

Table 40 lists all the specific musculoskeletal adverse events occurring by Day +42 follow-up. The drug-related musculoskeletal adverse events by Day +42 are listed in Table 41.

Clinical Reviewer's Comment: Tables 40 and 41 were created by the reviewer

Table 40
Musculoskeletal Adverse Events up to Day +42 Follow-Up
Patients Valid for Safety

Musculoskeletal Adverse Events	Ciprofloxacin N=335	Comparator N=349
Any Event	24 (7%)	14 (4%)
Arthralgia	17 (5%)	9 (3%)
Arthrosis	4 (1%)	1 (<1%)
Bone Pain	2 (<1%)	0 (0%)
Joint Disorder	2 (<1%)	0 (0%)
Leg cramps	1 (<1%)	0 (0%)
Myalgia	1 (<1%)	6 (2%)
Myopathy	1 (<1%)	0 (0%)
Tendon disorder	0 (0%)	1 (<1%)

TABLE 41
Drug-Related Musculoskeletal Adverse Events up to Day +42 Follow-Up
Patients Valid for Safety

Musculoskeletal Adverse Events	Ciprofloxacin N=335	Comparator N=349
Any Event	9 (3%)	5 (1%)
Arthralgia	5 (1%)	3 (<1%)
Arthrosis	2 (<1%)	0 (0%)
Bone Pain	1 (<1%)	0 (0%)
Joint Disorder	1 (<1%)	0 (0%)
Myalgia	1 (<1%)	2 (<1%)
Tendon disorder	0 (0%)	1 (<1%)

In order to understand the cases of arthralgia better, as this category of musculoskeletal events comprises the greatest proportion of the musculoskeletal events, the FDA Clinical Reviewer looked in greater detail at these patients. Table 42 lists the patients with arthralgia events occurring by Day +42 for ciprofloxacin and comparator, respectively,

Clinical Reviewer's Comment: Table 42 was created by the reviewer. The information in this table was obtained from the IPSC assessments of arthropathy. The number of patients is greater than what is shown in the applicant's table above (Table 41). For ciprofloxacin there are 16 patients (as opposed to 5) and 8 patients (as opposed to 3) for comparator in the reviewer's table. The discrepancy can be explained by the fact that the reviewer used all the patients assessed by the IPSC as having arthropathy and reclassified some patients as to when the arthropathy

occurred (i.e., by Day +42 or between Day +42 and one year of follow-up).

The average age for the patients experiencing arthralgia in the two groups was similar (9 years for the ciprofloxacin patients compared to 8 years for comparator patients). The mean duration of arthralgia was 13 days in both groups (in the ciprofloxacin group the range was1 to 49 days compared to 1 to 33 days in the comparator group).

TABLE 42
ARTHRALGIA Cases Occurring by Day +42

Ciprofloxacin				Comparator			
16 patients (22 events)/46 (35%)				8 patients (11 events)/33 (24%)			
Pt. Number	Age	Description	Duration	Pt. Number	Age	Description	Duration
301223	10	L knee arthralgia	2	1041 (2 events)	12	R ankle pain	5
						Knees hurt while squatting	1
307015	14	R knee pain and swelling	24	1051	7	Arthralgia (intermittent L knee and ankle pain)	12
307023 (2 events)	11	L shoulder pain	33				
		Bilateral ankle pain	33				
309019 (2 events)	7	Unspecified arthralgia**	6	23007 (2 events)	6	Bilateral shoulder tenderness	15
		Elbow pain	3			L knee pain	8
601043	6	Arthralgia in knees**	1	26001	12	R ankle pain	33
601052	6	Unspecified arthralgia	5	40003 (2 events)	6	Ankle pain	15
						Bilateral hip pain	18
601091	10	L hip pain	3	307003	6	Bilateral knee pain	1
504001	9	Shoulder pain	5	307020	9	Wrist pain	2
401115 (2 events)	9	Elbow arthralgia	13	201047 [3 additional events occurring @ Days 136, 257, and 357]	8	Mechanical gonalgia	25
		Knee arthralgia	13				
402049	8	Coxalgia	2	AVERAGE AGE 8 years Range (6 to 12 years) MEDIAN 7.5 years MEAN Duration 12 days (range 1 to 33 days)			
1021 (2 events)	10	Bilateral wrist	3				

Ciprofloxacin				Comparator			
16 patients (22 events)/46 (35%)				8 patients (11 events)/33 (24%)			
Pt. Number	Age	Description	Duration	Pt. Number	Age	Description	Duration
[a 3rd event @ Day 70]		tenderness**					
		L wrist discomfort	1				
11002 [2nd and 3rd events @ Day 215]	3	Knee pain	3				
13038*	12	R knee pain	10				
16001*	12	R ankle pain**	6				
		R ankle pain**	3				
16014 [2nd event @ Day 74]	12	Bilateral intermittent ankle pain	32				
27003 (3 events)	8	R elbow tenderness	49				
		R elbow pain	15				
		Bilateral elbow pain	28				
AVERAGE AGE 9 years Range (3 to 12 years) MEDIAN 9 years MEAN Duration 13 days (range 1 to 49 days)							

*Patient in Stratum II (IV or sequential therapy)
** associated with "accidental trauma"

The specific adverse events occurring by Day+42 for all body systems and occurring in at least 2% of either treatment group are shown in Table 43.

Clinical Reviewer's Comment: Table 43 was created by the reviewer.

TABLE 43
Adverse Events Occurring Day +42 in at Least 2% of Either Treatment Group
Patients Valid for Safety

Adverse Event	Ciprofloxacin (N=335)		Comparator (N=349)	
Any event	138	(41%)	109	(31%)
Abdominal pain	11	(3%)	2	(<1%)
Accidental injury	10	(3%)	5	(1%)
Fever	7	(2%)	4	(1%)
Headache	4	(1%)	10	(3%)
Diarrhea	16	(5%)	14	(4%)

Vomiting	16	(5%)	5	(1%)
Dyspepsia	9	(3%)	5	(1%)
Nausea	9	(3%)	3	(<1%)
Arthralgia	17	(5%)	9	(3%)
Rhinitis	10	(3%)	7	(2%)
Asthma	6	(2%)	8	(2%)
Rash	6	(2%)	12	(3%)
Pyelonephritis	7	(2%)	3	(<1%)
Urinary tract infection	5	(1%)	7	(2%)

In addition to the overall adverse events, the adverse events which were drug-related were also slightly higher through Day +42 in the ciprofloxacin group than the comparator (16% ciprofloxacin versus 12% comparator). As with the overall Day +42 event rates, the drug-related digestive system rates by Day +42 were higher in the ciprofloxacin group (9% ciprofloxacin versus 5% comparator). The largest specific event rate difference between treatment groups in drug-related Day +42 digestive system events was vomiting (3% ciprofloxacin versus <1% comparator). Other drug-related rates were similar between treatment groups.

11.26.7 All Adverse Events Occurring by One Year of Follow-Up

All adverse events grouped by body system occurring by 1 year and those experienced by at least 2% of patients in at least one treatment group are shown in Tables 44 and Table 45, respectively.

In general, the between treatment group findings by 1 year were similar to those at Day +42, with ciprofloxacin showing higher event rates. The overall 1-year event rate in both treatment groups increased by approximately 5% when compared to the Day +42 event rate. The overall incidence rate of adverse events by 1 year was 45% (151/335) for ciprofloxacin and 36% (124/349) for comparator as shown in Table 44.

TABLE 44
Adverse Events Occurring by One Year of Follow-Up by Body System
Patients Valid for Safety

Body System	Ciprofloxacin (N=335)		Comparator (N=349)	
Any body system	151	(45%)	124	(36%)
Body as a Whole	58	(17%)	44	(13%)
Cardiovascular	9	(3%)	4	(1%)
Digestive	50	(15%)	31	(9%)
Hemic and lymphatic	9	(3%)	10	(3%)
Metabolic & nutritional	2	(<1%)	2	(<1%)
Musculoskeletal	36	(11%)	25	(7%)
Nervous	17	(5%)	13	(4%)
Respiratory	23	(7%)	28	(8%)
Skin and appendages	10	(3%)	14	(4%)
Special senses	3	(<1%)	1	(<1%)
Urogenital	27	(8%)	22	(6%)

TABLE 45
Adverse Events Occurring by 1-Year Follow-Up in at Least 2% of Either Treatment Group
Patients Valid for Efficacy

Adverse Event	Ciprofloxacin (N=335)		Comparator (N=349)	
Any event	151	(45%)	124	(36%)
Accidental injury	17	(5%)	11	(3%)
Abdominal pain	12	(4%)	2	(<1%)
Fever	7	(2%)	4	(1%)
Headache	6	(2%)	11	(3%)
Diarrhea	16	(5%)	14	(4%)
Vomiting	16	(5%)	5	(1%)
Dyspepsia	9	(3%)	5	(1%)
Nausea	9	(3%)	3	(<1%)
Arthralgia	25	(7%)	16	(5%)
Myalgia	3	(<1%)	8	(2%)
Rhinitis	10	(3%)	7	(2%)
Asthma	6	(2%)	8	(2%)
Rash	6	(2%)	12	(3%)
Pyelonephritis	7	(2%)	3	(<1%)
Urinary tract infection	5	(1%)	7	(2%)

The drug-related event rates by 1 year remained similar to the drug-related event rates by Day +42. Body as a Whole event rates and drug-related Body as a Whole event rates were higher by 1 year in the ciprofloxacin group (17% ciprofloxacin versus 13% comparator for Body

as a Whole and 16% ciprofloxacin versus 13% comparator for drug-related Body as a Whole). Body as a Whole event rates in both treatment groups increased by 3% from those by Day +42. Drug-related Body as a Whole rates remained the same in both treatment groups. Both digestive system and drug-related digestive system events were the same by 1 year as they were by Day +42.

Of the adverse events occurring by one year, 47% (71/151) of ciprofloxacin events versus 38% (47/124) of comparator events were considered unrelated to treatment. In the ciprofloxacin group, 13/25 (52%) of arthralgias were considered unrelated to treatment. The corresponding number in the comparator group was 6/16 (38%).

Of patients treated with ciprofloxacin 34% (113/335) experienced adverse events that were mild in severity, 8% (26/335) had moderate events and 4% (12/335) had severe events. Twenty-three percent (82/349) of comparator patients had mild events, 9% (30/349) had moderate events and 3% (11/349) had severe events. Most musculoskeletal events in both treatment groups were of mild severity (31/36, 86% ciprofloxacin versus 21/25, 84% comparator). In the ciprofloxacin group, 131/151 (87%) events were resolved, compared to 105/124 (85%) in the comparator group. Twenty-two of the 25 (88%) arthralgias in the ciprofloxacin group resolved versus 12/16 (75%) in the comparator group.

11.26.8 Musculoskeletal Adverse Events at One Year of Follow-up

As shown in Table 46, the incidence of musculoskeletal adverse events any time up to 1 year was 10.7% in the ciprofloxacin group and 7.2% in the comparator group. Arthralgia was reported in 7.5% of the ciprofloxacin patients and 4.6% in the comparator patients. Arthrosis occurred in 1.2% of ciprofloxacin and 0.3% of the comparator patients. Myalgia occurred in 0.9% of the ciprofloxacin patients and in 2.3% of the comparator patients. Tendon disorder was reported in only 1 (0.3%) of the comparator patients and was not observed in the ciprofloxacin group. All other musculoskeletal events occurred in <1% of either treatment group.

Clinical Reviewer's Comment: Tables 46 and 47 were created by the reviewer.

TABLE 46
Musculoskeletal Adverse Events up to 1 Year Follow-Up
Patients Valid for Safety

Musculoskeletal Adverse Events	Ciprofloxacin N=335	Comparator N=349
Any Event	36 (11%)	25 (7%)
Arthralgia	25 (7%)	16 (5%)
Arthrosis	4 (1%)	1 (<1%)
Bone Pain	3 (<1%)	0 (0%)
Myalgia	3 (<1%)	8 (2%)
Joint Disorder	2 (<1%)	0 (0%)
Myasthenia	2 (<1%)	1 (<1%)
Musculoskeletal congenital anomaly	1 (<1%)	1 (<1%)
Pyogenic arthritis	1 (<1%)	0 (0%)
Leg cramps	1 (<1%)	0 (0%)
Myopathy	1 (<1%)	0 (0%)
Osteoporosis	0 (0%)	1 (<1%)
Rheumatoid arthritis	0 (0%)	1 (<1%)
Tendon disorder	0 (0%)	1 (<1%)

Table 47 shows the incidence of drug-related musculoskeletal adverse events any time up to 1 year. Arthralgia was considered by the investigator(s) to be drug-related in 1.5% of ciprofloxacin patients and 0.9% of the comparator group. All other drug-related musculoskeletal adverse events occurred in <1% of either treatment group.

Table 47
Drug-Related Musculoskeletal Adverse Events
up to 1 Year Follow-Up
Patients Valid for Safety

Musculoskeletal Adverse Events	Ciprofloxacin N=335	Comparator N=349
Any Event	9 (3%)	6 (2%)
Arthralgia	5 (1%)	3 (<1%)
Arthrosis	2 (<1%)	0 (0%)
Bone Pain	1 (<1%)	0 (0%)
Myalgia	1 (<1%)	3 (<1%)
Joint Disorder	1 (<1%)	0 (0%)
Tendon disorder	0 (0%)	1 (<1%)

The majority of musculoskeletal adverse events at 1 year follow-up were mild or moderate. Only two ciprofloxacin patients (2015 with arthralgia, and 301100 with myopathy) had a severe musculoskeletal adverse event. Patient 2015 had severe knee pain (no relationship to study drug) and severe hip pain (unlikely related to study drug). Patient 301100 had myopathy diagnosed as Duchenne's disease (no relationship to study

drug). One comparator patient (2012) had severe myalgia (fibromyalgia; not considered related to study drug).

The majority of musculoskeletal adverse events resolved by the end of the study. One ciprofloxacin patient (302026) with arthralgia and 2 ciprofloxacin patients (2015, 301100) with myalgia were "improved" at the end of the study. Patient 302026 had mild hip pain, patient 2015 had moderate fibromyalgia, and patient 301100 had myalgia thought to be related to underlying Duchenne's disease. These events were not considered by the investigators to be related to study drug. The outcome of two ciprofloxacin patients (13047, 44036) with arthralgia was unknown due to insufficient follow-up. Patient 13047 had moderate bilateral knee pain due to a fall and patient 44036 had mild bilateral ankle pain. The events were not considered by the investigators to be related to study drug. One comparator patient (306004) with arthralgia also had an unknown outcome due to insufficient follow-up. In the comparator group, 3 patients (12001, 32008, 307008) with arthralgia and one patient (2012) with myalgia had outcomes of "unchanged" at the end of the study.

In order to understand the cases of arthralgia better, as this category of musculoskeletal events comprises the greatest proportion of the musculoskeletal events, the FDA Clinical Reviewer looked in greater detail at these patients. Table 48 lists the patients with arthralgia events occurring by one year for ciprofloxacin and comparator, respectively,

Clinical Reviewer's Comment: Table 48 was created by the reviewer. The information in this table was obtained from the IPSC assessments of arthropathy. The number of patients differs from what is shown in the applicant's table above (Table 46) because the applicant's table is inclusive of all patients through one year of follow-up. As shown in Table 48, there 10 patients experiencing 12 events which occurred between Day +42 and one year of follow-up in the ciprofloxacin group and 5 patients with 6 events in the comparator group. It should also be noted that the reviewer used all the patients assessed by the IPSC as having arthropathy and reclassified some patients as to when the arthropathy occurred (i.e., by Day +42 or between Day +42 and one year of follow-up).

The average age for the patients experiencing arthralgia in the two groups was the same (8 years). The duration of the event was not noted in this table (as in Table 42, which contains arthralgia events occurring by Day +42) because the evaluation visits did not occurring as frequently and the duration of the event may be distorted by the timing of the return visits.

TABLE 48
ARTHRALGIA Cases Occurring
between Day +42 and 1 Year of Follow-up

Ciprofloxacin			Comparator		
10 patients (12 events)/46 (22%)			5 patients (6 events)/ 33 (24%)		
Pt. Number	Age	Description	Pt. Number	Age	Description
1021 [2 previous event]	10	Bilateral wrist discomfort**	12001	14	Intermittent L knee pain
11002 (2 events)# [1 previous event]	3	Bilateral wrist pain	13011#	7	R knee soreness**
		Bilateral elbow pain			
16014 [1 previous event]	12	R knee**	33025#	9	Bilateral hip pain
1001*	5	Generalized, non-specific joint pain	37001	4	L ankle pain
204033*	8	Bilateral knee pain	306004 (2 events)	5	Shoulder pain
					Knee pain
302026	9	Hip pain	AVERAGE AGE 8 years Range (4 to 14 years) MEDIAN 7 years		
2015 (2 events)	7	L hip arthralgia			
		Bilateral knee pain			
13047#	9	Bilateral knee pain**			
26018	7	Bilateral knee pain			
44036	7	Bilateral ankle pain			
AVERAGE AGE 8 years Range (3 to 12 years) MEDIAN 7.5 years					

* sponsor classified as occurring by Day 42
** associated with “accidental trauma”
#Patient in Stratum II (IV or sequential therapy)

11.26.9 Range of Motion Examination

The mean range of motion at baseline was similar between treatment groups over the various sites, sides and types of motion (data not shown). The mean change from baseline usually varied from -1 degree to 1 degree. There were 9 instances where the mean change in the treatment groups differed by 1 degree or more. In 7 of these cases, the ciprofloxacin patients had experienced a mean increase from baseline that was more than that of the comparator patients. In the remaining two instances, ciprofloxacin patients experienced smaller mean increases than comparator patients. These two instances were for change at 1 year in

the right hip, motion type flexion (mean change 0.9 for ciprofloxacin versus 1.9 for comparator) and motion type extension rotation (mean change 0.7 ciprofloxacin versus 1.9 comparator).

11.26.10 Joint Examination

At baseline the majority of patients had normal joint appearance and also at each subsequent visit for all the body sites, body sides and types of motion (data not shown). On joint examinations, more ciprofloxacin patients (28 patients; 8.4%) than comparator patients (15 patients; 4.3%) had an abnormal appearance. Most abnormalities were pain or tenderness, redness, swelling, or warmth. Of these, 10 ciprofloxacin and 7 comparator patients had these abnormalities at baseline. Most abnormalities were seen in the knees or ankles. All cases of joint appearance abnormalities, regardless of whether it was a baseline finding or treatment-emergent, were reviewed by the IPSC for possible arthropathy. Of the 26 patients with treatment-emergent joint appearance abnormalities, 25 were assessed by the IPSC as having arthropathy.

11.26.11 Gait Assessment

On gait (stance/swing) assessments, more ciprofloxacin patients (35 patients; 10.4%) than comparator patients (18 patients; 5.2%) had an abnormal finding. Of these, 28 ciprofloxacin patients and 12 comparator patients had the abnormalities at baseline. All cases of gait abnormality, whether it was a baseline finding or treatment-emergent, were assessed by the IPSC for possible arthropathy. Of the 13 patients with treatment-emergent gait abnormalities, 6 were assessed by the IPSC as having arthropathy.

11.26.12 Findings from Other Diagnostic Tests

The treatment groups were generally similar with respect to number of procedures performed and procedure findings. Most findings were post-treatment and the majority of abnormal findings occurred less than 5 times per treatment group (data not shown) . The most common locations for procedures were renal/kidneys and urinary tract, and the majority of these procedures yielded normal or abnormal, clinically insignificant findings as per the reviewing physician.

Very few EEG procedures were performed. Four abnormal, clinically significant findings were present post-therapy in the ciprofloxacin group versus none in the comparator group. The abnormal findings were for a muscle electromyogram, head electroencephalogram, brain electroencephalogram, and muscle biopsy.

11.26.13 Caregiver Questionnaire

Most patients in both groups had some abnormal baseline findings on the Caregiver Questionnaire and had improvement or no change in these items on subsequent timepoints (data not shown). For the questions on

stiffness or swelling of the joints, both groups were comparable except for a slightly higher incidence in the comparator group for stiffness of the knees, stiffness of the shoulders, and swelling around the ankles at the 1 year timepoint.

11.26.14 Neurological Adverse Events

Neurological adverse events were also of particular interest as a safety endpoint in this study. All the neurological adverse events occurring by Day +42 are shown in Table 49 and drug-related events are shown in Table 50. All the neurological adverse events occurring between Day +42 and one year of follow-up are shown in Table 51 and drug-related events are shown in Table 52.

Clinical Reviewer's Comment: Overall the number of adverse neurological events during the study was low and comparable between the treatment groups (5.1% versus 3.7% for ciprofloxacin and comparator, respectively, at one year; 95% CI of the difference [-1.8%, 4.7%]. In addition, the rates are similar to what is reported in the currently approved ciprofloxacin label obtained from adult clinical trials (i.e., less than 1% for dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, and paresthesia. Only headache had a higher incidence of 1.2% in adults. In addition, it should be noted that the adult trials did not have the extent of follow-up (i.e., one year) that the current study had.

TABLE 49
Neurological Adverse Events Occurring up to Day +42 Follow-Up
Patients Valid for Safety

Neurological Adverse Events	Ciprofloxacin N=335	Comparator N=349
Any Event	9 (3%)	7 (2%)
Dizziness	3 (<1%)	1 (<1%)
Nervousness	3 (<1%)	1 (<1%)
Insomnia	2 (<1%)	0 (0%)
Somnolence	2 (<1%)	0 (0%)
Abnormal Dreams	0 (0%)	2 (<1%)
Convulsion	0 (0%)	2 (<1%)
Hypertonia	0 (0%)	1 (<1%)
Abnormal Gait	0 (0%)	1 (<1%)

TABLE 50
Drug-Related Neurological Adverse Events Occurring up to Day +42 Follow-Up
Patients Valid for Safety

Neurological Adverse Events	Ciprofloxacin N=335	Comparator N=349
Any Event	5 (1%)	2 (<1%)
Dizziness	2 (<1%)	0 (0%)
Nervousness	2 (<1%)	0 (0%)
Insomnia	1 (<1%)	0 (0%)
Somnolence	1 (<1%)	0 (0%)
Abnormal Dreams	0 (0%)	1 (<1%)
Abnormal Gait	0 (0%)	1 (<1%)

TABLE 51
Neurological Adverse Events up to 1 Year Follow-Up
Patients Valid for Safety

Neurological Adverse Events	Ciprofloxacin N=335	Comparator N=349
Any Event	17 (5%)	13 (4%)
Convulsion	3 (<1%)	4 (1%)
Dizziness	3 (<1%)	1 (<1%)
Nervousness	3 (<1%)	1 (<1%)
Insomnia	2 (<1%)	0 (0%)
Somnolence	2 (<1%)	0 (0%)
Abnormal Gait	2 (<1%)	2 (<1%)
Confusion	1 (<1%)	0 (0%)
Hypotonia	1 (<1%)	0 (0%)
Movement Disorder	1 (<1%)	1 (<1%)
Hypesthesia	1 (<1%)	1 (<1%)
Neuropathy	1 (<1%)	1 (<1%)
Abnormal Dreams	0 (0%)	2 (<1%)
Cerebral Hemorrhage	0 (0%)	1 (<1%)
Hypertonia	0 (0%)	2 (<1%)
Meningomyelocele	0 (0%)	2 (<1%)
Subdural Hematoma	0 (0%)	1 (<1%)

TABLE 52
Drug-Related Neurological Adverse Events up to 1 Year Follow-Up
Patients Valid for Safety

Neurological Adverse Events	Ciprofloxacin N=335	Comparator N=349
Any Event	5 (1%)	2 (<1%)
Dizziness	2 (<1%)	0 (0%)
Nervousness	2 (<1%)	0 (0%)
Insomnia	1 (<1%)	0 (0%)
Somnolence	1 (<1%)	0 (0%)
Abnormal Dreams	0 (0%)	1 (<1%)
Abnormal Gait	0 (0%)	1 (<1%)

11.26.15 *Deaths*

One ciprofloxacin patient (306-056) died on Day +14. The cause of death was infantacide. One comparator patient (204-016) died on Day +661. He died of complications of retroviral (HIV) disease. In both cases the cause of death was judged by the investigator to be unrelated to study drug.

Patient narratives are included:

Patient 306056

A 3 year old female received oral study drug (b) (6) (20 doses) for the indication of pyelonephritis. Past medical history is significant for urinary incontinence and cellulitis of the right arm. No baseline concomitant medications were reported. During the treatment phase, she had the non-serious adverse event of a Mod-severity broken right collarbone (b) (6) The patient fell from bed. The collarbone was immobilized with plaster. (b) (6) The event was not considered related to study drug.

Patient 204016

Patient is a 2 year old male who was treated with oral study drug from March 29, 2001 to April 8, 2001 (20 doses) for the indication of cUTI. Past medical history was significant for adenopathy on March 29, 2001. Baseline concomitant medications included multivitamins due to malnourishment. Starting on June 8, 2001, he received Bactrim® DS for prophylaxis.

During the treatment period, the adverse event of mild thrombocytopenia was reported on April 4, 2001. The event was considered unlikely to be related to study drug. The event resolved on April 7, 2001.

During the follow-up period, the adverse event of severe scabies was reported on April 17, 2001. Tetmosol® soap was prescribed. The event was considered unlikely related to study drug. The event was reported as

unchanged. Also on April 17th, mild hepatomegaly was noted and attributed to HIV status of the patient. The event was not considered related to study drug. The event worsened by the end of the study.

On [redacted] joint exam revealed warmth, pain, and tenderness on the left shoulder. Exam [redacted] revealed tenderness and bruising of left shoulder. The patient fell from a chair. Exams [redacted] were normal. On [redacted] the patient died from complications of retroviral disease.

Clinical Reviewer's Comment: The reviewer agrees with the applicant's assessments.

11.26.16 Serious Adverse Events

Overall, 25 ciprofloxacin patients (7.5%) and 20 comparator patients (5.7%) had serious adverse events as shown in Table 53 in Appendix 1. Three patients (201003, 107001, and 502001) had serious adverse events that were initially reported to Global Drug Safety. However, these 3 evaluations did not match with the predetermined protocol specifications for serious adverse events and were not included in the final database. The decision not to include these patients was made by the applicant prior to unblinding. After unblinding the database, it was determined that these patients were all part of the comparator group.

All serious adverse events reported in the ciprofloxacin group were judged by the investigators to be unlikely or not related to study drug. One patient (301100) had a musculoskeletal serious adverse event (myopathy; Duchenne's disease).

11.26.17 Discontinuations Due to Adverse Event

Table 54 provides a listing of all patients that discontinued due to an adverse event. Overall, 12 ciprofloxacin patients (3.6%) and 6 comparator patients (1.7%) discontinued due to an adverse event.

Clinical Reviewer's Comment: Table 54 was created by the reviewer.

TABLE 54
Discontinuations Due to Adverse Events
Patients Valid for Safety

Patient Number	COSTART Term	Relative Day of Start of Event	Relative Day of End of Event	Severity	Outcome	Reason For Premature Termination
Ciprofloxacin						
14001	Nausea	1	5	Sev	Res	AE
14001	Abdominal Pain	2	5	Mild	Res	AE
27001	Vaginal moniliasis	8	87	Mod	Res	AE
27007	Palpitation	2	2	Mild	Res	AE
27007	Somnolence	2	2	Mild	Res	AE
306003	Vomiting	3	5	Mod	Res	Insufficient Therapeutic Effect
306003	Nausea	3	5	Mod	Res	Insufficient Therapeutic Effect
306005	Hepatitis	8	37	Mod	Res	AE
304001	Moniliasis	6	36	Mild	Res	AE
707021	Carcinoma	6	264	Sev	Imp	AE
707033	Dyspepsia	1	4	Mod	Res	AE
707033	Vomiting	1	4	Mild	Res	AE
401048	Nervousness	2	7	Mod	Res	AE
401048	Diarrhea	2	3	Mild	Res	AE
506014	Urticaria	6	6	Mod	Imp	AE
11017	Vomiting	2	11	Mild	Res	AE
309014	Pyelonephritis	1	5	Sev	Res	Protocol Violation
Ceftazadime						
15060	Sepsis	12	16	Mod	Res	AE
303046	Pyelonephritis	3	5	Mod	Res	Insufficient Therapeutic Effect
Cefixime						
16009	Urinary tract infection	10	17	Mod	Res	AE
307024	Urinary tract disorder	8	26	Mod	Res	AE
401069	Urticaria	3	NR	Mild	Insuf f/u	AE
401095	Liver function tests abnormal	4	101	Mod	Res	AE

NR = not reported

11.26.18 Laboratory Parameters

Hemic and lymphatic adverse events were reported for 3% of ciprofloxacin and 3% of comparator patients (data not shown). The adverse events of abnormal liver function tests (0% for ciprofloxacin and <1% [3 patients] for comparator), hyperuricemia (1 patient [<1%] versus 0, respectively), increased lactic dehydrogenase (0 versus 1 patient [<1%], respectively), and alkalosis (0 versus 1 patient [<1%], respectively) were also reported.

Changes in laboratory values that were judged to be clinically significant by the applicant are shown in Table 55. The most common clinically significant changes were $\leq$ 0.75 times the lower limit of normal for hemoglobin (4% for the ciprofloxacin group, 3% for the comparator group), and $\geq$ 1.8 times the upper limit of normal for SGPT (3% in each group).

TABLE 55
Clinically Significant Changes in Laboratory Values
Patients Valid for Analysis of Safety

	LABORATORY TEST	CLINICALLY SIGNIFICANT CHANGE FROM BASELINE	CIPROFLOXACIN N	CIPROFLOXACIN TOTAL@	CIPROFLOXACIN %	COMPARATOR N	COMPARATOR TOTAL@	COMPARATOR %
BLOOD CHEMISTRY								
	BILIRUBIN, TOTAL	>=1.8 TIMES OF THE UPPER NORMAL LIM	1	294	0	1	303	0
	BILIRUBIN, TOTAL	>3 TIMES OF THE UPPER NORMAL LIMIT	1	294	0	0	303	0
	CREATININE	INCREASE OF 0.5MG/DL FROM BASELINE	6	315	2	5	325	2
	CREATININE	INCREASE OF 1MG/DL FROM BASELINE	0	315	0	0	325	0
	SGOT/AST	>=1.8 TIMES THE UPPER NORMAL LIMIT	5	308	2	7	319	2
	SGOT/AST	>3 TIMES THE UPPER NORMAL LIMIT	3	308	1	3	319	1
	SGPT/ALT	>=1.8 TIMES THE UPPER NORMAL LIMIT	8	308	3	8	318	3
	SGPT/ALT	>3 TIMES THE UPPER NORMAL LIMIT	2	308	1	5	318	2
HEMATOLOGY								
	HEMOGLOBIN	<=.75 TIMES THE LOWER NORMAL LIMIT	13	316	4	11	328	3
	PLATELETS	LESS THAN 100 GIGA/L	0	311	0	1	326	0

11.26.19 Vital Signs

No treatment differences were judged to be clinically significant by the applicant in mean diastolic blood pressure, systolic blood pressure, or heart rate. During therapy, mean diastolic blood pressure (range) was 59.7 (40-90) mmHg and 59.7 (40-100) mmHg for ciprofloxacin and comparator, respectively. Mean systolic blood pressure (range) was 96.6 (70-139) mmHg and 96.5 (80-160) mmHg for ciprofloxacin and comparator, respectively. Mean heart rate (range) was 90.2 (63-152) bpm and 90.6 (60-141) bpm for ciprofloxacin and comparator, respectively.

However, of note, 4 ciprofloxacin patients had the adverse event of hypertension. All 4 patients had a medical history of hypertension. Patient 305-007 had the adverse event of hypertension during the treatment phase. The investigator reports that generally, the increased blood pressure occurred while the patient was experiencing pain. Patient 307-006 also had hypertension during the treatment phase. Patient 306-003 had hypertension reported 2 days after study drug had been

prematurely discontinued due to an adverse event of vomiting. Patient 36-002 had the adverse event of hypertension in the follow-up phase (4 months after study drug). None of these events were considered by the investigators to be related to study drug. No comparator patients had an adverse event of hypertension. One comparator patient (and no ciprofloxacin patients) had the adverse event of tachycardia. No adverse event of bradycardia was reported.

Clinical Reviewer's Comment: Although an additional safety analysis to assess hypertension was added to the protocol in Amendment 2, the analysis was not performed since only 4 patients experienced hypertension as an adverse event.

11.27 Safety Summary

Of the 689 patients enrolled in the study, 684 (99.3%; 335 ciprofloxacin, 349 comparator) received at least one dose of study drug and were valid for the analysis of safety. Overall, 307 (92%) of ciprofloxacin patients and 314 (90%) comparator patients completed the 1 year post-treatment follow-up. The majority of patients were female (81%). Although the majority of patients in this study were Caucasian (39%) or Hispanic (31%), patients of other ethnic origins were represented (2% Black; 1% of patients were Asian and 27% were uncodable by the applicant's coding system). Of those who could not be coded, more than 90% were Mestizo. The mean age of all patients valid for safety was 6.3 years, with a range of 12 months to 17 years. No clinically meaningful differences in baseline demographics were noted between the treatment groups.

This protocol was specifically designed to evaluate musculoskeletal and neurological events during the treatment phase and up to 1-year post-treatment follow-up. The incidence of musculoskeletal adverse events any time up to 1 year was 11% (36/335) in the ciprofloxacin group and 7% (25/349) in the comparator group. Arthralgia was the most frequently reported musculoskeletal event in either group and was reported in 7% (25/330) of the ciprofloxacin patients and 5% (16/349) of the comparator patients. Arthrosis occurred in 1% (4/335) of ciprofloxacin and 0.3% (1/349) of the comparator patients. Myalgia occurred in 0.9% (3/335) of the ciprofloxacin patients and in 2% (8/349) of the comparator patients. Tendon disorder was reported in only 1 (0.3%) of the comparator patients and was not observed in the ciprofloxacin group. All other musculoskeletal events occurred in <1% of either treatment group.

The majority of musculoskeletal adverse events at 1 year follow-up were mild or moderate. Only two ciprofloxacin patients had a severe musculoskeletal adverse event. One patient had severe knee pain (no relationship to study drug, as per the investigator) and severe hip pain (unlikely related to study drug, as per the investigator). Another patient had myopathy diagnosed as Duchenne's disease (no relationship to study drug, as per the investigator). One comparator patient had severe myalgia (fibromyalgia; not considered related to study drug, as per the investigator).

The majority of musculoskeletal adverse events resolved by the end of the study. One ciprofloxacin patient with arthralgia and 2 ciprofloxacin patients with myalgia were "improved" at the end of the study. These events were not considered by the investigators to be related to study drug. The outcome of two ciprofloxacin patients with arthralgia was unknown due to insufficient follow-up. The events were not considered by the investigators to be related to study drug. One comparator patient with arthralgia also had an unknown outcome due to insufficient follow-up. In the comparator group, 3 patients with arthralgia and one patient with myalgia had outcomes of "unchanged" at the end of the study.

To further evaluate any possible musculoskeletal events, the IPSC reviewed all cases with an adverse event that coded to the musculoskeletal system, all patients with an abnormal joint appearance (baseline and treatment-emergent), and all patients with an abnormal gait (baseline and treatment-emergent). Additionally, all cases of adverse events of leg pain, hand pain, arm pain, movement disorder, abnormal gait, peripheral edema, and selected accidental injury (related to joints or extremities) were reviewed. All cases were evaluated in a blinded fashion by the IPSC. Cases were evaluated as no evidence of arthropathy or at least possible evidence of arthropathy (arthropathy defined 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; this definition was seen as broad and inclusive of such phenomena as bursitis, enthesitis and tendonitis).

Of the 141 patients reviewed by the IPSC, 4 were excluded from the statistical analyses, 57 were deemed not to have arthropathy, and an additional 2 patients were excluded from the applicant's statistical analyses because their events occurred pre-treatment (i.e., were pre-existing). The reviewer agrees with the removal of these patients. In total, 79 patients were deemed by the IPSC to have possible, probable, or definite arthropathy. There were 46 cases of arthropathy in the ciprofloxacin arm and 33 in the comparator arm by one year of follow-up.

The primary safety endpoint was the arthropathy rate, as assessed by the IPSC, by the follow-up visit (Day +28 to +42). The results of the IPSC assessment revealed arthropathy in 9.3% (31/335) of ciprofloxacin patients and 6.0% (21/349) of comparator patients by Day +42. The 95% confidence interval for the treatment difference in arthropathy (-0.8%, 7.2%) indicated inferiority of ciprofloxacin to comparator, using the protocol defined definition of non-inferiority of an upper bound of the 95% confidence interval of not more than 6%.

Arthropathy rates were slightly lower than the overall rates in Mexico (0% both treatment groups) and Peru (2% [2/87] ciprofloxacin versus 3% [3/88] comparator). The arthropathy rate was higher than the overall rate in Caucasians (14% [18/130] ciprofloxacin versus 10% [13/134] comparator) and lower than the overall rate in Hispanics (8% [8/102] ciprofloxacin versus 3% [3/109] comparator) and the uncodable race group (5% [5/95] ciprofloxacin versus 3% [3/93] comparator). The arthropathy rates were quite similar between males and females and consistent between treatment groups. Route of administration of study drug appeared to have little effect. The incidence of arthropathy did increase with increasing age, in both groups. The highest arthropathy rate was seen in the $\geq$12 year to <17 year age group, where the rate was 22% 7/32] for ciprofloxacin patients and 14% [5/35] for

comparator patients. Arthropathy rates were higher than the overall rates in both treatment groups for patients with cUTI (12% [20/164] ciprofloxacin versus 10% [16/166] comparator), and lower than the overall rates in both treatment groups for patients with pyelonephritis (6% [11/171] ciprofloxacin versus 3% [5/183] comparator).

By the 1-year follow-up, 13.7% (46/335) of ciprofloxacin patients and 9.5% (33/349) of comparator patients had arthropathy at any point during the trial (treatment phase through the 1-year post-treatment follow-up phase).

No substantial differences between treatment groups were observed in mean change from baseline in the range of motion examination for any joint at any timepoint.

On joint examinations, more ciprofloxacin patients (28 patients; 8.4%) than comparator patients (15 patients; 4.3%) had an abnormal appearance. Most abnormalities were pain or tenderness, redness, swelling, or warmth. Of these, 10 ciprofloxacin and 7 comparator patients had these abnormalities at baseline. Most abnormalities were seen in the knees or ankles. All cases of joint appearance abnormalities, regardless of whether it was a baseline finding or treatment-emergent, were reviewed by the IPSC for possible arthropathy. Of the 26 patients with treatment-emergent joint appearance abnormalities, 25 were assessed by the IPSC as having arthropathy.

On gait assessments, more ciprofloxacin patients (35 patients; 10.4%) than comparator patients (18 patients; 5.2%) had an abnormal finding. Of these, 28 ciprofloxacin patients and 12 comparator patients had the abnormalities at baseline. All cases of gait abnormality, whether it was a baseline finding or treatment-emergent, were assessed by the IPSC for possible arthropathy. Of the 13 patients with treatment-emergent gait abnormalities, 6 were assessed by the IPSC as having arthropathy.

Most patients in both groups had some abnormal baseline findings on the Caregiver Questionnaire and had improvement or no change in these items on subsequent timepoints. For the questions on stiffness or swelling of the joints, both groups were comparable except for a slightly higher incidence in the comparator group for stiffness of the knees, stiffness of the shoulders, and swelling around the ankles at the 1 year timepoint.

The incidence of neurological events, up to 1-year post-treatment, follow-up was 5.1% (17/335) n the ciprofloxacin group and 3.7% (13/349) in the comparator group. Convulsion occurred in 0.9% (3/335) of ciprofloxacin patients and 1.1% (4/349) of comparator patients. Neuropathy and hypesthesia were reported at the same incidence in both groups (one patient in each group for each event; 0.3% incidence). Due to coding conventions, an investigator term of “tethered cord” coded to neuropathy; this accounted for both cases of neuropathy. Both cases of hypesthesia were not considered drug-related and resolved within 5 days. All other neurological events were reported in <1% of patients in either group. No clear evidence of neurological sequelae was observed in this study.

Two patient deaths were reported during the study. One ciprofloxacin-treated patient (Patient 306056) was a victim of infanticide. The second patient (comparator group,

Patient 204016) died of complications of retroviral (HIV) infection. In both cases, the death was judged by the investigator (and concurred by the reviewer) to be of no relationship to study drug.

In the ciprofloxacin group, 12/335 (3.6%) patients experienced adverse events with an action taken of study drug permanently discontinued, and 25/335 (7.5%) patients experienced adverse events that fulfilled the definition of serious. The incidence of premature discontinuation due to an adverse event and serious adverse events was similar in the comparator group (6 [1.7%] and 20 [5.7%], respectively).

All serious adverse events reported in the ciprofloxacin group were judged by the investigators to be unlikely or not related to study drug. One patient (301100) had a musculoskeletal serious adverse event (myopathy; Duchenne's disease). The most common adverse events leading to premature discontinuation of ciprofloxacin therapy were vomiting (3 patients), nausea (2 patients), and moniliasis (2 patients). No patient discontinued due to a musculoskeletal event.

The overall 1-year event rate in both treatment groups increased by approximately 5% when compared to the Day +42 event rate. The overall incidence rate of adverse events by 1 year was 45% (151/335) for ciprofloxacin and 36% (124/349) for comparator. The most common adverse events in both treatment groups were those occurring in the Body as a Whole (17% [58/335] and 9% [31/349], respectively), digestive (15% [50/335] for ciprofloxacin and 9% [31/349] for comparator), musculoskeletal (11% [36/335] and 7% [25/349], respectively), respiratory (7% [23/335] and 8% [28/349], respectively), and urogenital (8% [27/335] and 6% [22/349], respectively) body systems. The investigator(s) assessed most adverse events as mild or moderate in intensity for both treatment groups.

Adverse events, other than those affecting the musculoskeletal and central nervous systems, that occurred in > 1% of the 335 ciprofloxacin treated patients, up to 1-year post-treatment were: accidental injury 5% (17); abdominal pain 4% (12); diarrhea 5% (16); vomiting 5% (16); dyspepsia 3% (9); nausea 3% (9); rhinitis 3% (10); fever 2% (7); headache 2% (6); asthma 2% (6); rash 2% (6); and pyelonephritis 2% (7).

The incidence of laboratory test abnormalities was comparable between the 2 treatment groups. No trends that appear to be uniquely associated with ciprofloxacin treatment were identified. The most common clinically significant changes (as defined by the applicant) were $\leq$ 0.75 times the lower limit of normal for hemoglobin (4% [13/316] for the ciprofloxacin group, 3% 11/328] for the comparator group), and $\geq$ 1.8 times the upper limit of normal for SGPT (3% in each group, [8/308] and [8/318], respectively).

No clinically meaningful (as defined by the applicant) treatment differences were observed in mean diastolic blood pressure, systolic blood pressure, or heart rate. Of note, 4 ciprofloxacin patients had the adverse event of hypertension. All 4 patients had a medical history of hypertension. None of these events were considered by the investigators to be related to study drug. No comparator patients had an adverse event of hypertension. One comparator patient (and no ciprofloxacin patients) had the adverse event of tachycardia. No adverse event of bradycardia was reported.

11.28 Study Conclusions

This study was a prospective, double-blind, randomized, parallel-group comparison of ciprofloxacin versus an active control regimen in pediatric patients with complicated urinary tract infection (cUTI) or pyelonephritis for 10 to 21 days. The primary endpoint was to determine the musculoskeletal safety (i.e., joint, articular cartilage, tendon and ligament) in patients with cUTI or pyleonephritis. Secondary endpoints were to assess the neurological safety of these dosage regimens and to collect clinical and microbiological response data at the Test-of-Cure (TOC) visit (Day +5 to +9).

Efficacy Conclusions
The clinical success rate at the TOC visit (5 to 9 days following the end of therapy) was 96% (202/211) for ciprofloxacin and 93% (214/231) for comparator. The 95% confidence interval for the treatment difference in clinical success at the TOC visit (-1.3%, 7.3%) indicated that ciprofloxacin in the treatment of pediatric patients with cUTI or pyelonephritis, is non-inferior to the comparator.

The bacteriological eradication rate at the TOC visit in patients valid for efficacy was 84% [178/211] in the ciprofloxacin group and 78% [181/231] in the comparator group. The 95% confidence interval for the treatment difference in eradication rate (-1.3%, 13.1%) indicated that ciprofloxacin is non-inferior to the comparator in the treatment of pediatric patients with cUTI or pyelonephritis. For this analysis, missing and indeterminate results were included as failures.

Clinical cure rates and bacteriological eradication rates were not substantially impacted by age, race, or sex of the patient.

Safety Conclusions
Overall, ciprofloxacin and active control administered to pediatric patients with cUTI or pyelonephritis, exhibited similar safety profiles. For cases of arthropathy, ciprofloxacin was found to be not non-inferior to comparator (95% confidence interval of the difference between ciprofloxacin and control [-0.8%, 7.2%]). Non-inferiority was defined as a upper bound of the 95% confidence interval of the difference between ciprofloxacin and comparator of not more than 6%.

Race and gender of the patient appeared to have little effect on the incidence of arthropathy.
The incidence of arthropathy did increase with increasing age, in both groups. This difference might be explained by the greater physical activity, more accurate ability to report pain, and greater weight across weight-bearing joints of adolescents versus younger children.

No other clinically meaningful differences were observed between ciprofloxacin and comparator. Specifically, no definite treatment differences were observed in adverse events and drug-related arthropathy events appeared to be self-limited without sequelae.

11.29 APPENDIX – Additional Tables from Study 100169

TABLE 1 List of COSTART Terms for the Musculoskeletal System

COSTART NUMBER	COSTART TERM
7010010	Bone Disorder
7010020	Bone Implant Lysis
7010030	Bone Necrosis
7010040	Bone Neoplasm
7010050	Bone Pain
7010060	Bone Sarcoma
7010070	Epiphysis Closure Delayed
7010080	Fluorosis
7010090	Osteomalacia
7010100	Osteomyelitis
7010110	Osteoporosis Fracture
7010120	Osteoporosis
7010130	Osteosclerosis
7010140	Pathological Fracture
7010150	Periosteal Disorder
7010160	Premature Epiphyseal Closure
7010170	Spina Bifida
7020010	Bursitis
7030010	Chondrodystrophy
7040010	Musculoskeletal Congenital Anomaly
7050010	Arthralgia
7050020	Arthritis
7050030	Arthrosis
7050040	Joint Disorder
7050050	Pyogenic Arthritis
7050060	Rheumatoid Arthritis
7050065	Synovitis
7060010	Extraocular Palsy
7060020	Generalized Spasm
7060030	Hypocalcemic Tetany
7060035	Leg Cramps
7060040	Muscle Atrophy
7060050	Muscle Hemorrhage
7060060	Myalgia
7060070	Myasthenia
7060080	Myopathy
7060090	Myositis
7060100	Ptosis
7060105	Rhabdomyolysis
7060110	Strabismus
7060120	Tetany
7060130	Twitching
7070010	Tendinous Contracture
7070015	Tendon Disorder

COSTART NUMBER	COSTART TERM
7070020	Tendon Rupture
7070030	Tenosynovitis
7999998	Diagnostic Procedure
7999999	Surgery

TABLE 2
Enrollment by Study Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
1	SKOOG	19JAN00	12OCT01	CIPROFLOXACIN	6	6	6	3	6
				COMPARATOR	7	7	7	2	6
				TOTAL	13	13	13	5	12
2	HARMON	04NOV99	01SEP01	CIPROFLOXACIN	2	2	2	0	1
				COMPARATOR	2	2	2	1	2
				TOTAL	4	4	4	1	3
8	PAREDES	29FEB00	29MAR01	CIPROFLOXACIN	5	5	5	3	3
				COMPARATOR	5	5	5	3	5
				TOTAL	10	10	10	6	8
9	DEETHS	09SEP99	17JUL00	CIPROFLOXACIN	3	3	3	2	3
				COMPARATOR	3	3	3	3	3
				TOTAL	6	6	6	5	6
11	GRADY	23MAY00	11DEC01	CIPROFLOXACIN	4	4	4	1	2
				COMPARATOR	4	4	4	0	4
				TOTAL	8	8	8	1	6
12	KOYLE	10AUG00	01MAR01	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	2	2	2	1	2
				TOTAL	4	4	4	3	4
13	LIEBERMAN	02JUN00	11APR02	CIPROFLOXACIN	8	8	8	3	8
				COMPARATOR	9	9	9	4	8
				TOTAL	17	17	17	7	16
14	RICHARD	05JAN00	06JAN00	CIPROFLOXACIN	1	1	1	0	0
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	0	0
15	KENNEDY	20DEC99	05OCT00	CIPROFLOXACIN	5	5	5	1	4
				COMPARATOR	5	5	5	1	3
				TOTAL	10	10	10	2	7
16	ARRIETA	18OCT99	15JUN01	CIPROFLOXACIN	3	3	3	0	3
				COMPARATOR	3	3	3	1	0
				TOTAL	6	6	6	1	3

TABLE 2 (continued)
Enrollment by Study Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
17	DEAN	18FEB00	09FEB01	CIPROFLOXACIN	2	2	2	0	1
				COMPARATOR	3	3	3	1	2
				TOTAL	5	5	5	1	3
18	CASALE	29MAR00	23OCT00	CIPROFLOXACIN	2	2	2	0	2
				COMPARATOR	1	1	1	0	0
				TOTAL	3	3	3	0	2
19	GREENFIELD	17APR00	13OCT00	CIPROFLOXACIN	2	2	2	1	2
				COMPARATOR	1	1	1	1	0
				TOTAL	3	3	3	2	2
23	JOSEPH	02OCT00	21MAR01	CIPROFLOXACIN	0	0	0	0	0
				COMPARATOR	2	2	2	1	1
				TOTAL	2	2	2	1	1
26	GOLDFARB	17FEB00	05JUN01	CIPROFLOXACIN	1	1	1	0	0
				COMPARATOR	2	2	2	0	2
				TOTAL	3	3	3	0	2
27	SMITH	06APR00	02JUN00	CIPROFLOXACIN	4	4	4	1	2
				COMPARATOR	3	3	3	3	3
				TOTAL	7	7	7	4	5
28	CARSON	26JAN01	20FEB01	CIPROFLOXACIN	0	0	0	0	0
				COMPARATOR	2	2	2	2	2
				TOTAL	2	2	2	2	2
29	MEVORACH	27MAR00	05APR00	CIPROFLOXACIN	0	0	0	0	0
				COMPARATOR	1	1	1	1	1
				TOTAL	1	1	1	1	1
32	TENNEY	27APR00	25OCT00	CIPROFLOXACIN	1	1	1	0	0
				COMPARATOR	1	1	1	0	1
				TOTAL	2	2	2	0	1
33	KOGAN	19SEP00	06FEB02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	4	4	4	1	4
				TOTAL	5	5	5	2	5

TABLE 2 (continued)
Enrollment by Study Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
36	MAHAN	08SEP00	03JAN01	CIPROFLOXACIN	2	2	2	0	2
				COMPARATOR	1	1	1	1	1
				TOTAL	3	3	3	1	3
37	REITELMAN	06NOV00	20AUG01	CIPROFLOXACIN	0	0	0	0	0
				COMPARATOR	2	2	2	0	1
				TOTAL	2	2	2	0	1
38	KRYGER	05APR01	16SEP01	CIPROFLOXACIN	2	2	2	1	2
				COMPARATOR	2	2	2	1	2
				TOTAL	4	4	4	2	4
39	CONGENI	19OCT00	31OCT00	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	1	1	1	0	0
				TOTAL	2	2	2	1	1
40	AZIMI	22MAR01	09JUL01	CIPROFLOXACIN	1	1	1	0	1
				COMPARATOR	1	1	1	0	1
				TOTAL	2	2	2	0	2
42	PLAIRE	31OCT01	10FEB02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	2	2	2	0	2
				TOTAL	3	3	3	1	3
44	MINEVICH	15JUN01	17APR02	CIPROFLOXACIN	3	3	3	1	2
				COMPARATOR	2	2	2	1	1
				TOTAL	5	5	5	2	3
102	KHOURY	19SEP00	05JUN01	CIPROFLOXACIN	3	3	3	1	3
				COMPARATOR	2	2	2	0	2
				TOTAL	5	5	5	1	5
103	SALLE	17OCT00	23MAR01	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	4	4	4	2	3
				TOTAL	6	6	6	4	5
105	LEONARD	14SEP00	09MAR02	CIPROFLOXACIN	3	3	3	0	3
				COMPARATOR	4	4	4	3	4
				TOTAL	7	7	7	3	7

TABLE 2 (continued)
Enrollment by Study Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
107	MIX	09JAN01	20JAN01	CIPROFLOXACIN	0	0	0	0	0
				COMPARATOR	1	1	1	1	1
				TOTAL	1	1	1	1	1
201	BAHLMAN	02NOV00	23FEB02	CIPROFLOXACIN	4	4	4	3	4
				COMPARATOR	4	4	4	2	4
				TOTAL	8	8	8	5	8
202	BIGALKE	06FEB01	12NOV01	CIPROFLOXACIN	2	2	2	1	2
				COMPARATOR	2	2	2	2	2
				TOTAL	4	4	4	3	4
204	MCCULLOCH	29MAR01	03AUG01	CIPROFLOXACIN	1	1	1	0	1
				COMPARATOR	2	2	2	2	2
				TOTAL	3	3	3	2	3
205	SHIRES	20JUL01	03NOV01	CIPROFLOXACIN	2	2	2	1	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	1	2
206	STRASHEIM	26OCT00	30APR01	CIPROFLOXACIN	2	2	2	0	0
				COMPARATOR	1	1	1	0	0
				TOTAL	3	3	3	0	0
301	BOLOGNA	26OCT00	25FEB02	CIPROFLOXACIN	12	12	12	10	11
				COMPARATOR	14	14	14	10	11
				TOTAL	26	26	26	20	22
302	CASELLAS	03SEP01	25MAR02	CIPROFLOXACIN	2	2	2	1	1
				COMPARATOR	2	2	2	0	0
				TOTAL	4	4	4	1	1
303	EZCURRA	27NOV00	09APR02	CIPROFLOXACIN	6	5	5	3	5
				COMPARATOR	6	6	6	6	5
				TOTAL	12	11	11	9	10
304	PAOLUCCI	22NOV00	03FEB01	CIPROFLOXACIN	3	3	3	1	2
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	1	2

TABLE 2 (continued)
Enrollment by Study Center

					NUMBER OF PATIENTS				
CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	RANDOM-IZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
305	REPETTO	23JAN01	09NOV01	CIPROFLOXACIN	2	2	2	1	2
				COMPARATOR	2	2	2	2	2
				TOTAL	4	4	4	3	4
306	TORRES	31OCT00	25APR02	CIPROFLOXACIN	35	35	35	35	33
				COMPARATOR	35	35	35	33	33
				TOTAL	70	70	70	68	66
307	LOPEZ	07NOV00	10MAR02	CIPROFLOXACIN	11	11	11	5	10
				COMPARATOR	11	11	11	7	9
				TOTAL	22	22	22	12	19
308	TEIJEIRO	15JAN02	25JAN02	CIPROFLOXACIN	0	0	0	0	0
				COMPARATOR	1	1	1	1	1
				TOTAL	1	1	1	1	1
309	SENTAGNE	22NOV01	21APR02	CIPROFLOXACIN	7	7	7	5	5
				COMPARATOR	8	8	8	8	8
				TOTAL	15	15	15	13	13
401	HUICHO	25JUN01	23APR02	CIPROFLOXACIN	47	47	47	38	39
				COMPARATOR	49	48	48	36	40
				TOTAL	96	95	95	74	79
402	CHEA-WOO	26JUN01	06APR02	CIPROFLOXACIN	19	19	19	7	10
				COMPARATOR	18	18	18	14	15
				TOTAL	37	37	37	21	25
403	RETO	20JUN01	11APR02	CIPROFLOXACIN	21	21	21	17	18
				COMPARATOR	22	22	22	19	20
				TOTAL	43	43	43	36	38
501	ZIMMERHACKL	06MAR01	16MAR01	CIPROFLOXACIN	1	1	1	0	1
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	0	1
502	FEHRENBACH	16FEB01	10OCT01	CIPROFLOXACIN	3	3	3	1	3
				COMPARATOR	3	3	3	2	2
				TOTAL	6	6	6	3	5

TABLE 2 (continued)
Enrollment by Study Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS				
					RANDOM-IZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
503	DIPPEL	19JUN01	28AUG01	CIPROFLOXACIN	1	1	1	0	1
				COMPARATOR	2	2	2	2	2
				TOTAL	3	3	3	2	3
504	MISSELWITZ	21FEB01	09NOV01	CIPROFLOXACIN	2	2	2	1	2
				COMPARATOR	2	2	2	0	2
				TOTAL	4	4	4	1	4
505	RASCHER	23APR01	02OCT01	CIPROFLOXACIN	3	3	3	2	2
				COMPARATOR	1	1	1	0	1
				TOTAL	4	4	4	2	3
506	MULLER-WIEFEL	03JUL01	25OCT01	CIPROFLOXACIN	3	3	3	1	2
				COMPARATOR	3	3	3	0	3
				TOTAL	6	6	6	1	5
601	JIMENEZ-FONSECA	05OCT01	22APR02	CIPROFLOXACIN	21	21	21	17	19
				COMPARATOR	21	20	20	13	14
				TOTAL	42	41	41	30	33
701	CORTES GUDINO	08DEC00	30APR02	CIPROFLOXACIN	23	22	22	17	19
				COMPARATOR	24	24	24	20	22
				TOTAL	47	46	46	37	41
702	HERNANDEZ PORRAS	27DEC00	19APR02	CIPROFLOXACIN	8	8	8	4	5
				COMPARATOR	10	10	10	2	7
				TOTAL	18	18	18	6	12
704	MARTINEZ MENDIZA	22DEC00	22APR02	CIPROFLOXACIN	10	10	10	9	10
				COMPARATOR	10	10	10	9	10
				TOTAL	20	20	20	18	20
705	DEL RIO ALMENDAR	23MAY01	16FEB02	CIPROFLOXACIN	8	8	8	1	7
				COMPARATOR	8	8	8	3	8
				TOTAL	16	16	16	4	15
706	VICTORIA MORALES	14FEB01	27FEB02	CIPROFLOXACIN	6	6	6	5	6
				COMPARATOR	7	6	6	3	6
				TOTAL	13	12	12	8	12

TABLE 2 (continued)
Enrollment by Study Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS RANDOM-IZED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
707	AVILA FIGUEROA	09MAR01	14MAY01	CIPROFLOXACIN	2	2	2	0	0
				COMPARATOR	2	2	2	0	0
				TOTAL	4	4	4	0	0
ALL CENTERS		09SEP99	30APR02	CIPROFLOXACIN	337	335	335	211	279
				COMPARATOR	352	349	349	231	296
				TOTAL	689	684	684	442	575

TABLE 20
Ciprofloxacin Cases of Arthropathy Through One Year as Assessed by the IPSC
N=46

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
301213/M/1	ARG	NO	ABNORMAL GAIT/ R leg limp	Pos	Pos	Other: hip x-ray (normal)	MILD	91	13	Eval by traumatologist was normal	RES
301223/F/10	ARG	NO	ARTHRALGIA/ L knee arthralgia	Pos	Pos	None	MILD	-8	2	Resolved while on drug	RES
302026/F/9	ARG	YES[1]	ARTHRALGIA/ Hip pain	Pos	Pos	RDT: ibuprofen Other: lumbosacral x-ray (neg)	MILD	158	22		RES
			BACK PAIN/ Lumbar pain				MILD	158	22		RES
306054/F/5	ARG	NO	PYOGENIC ARTHRITIS/ Septic arthritis in R knee due to trauma	Def	NONE	Hosp RDT: antibiotics Other: X-rays of R knee x 2 (neg), L knee (neg)	MOD	53	21	Serious event; trauma due to nail wound	RES
307004/M/16	ARG	YES[2]	BONE PAIN/Cervical spine pain	Prob	Pos	Other: X-ray of spine and hips (neg)	MILD	92	UNK	Intermittent back pain possibly related to	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										kyphosis (pre-existing)	
			BACK PAIN				MILD	7	1		
			BACK PAIN/ Thoracolumbar pain			None	MILD	404	UNK		
			BONE PAIN/Thoracic spine pain			None	MILD	92	UNK	RES	
307006/F/6	ARG	NO	INFECTION VIRAL/ Syndrome with fever, rash, and R ankle arthralgia/ Swelling (on exam)	Def	Prob	Hosp RDT: meds for fever and rash Other; X-ray of ankle (neg)	MILD	-8	6	RES Serious event; IPSC: arthralgia RES possibly related to viral syndrome (Rubeola??)	RES
307015/M/14	ARG	YES[3]	ARTHRALGIA/ R knee pain and swelling	Def	Pos	Other: X-ray bilateral knees (bilateral genu valgum, no other abnormalities)	MILD	7	24	Eval by Traumatologist: ”inner ligament lesion, traumatic, and mild”	RES
307023/F/11	ARG	NO	BONE PAIN/ Coccyx pain	Prob	Prob	RDT: topical analgesic	MILD	22	7	Pt examined by orthopedist	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										exam)	
			ARTHRALGIA/ L shoulder pain			None	MILD	4	33 (normal		RES
			ARTHRALGIA/ Bilateral ankle pain			None	MILD	4	33		RES
309001/M/13	ARG	YES[4]	ACCIDENTAL INJURY/ knee bruise	Def	NONE	None	MILD	24	10	2 doses of ciprofloxacin; Accidental trauma (hit knee on bed); also intermittent tendon pain (pre-exisiting)	RES
309007/F/11	ARG	YES[5]	--/ bilateral hip warmth	Def	Prob	None	--	-10	3	possibly due to fever; no evidence of articular pathology; bilateral ankle edema (pre-exisiting)	RES
309014/F/11	ARG	NO	PAIN/ Growing pains (legs, ankle, knee)	Pos	NONE	Other: x-rays of ankle, knee, and feet (all normal)	MILD	199	72	One dose of ciprofloxacin; IPSC: too remote to be drug-related	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			MYASTHENIA/ Muscle weakness			None	MILD	199	72		
309019/F/7	ARG	NO	ARTHRALGIA/ Arthralgia	Pos	Pos	None	MILD	5	6	Accidental trauma (pt. hit while playing)	RES
			ARTHRALGIA/ Elbow pain			None	MILD	29	3	Pt. doing physical exercise the day prior	RES
103001/F/5	CAN	YES[6]	--/ bilateral knee pain	Def	NONE	None	--	368	UNK	Also pain in L hip and L ankle (pre-existing)	INSUF F/U
601043/F/6	CR	NO	ARTHRALGIA/ Arthralgia in knees due to trauma	Def	NONE	None	MILD	28	1	Accidental trauma (fell down)	RES
601052/F/6	CR	NO	ARTHRALGIA/ Arthralgia	Pos	Pos	None	MILD	-12	5		RES
			LEG PAIN			None	MILD	2	10		RES
			HAND PAIN			None	MILD	2	10		RES
601091/F/10	CR	NO	ARTHRALGIA/ L hip pain	Pos	Pos	None	MILD	-6	3		RES
601104/F/11	CR	NO	LEG PAIN/ L leg pain	Pos	Pos	None	MILD	-8	3	Resolved while on study	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
504001/F/9	GER	NO	ARTHRALGIA/ Shoulder pain	Pos	Pos	None	MILD	2	5drug	Attributed to common cold; IPSC: usually shoulder pain leads to ↓ ROM, but ROM was normal	RES
701014/F/11	MEX	NO	LEG PAIN	Pos	NONE	None	MILD	335	29	Eval by physiotherapist (no inflammation problems); IPSC: may be related to toting heavy backpack	RES
			BACK PAIN			None	MILD	335	30		
			MUSCULO-SKELETAL CONGENITAL ANOMALY/ R foot deformity			None	MILD	335	29	RES	RES
			HYPOTONIA/ Poor lumbar tone			None	MILD	335	29	Poor posture	RES
707033/F/4	MEX	YES[7]	--/	Pos	NONE	None	--	150	273	IPSC: history	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			bilateral ankle and foot tenderness on joint exam							of ankle pain while running – growing pains or bony abnormality	
401115/F/9	PERU	NO	ARTHRALGIA/ Elbow arthralgia	Pos	Pos	None	MILD	31	13	2 days of ciprofloxacin; mild sporadic arthralgia	RES
			ARTHRALGIA/ Knee arthralgia			None	MILD	31	13		RES
402049/F/8	PERU	NO	ARTHRALGIA/ Coxalgia	Pos	Pos	None	MILD	4	2	Myalgia vs. athralgia; pt. playing basketball and doing martial arts on day prior	RES
402052/F/11	PERU	YES[8]	ACCIDENTAL INJURY/ worsening articular hypermotility	Pos	NONE	None	MILD	215	39	Eval by rheumatologist: episodic pain in knees lasting for < 1 hour, related to articular hypermotility	RES
1001/F/5	US	NO	--/ bilateral knee redness and warmth on joint	Def	Pos	None	--	-10	14	IPSC: transient arthralgia during	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			exam							infection is not unusual	
			--/ bilateral ankle warmth			None	--	4	35		RES
			ARTHRALGIA/ Joint pain, non-specific, generalized			None	MILD	229	10	Pt doing increased physical activity prior to joint pain; normal joint exam	RES
1003/F/8	US	NO	JOINT DISORDER/ R ankle warmth	Pos	Prob	None	MILD	-7	15	No change in ROM; attributed to common cold	RES
			ARTHROSIS/ R ankle effusion			None	MILD	-7	15		
1021/F/10	US	NO	ARTHRALGIA/ Bilateral wrist tenderness	Def	Pos	RDT: APAP	MILD	5	3	Associated with wrestling event	RES
			ARTHRALGIA/ L wrist discomfort			None	MILD	9	1	RES	RES
			LEG CRAMPS/ change in knee flexion (stiffness)			RDT: APAP	MILD	5	3		RES
			ARTHRALGIA/			None	MILD	70	14	Hyper-	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			Bilateral wrist discomfort							extended wrists during volleyball game	
1031/F/10	US	NO	LEG PAIN/ R foot arch pain and collapse	Def	NONE	Other	MILD	87	6	Accidental trauma (twisted ankle)	RES
1040/F/4	US	YES[9]	--/ L ankle and foot redness on joint exam	Def	NONE	None	MILD	-5	11		RES
2015/F/7	US	YES[10]	--/ ballotable fluid on L knee	Def	Pos	Other: MRI of L knee (normal, small amount of fluid)	--	47	3		RES
			ARTHRALGIA/ L hip arthralgia			Other	SEV	45	5		RES
			ARTHRALGIA/ Bilateral knee pain			Other:	SEV	186	52		RES
			MYALGIA/ Fibromyalgia			RDT	MOD	202	Ongoing		RES
			ACCIDENTAL INJURY/joint hypermobility			None	MILD	66	Ongoing	Diagnosis performed by rheuma-	UNCH

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			(wrists/elbows/ hips/etc.)							tologist	
8001/F/5	US	NO	--/ L ankle swelling noted on joint exam	Def	NONE	None	--	125	242	Accidental trauma (pt. tripped and rolled ankle)	RES
11002/F/3 (Stratum II)	US	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	0	3		RES
			ARTHRALGIA/ Bilateral wrist pain			None	MILD	215	19		RES
			ARTHRALGIA/ Bilateral elbow pain			None	MILD	215	19		RES
13038/M/12 (Stratum II)	US	NO	ARTHRALGIA/ R knee pain due to trauma	Def	NONE	None	MILD	6	10	Accidental trauma (pt. fell); noted during PT eval of joints	RES
			RASH/ R knee redness due to trauma			None	MILD	6	10	Accidental trauma (pt. fell); noted during PT eval of joints	RES
13047/F/9 (Stratum II)	US	NO	ARTHRALGIA/ Bilateral knee pain	Prob	NONE	RDT: ibuprofen	MILD	199	UNK	Accidental trauma (pt. fell on stairs); lost to follow-up	INSUF F/U
		NO	ACCIDENTAL	Def	Pos	Other:	SEV	29	8	Accidental	RES

US

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
14001/F/15			INJURY/ R knee ligaments pulled/sprained			splints				trauma (pt. fell while skiing)	
			ACCIDENTAL INJURY/ R sprained ankle			Other: brace	MOD	29	6	Accidental trauma (pt. fell while skiing)	RES
16001/F/12 (Stratum II)	US	NO	ARTHRALGIA/ R ankle pain	Def	Pos	Other: MRI (negative)	MILD	27	6	Pt. fell at school one week prior	RES
			ARTHROSIS/ R ankle swelling			Other: MRI (negative)	MILD	27	6		RES
			ARTHRALGIA/ R ankle pain			Other: X-ray of ankle (lateral soft tissue swelling no definite osseous abnormality)	MOD	-11	3	Pt. twisted and injured ankle prior to study	RES
16010/F/9	US	NO	ARTHROSIS/ Bilateral ankle swelling	Prob	Prob	None	MILD	-7	114* present at TOC exam and resolved by 3 mo. Exam at	Cortef and florinef for congenital adrenal hyperplasia	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
									1 mo. was not done		
16014/F/12	US	YES[11]	ARTHRALGIA/ Bilateral intermittent ankle pain	Def	Pos	None	MILD	14	32	Pt. active in sports	RES
			ACCIDENTAL INJURY/ L foot trauma			None	MOD	102	3	Accidental trauma (horse stepped on pt. foot during an equestrian event)	RES
			PAIN/ Bilateral intermittent foot pain			None	MILD	14	32	Pt. active in sports	RES
			ACCIDENTAL INJURY/ Lateral-collateral ligament injury			None	MOD	246	217	Accidental trauma (soccer injury)	RES
			ACCIDENTAL INJURY/ R ankle injury			None	MILD	522	1	Accidental trauma (soccer injury)	RES
			ARTHRALGIA/ R knee pain			None	MILD	74	31	Accidental trauma (soccer injury)	RES
			LEG PAIN/ Plantar surface			None	MILD	23	23	Accidental trauma	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			heel pain (sports injury)							(sports injury)	
19004/M/10	US	NO	--/ bilateral redness of knee joints	Prob	Pos	None	--	7	35	Discounted by IPSC	RES
			JOINT DISORDER/ Bilateral ankle stiffness			None	MILD	-2	2	Not discounted	RES
26018/F/7	US	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	None	MILD	89	93	2 days of ciprofloxacin; IPSC: pain attributed to growing pains; not usually found in knees	RES
27001/F/6	US	YES[12]	--/ bilateral swelling of ankle/foot on joint exam	Def	Pos	None	MILD	-2	10	IPSC: Gymnastics may have been a factor	RES
27003/F/8	US	NO	ARTHRALGIA/ R elbow tenderness	Def	Prob	None	MILD	18	49	Sports activities may have contributed to recurrent elbow tenderness	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			ARTHRALGIA/ R elbow pain			None	MILD	25	15		
			ARTHRALGIA/ Bilateral elbow pain			Other: PT	MILD	39	28		
40001/M/4 (Stratum II)	US	YES[13]	ARTHROSIS/ Knee swelling	Pos	Pos	None	MILD	-5	11	History of episodes of recurrent knee pain	RES
44036/F/7	US	YES[14]	ARTHRALGIA/ Bilateral ankle pain	Pos	NONE	None	MILD	370	UNK	2 days of ciprofloxacin; intermittent pain (few times per week and worse after increased activity); IPSC: abnormal spinal cord terminus may be reason for asymmetry on ROM, ankle pain	INSUF F/U
204033/F/8	SA	YES[15]	ARTHRALGIA/ Bilateral painful knees	Def	Pos	Other: Patellar tap (negative)	MILD	331	66	Painful knees at night and after walking	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										long distances	
205010/F/4	SA	NO	MOVEMENT DISORDER/ Hip rotation decreased	Pos	NONE	None	MILD	368	UNK	No pain, normal walking pattern; IPSC: not considered significant, baseline values suggest improper positioning	UNCH
206001/M/1	SA	NO	PERIPHERAL EDEMA/ R ankle swelling (grade 1)	Def	Prob	None	MILD	10	20	Accidental trauma (pt. sprained ankle)	RES

KEY for Table 20 (Study 100169)

Pos= possible; prob=probable; def = definite
Arg = Argentina; US = United States; Mex = Mexico; SA = South Africa; Ger = Germany; CR = Costa Rica; CAN = Canada;
Unk = unknown; Hosp = hospitalization; RDT = remedial drug therapy;
Mod = Moderate; Sev = servere
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

[1]History of R thigh pain
[2]Kyphosis
[3]Genu valgum R/L; metatarsus adductus R/L
[4] Clubbed feet; kyphosis; Achilles tendon pain (R ankle and L ankle/foot)
[5] Bilateral ankle edema
[6] pain in L hip at quadriceps area and L ankle
[7] History of ankle pain when running
[8] Articular hypermotility
[9] Abnormal gait (myelomeningocele; in a walker)
[10] History of pain in leg, back, knee, hip, which was diagnosed as “growing pains”; myelomeningocele
[11]Abnormal gait (decreased hip extension bilaterally); swelling of R and L knees
[12] Gait with hyperpronation and mild valgus
[13]Recurrent knee pain; swelling
[14] Abnormal spinal cord terminus @ T12
[15]L shoulder pain

TABLE 21
Comparator Cases of Arthropathy Through One Year as Assessed by the IPSC
N=33

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
1041/F/12	US	NO	ARTHRALGIA/ R ankle pain	Pos	Pos	None	MILD	1	5	Accidental trauma (pt. hit ankle on a metal bar while swinging)	RES
			ARTHRALGIA/ Knees hurt while squatting			None	MILD	-1	1	Cause of pain unable to be determined	RES
1051/F/7	US	NO	ARTHRALGIA/ Arthralgia	Pos	Prob	None	MOD	-2	12	Intermittent L knee and ankle pain; usually at night IPSC: joint problem vs. growing pains vs. muscle cramps	RES
			ABNORMAL GAIT/ Difficulty walking			None	MILD	-2	10		RES
12001/F/14	US	YES[1]	ARTHRALGIA/ Intermittent L knee pain	Def	Pos	RDT: ibuprofen, APAP	MILD	160	Ongoing	Possible retropatellar syndrome	INSUF F/U
13011/F/7 (Stratum II)	US	NO	ARTHRALGIA/ R knee soreness and R ankle warmth	Prob	NONE	None	MILD	363	81	Accidental trauma (pt. fell); Pre-existing condition	RES
15059/M/3	US	YES[2]	ARM PAIN/	Def	NONE	None	MILD	-10	4	Accidental	RES

			Arm pain and R elbow pain							trauma (pt. fell), pre-existing	
16011/F/16	US	YES[3]	--/ abnormal joint and gait exam (knees, ankles, feet)	Def	NONE	None	--	-10	Ongoing	Abnormalities noted at baseline, related to pre-existing conditions; Pt lost to F/u	INSUF F/U
2012/F/9	US	NO	MYALGIA/ fibromyalgia	Def	NONE	RDT: APAP, Flexeril	SEV	326	Ongoing	Eval by rheumatologist, dx fibromyalgia	UNCH
23007/F/6	US	NO	ARTHRALGIA/ Bilateral shoulder tenderness	Def	Pos	None	MILD	-7	15	IPSC: possibly reactive arthritis	RES
			ARTHRALGIA/ L knee pain			None	MILD	8	22	Eval by orthopedist: possible inflammatory arthritis	RES
26001/F/12	US	YES[4]	ARTHROSIS/ L ankle swelling	Def	NONE	None	MILD	-6	15	Accidental trauma (soccer injury); pre-existing	RES
			ARTHRALGIA/ R ankle pain			None	MILD	7	33	Sports activity	RES
27006/F/9	US	NO	ARM PAIN/ L forearm soreness	Pos	Pos	None	MILD	5	28	Not related to sports, may be soft tissue (and not joint) soreness	RES
33025/M/9 (Stratum II)	US	NO	ARTHRALGIA/ Bilateral hip pain	Prob	Pos	None	MILD	99	15	Anterior pain with extension; gluteal pain when sitting 30 min	RES
37001/F/4	US	NO	ARTHRALGIA/ L ankle pain	Pos	Pos	Other: x-ray (negative)	MILD	85	12	Noted when running	RES

40003/F/6	US	NO	ARTHRALGIA/ ankle pain; guarding in foot and stance	Prob	Prob	None	MILD	-7	15		RES
			ARTHRALGIA/ Bilateral hip pain			None	MILD	7	18	Noted when running; possible growing pains	RES
102002/F/17	CAN	YES[5]	--/ bilateral ankle redness	Def	NONE	None	--	-11	Ongoing	Pre-existing deformity, wears KAFOs	UNCH
103015/F/6	CAN	NO	--/ on caregiver questionnaire noted difficulty walking, bending, kneeling, and stooping; trouble climbing stairs	Pos	NONE	None	--	192	169	Bilateral knee pain, and ankle/foot pain on joint exam; possibly related to obesity	RES
204016/M/2	SA	YES[6]	-- L shoulder warmth, pain, tenderness, and bruising	Def	Pos	None	--	-9	19	Accidental trauma (pt. fell from a chair)	RES
301089/F/7	ARG	NO	TENDON DISORDER/ R Achilles tendon ache	Pos	Pos	None	MILD	6	2	No history of trauma	RES
301090/F/7	ARG	NO	PAIN/ dorsal feet ache	Pos	Pos	None	MILD	3	2	No swelling or redness noted IPSC: unusual complaint, may be joints in mid foot	RES
301224/F/8	ARG	NO	LEG PAIN/ L thigh pain	Pos	Pos	None	MILD	24	4	IPSC: doubt arthropathy, since lasted only	RES

										3 days	
301297/M/12	ARG	YES[7]	--/ worsening pubic pain	Pos	Pos	RDT: diclofenac	--	40	Ongoing	Worsening of pre-existing condition IPSC: could remotely be tendonitis	UNCH
306004/F/5	ARG	NO	ARTHRALGIA/ Shoulder pain	Pos	NONE	None	MILD	364	Ongoing		INSUF F/U
			ARTHRALGIA/ Knee pain			None	MILD	364	Ongoing		INSUF F/U
307003/M/6	ARG	YES[8]	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	None	MILD	0	1	Sporadic episodes of knee pain prior to study	RES
307020/F/9	ARG	YES[9]	ARTHRALGIA/ Wrist pain	Def	Pos	None	MILD	-8	2	Ehlers Danlos Syndrome is pre-exisitng	RES
309015/F/8	ARG	NO	MYALGIA/ Quadriceps pain	Pos	Pos	None	MILD	8	25	Possibly related to excessive playing; IPSC: hip pain often referred to thigh, could also be quadriceps tendonitis	RES
309018/F/9	ARG	YES[10]	--/ elbow pain and weakness in forearm	Pos	NONE	None	--	93	4	Pre-existing	RES
401047/F/8	PERU	NO	ARTHRALGIA/ Mechanical gonalgia	Pos	Pos	RDT: topical diclofenac Other: articular protection	MILD	20	25	Unknown location on body; Dx by rheumatologist	RES

			ARTHRALGIA/ Oligoarthraligia in knee and ankle			RDT: topical diclofenac, APAP Other: X-ray of bilateral knees (negative)	MILD	136	15		RES
			ARTHRALGIA/ R ankle arthralgia			None	MILD	257	1	Dx by rheumatologist	RES
			ARTHRALGIA/ Mechanical arthralgia			None	MILD	357	16	Unknown location on body; Dx of gonalgia by rheumatologist	RES
402007/F/6	PERU	YES[11]	MYALGIA/ Myalgia	Pos	Pos	None	MILD	124	69	Growing pains pre-existing; IPSC: possible myalgia vs. arthralgia	RES
402012/F/12	PERU	YES[12]	PAIN/ Worsening of non-specific growing pains	Pos	Pos	RDT: topical analgesic	MILD	31	22	Worsening of pre-existing condition	RES
402027/F/13	PERU	NO	MYALGIA/ myalgia	Prob	Prob	None	MILD	-6	3	Pain in R lower rib muscles	RES
			MYALGIA/ Coxalgia			None	MILD	2	6	Pain in both “coxfemoral joints”; IPSC: coxalgia is arthropathy	RES
402037/F/12	PERU	YES[13]	ACCIDENTAL INJURY/ Worsening of articular hypermotility	Pos	NONE	None	MOD	159	31	Worsening of pre-existing condition	RES

502008/F/9 (Stratum II)	GER	NO	--/ R ankle pain on joint exam	Pos	NONE	None	--	363	Ongoing	Pt. played soccer on the day prior	INSUF F/U
504005/F/5	GER	YES[14]	--/ L hip pain	Pos	NONE	None	--	10	99	Pre-existing condition	RES
506009/F/2 (Stratum II)	GER	NO	MOVEMENT DISORDER/ Reduced hip movement	Pos	NONE	Other: ultrasound of both hips (WNL)	MILD	271	Ongoing	IPSC: would have expected fluid on US if arthropathy	INSUF F/U

KEY for Table 21 (Study 100169)

Pos= possible; prob=probable; def = definite
Arg = Argentina; US = United States; Mex = Mexico; SA = South Africa; Ger = Germany; CR = Costa Rica; CAN = Canada;
Unk = unknown; Hosp = hospitalization; RDT = remedial drug therapy;
Mod = Moderate; Sev = servere
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

[1]Spina bifida occulta; basline stiff knees and L ankle swelling; gait abnormal
[2]R elbow painful on baseline exam(patient fell a few days prior to enrollment)
[3]Spina bifida; meningomyelocele; bilateral ankle and knee swelling; wears KAFOs
[4]History of fractured hand; R ankle swelling at baseline (soccer tournament prior to enrollment)
[5]Spina bifida; bilateral deformity of hips, knees, and ankles
[6]Gait abnormal (possibly due to developmental delays)
[7]History of pubic pain
[8]History of sporadic knee pain
[9]History of generalized ligamentous laxity and sporadic mild joint pain; Ehlers Danlos Syndrome
[10]L elbow pain
[11]History of growing pains
[12]History of growing pains (ankles)
[13] articular hypermotility
[14] hip pain

TABLE 24
Ciprofloxacin Cases of Arthropathy Occurring by Day +42 as Assessed by the IPSC
N= 30 patients (5 patients also had events occurring after Day 42)
ARTHRALGIA as the Event occurring by Day +42
Patients with an Arthropathy Event (any type of event, not just arthralgia) both pre-Day 42 and after Day 42

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
301223/F/10	ARG	NO	ARTHRALGIA/ L knee arthralgia	Pos	Pos	None	MILD	-8	2	Resolved while on drug	RES
307004/M/16	ARG	YES[2]	BONE PAIN/Cervical spine pain	Prob	Pos	None	MILD	92	UNK	Intermittent back pain possibly related to kyphosis (pre-existing)	RES
			BACK PAIN			Other: x-ray of hips (negative), x-ray of "spinal cord" (negative)	MILD	7	1		
			BACK PAIN/ Thoracolumbar pain			None	MILD	404	UNK	RES	
			BONE PAIN/Thoracic spine pain			None	MILD	92	UNK		
307006/F/6	ARG	NO	INFECTION VIRAL/ Syndrome with	Def	Prob	Hosp RDT: meds for fever	MILD	-8	6	Serious event; IPSC: arthralgia RES	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			fever, rash, and R ankle arthralgia/ swelling			and rash				possibly related to viral syndrome (Rubeola??)	
307015/M/14	ARG	YES[3]	ARTHRALGIA/ R knee pain and swelling	Def	Pos	None	MILD	7	24	Eval by Traumatologist: "inner ligament lesion, traumatic, and mild"	RES
307023/F/11	ARG	NO	BONE PAIN/ Coccyx pain	Prob	Prob	RDT: topical analgesic	MILD	22	7	Pt examined by orthopedist (normal exam)	RES
			ARTHRALGIA/ L shoulder pain			None	MILD	4	33		RES
			ARTHRALGIA/ Bilateral ankle pain			None	MILD	4	33		RES
309001/M/13	ARG	YES[4]	ACCIDENTAL INJURY/knee bruise	Def	NONE	None	MILD	24	10	2 doses of ciprofloxacin; Accidental trauma (hit knee on bed); also intermittent tendon pain (pre-exisiting)	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
309007/F/11	ARG	YES[5]	--/ bilateral hip warmth	Def	Prob	None	--	-10	3	possibly due to fever; no evidence of articular pathology; bilateral ankle edema (pre-exisiting)	RES
309019/F/7	ARG	NO	ARTHRALGIA/ Arthralgia	Pos	Pos	None	MILD	5	6	Accidental trauma (pt. hit while playing)	RES
			ARTHRALGIA/ Elbow pain			None	MILD	29	3	Pt. doing physical exercise the day prior	RES
601043/F/6	CR	NO	ARTHRALGIA/ Arthralgia in knees due to trauma	Def	NONE	None	MILD	28	1	Accidental trauma (fell down)	RES
601052/F/6	CR	NO	ARTHRALGIA/ Arthralgia	Pos	Pos	None	MILD	-12	5		RES
			LEG PAIN			None	MILD	2	10		RES
			HAND PAIN			None	MILD	2	10		RES
601091/F/10	CR	NO	ARTHRALGIA/ L hip pain	Pos	Pos	None	MILD	-6	3		RES
601104/F/11	CR	NO	LEG PAIN/	Pos	Pos	None	MILD	-8		Resolved	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			L leg pain						3	while on study drug	
504001/F/9	GER	NO	ARTHRALGIA/ Shoulder pain	Pos	Pos	None	MILD	2	5	Attributed to common cold; IPSC: usually shoulder pain leads to ↓ ROM, but ROM was normal	RES
401115/F/9	PERU	NO	ARTHRALGIA/ Elbow arthralgia	Pos	Pos	None	MILD	31	13	2 days of ciprofloxacin; mild sporadic arthralgia	RES
			ARTHRALGIA/ Knee arthralgia			None	MILD	31	13		RES
402049/F/8	PERU	NO	ARTHRALGIA/ Coxalgia	Pos	Pos	None	MILD	4	2	Myalgia vs. athralgia; pt. playing basketball and doing martial arts on day prior	RES
1001/F/5	US	NO	--/ bilateral knee redness and warmth on joint exam	Def	Pos	None	--	-10	14	IPSC: transient arthralgia during infection is not unusual	RES
			--/			None	--	4	35		RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			bilateral ankle warmth								
			ARTHRALGIA/ Joint pain, non-specific, generalized			None	MILD	229	10	Pt doing increased physical activity prior to joint pain; normal joint exam	RES
1003/F/8	US	NO	JOINT DISORDER/ R ankle warmth	Pos	Prob	None	MILD	-7	15	No change in ROM; attributed to common cold	RES
			ARTHROSIS/ R ankle effusion			None	MILD	-7	15		
1021/F/10	US	NO	ARTHRALGIA/ Bilateral wrist tenderness	Def	Pos	RDT: APAP	MILD	5	3	Associated with wrestling event	RES
			ARTHRALGIA/ L wrist discomfort			None	MILD	9	1	RES	RES
			LEG CRAMPS/ change in knee flexion (stiffness)			RDT: APAP	MILD	5	3		RES
			ARTHRALGIA/ Bilateral wrist discomfort			None	MILD	70	14	Hyper-extended wrists during volleyball	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										game	
1040/F/4	US	YES[9]	--/ L ankle and foot redness on joint exam	Def	NONE	None	MILD	-5	11		RES
11002/F/3 (Stratum II)	US	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	0	3		RES
			ARTHRALGIA/ Bilateral wrist pain			None	MILD	215	19		RES
			ARTHRALGIA/ Bilateral elbow pain			None	MILD	215	19		RES
13038/M/12 (Stratum II)	US	NO	ARTHRALGIA/ R knee pain due to trauma	Def	NONE	None	MILD	6	10	Accidental trauma (pt. fell); noted during PT eval of joints	RES
			RASH/ R knee redness due to trauma			None	MILD	6	10	Accidental trauma (pt. fell); noted during PT eval of joints	RES
14001/F/15	US	NO	ACCIDENTAL INJURY/ R knee ligaments pulled/sprained	Def	Pos	Other: splints	SEV	29	8	Accidental trauma (pt. fell while skiing)	RES
			ACCIDENTAL			Other: brace	MOD	29		Accidental	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			INJURY/ R sprained ankle						6	trauma (pt. fell while skiing)	
16001/F/12 (Stratum II)	US	NO	ARTHRALGIA/ R ankle pain	Def	Pos	Other: MRI (negative)	MILD	27	6	Pt. fell at school one week prior	RES
			ARTHROSIS/ R ankle swelling			Other: MRI (negative)	MILD	27	6		RES
			ARTHRALGIA/ R ankle pain			None	MOD	-11	3	Pt. twisted and injured ankle prior to study	RES
16010/F/9	US	NO	ARTHROSIS/ Bilateral ankle swelling	Prob	Prob	None	MILD	-7	114* present at TOC exam and resolved by 3 mo. Exam at 1 mo. was not done	Cortef and florinef for congenital adrenal hyperplasia	RES
16014/F/12	US	YES[11]	ARTHRALGIA/ Bilateral intermittent ankle pain	Def	Pos	None	MILD	14	32	Pt. active in sports	RES
			ACCIDENTAL INJURY/			None	MOD	102	3	Accidental trauma (horse	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			L foot trauma							stepped on pt. foot during an equestrian event)	
			PAIN/ Bilateral intermittent foot pain			None	MILD	14	32	Pt. active in sports	RES
			ACCIDENTAL INJURY/ Lateral-collateral ligament injury			None	MOD	246	217	Accidental trauma (soccer injury)	RES
			ACCIDENTAL INJURY/ R ankle injury			None	MILD	522	1	Accidental trauma (soccer injury)	RES
			ARTHRALGIA/ R knee pain			None	MILD	74	31	Accidental trauma (soccer injury)	RES
			LEG PAIN/ Plantar surface heel pain (sports injury)			None	MILD	23	23	Accidental trauma (sports injury)	RES
19004/M/10	US	NO	--/ bilateral redness of knee joints	Prob	Pos	None	--	7	35	Discounted by IPSC	RES
			JOINT DISORDER/ Bilateral ankle			None	MILD	-2	2	Not discounted	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			stiffness								
27001/F/6	US	YES[12]	--/ bilateral swelling of ankle/foot on joint exam	Def	Pos	None	MILD	-2	10	IPSC: Gymnastics may have been a factor	RES
27003/F/8	US	NO	ARTHRALGIA/ R elbow tenderness	Def	Prob	None	MILD	18	49	Sports activities may have contributed to recurrent elbow tenderness	RES
			ARTHRALGIA/ R elbow pain			None	MILD	25	15		RES
			ARTHRALGIA/ Bilateral elbow pain			Other: PT	MILD	39	28		RES
40001/M/4 (Stratum II)	US	YES[13]	ARTHROSIS/ Knee swelling	Pos	Pos	None	MILD	-5	11	History of episodes of recurrent knee pain	RES
206001/M/1	SA	NO	PERIPHERAL EDEMA/ R ankle swelling (grade 1)	Def	Prob	None	MILD	10	20	Accidental trauma (pt. sprained ankle)	RES

KEY for Table 24 (Study 100169)

Pos = possible, Prob = probable; Def = definite
Arg = Argentina; US = United States; Mex = Mexico; SA = South Africa; Ger = Germany; CR = Costa Rica; CAN = Canada;
Unk = unknown; Hosp = hospitalization; RDT = remedial drug therapy;
Mod = Moderate; Sev = severe
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

[2]Kyphosis
[3]Genu valgum R/L; metatarsus adductus R/L
[4] Clubbed feet; kyphosis; Achilles tendon pain (R ankle and L ankle/foot)
[5] Bilateral ankle edema
[9] Abnormal gait (myelomeningocele; in a walker)
[10] History of pain in leg, back, knee, hip, which was diagnosed as “growing pains”; myelomeningocele
[11]Abnormal gait (decreased hip extension bilaterally); swelling of R and L knees
[12] Gait with hyperpronation and mild valgus
[13]Recurrent knee pain; swelling

TABLE 25
Comparator Cases of Arthropathy Occurring by Day +42 as Assessed by the IPSC
N= 21 patients (1 patient also had events occurring after Day 42)
ARTHRALGIA as the Event occurring by Day +42
Patients with an Arthropathy Event (any type of event, not just arthralgia) both pre-Day 42 and after Day 42

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
1041/F/12	US	NO	ARTHRALGIA/ R ankle pain	Pos	Pos	None	MILD	1	5	Accidental trauma (pt. hit ankle on a metal bar while swinging)	RES
			ARTHRALGIA/ Knees hurt while squatting			None	MILD	-1	1	Cause of pain unable to be determined	RES
1051/F/7	US	NO	ARTHRALGIA/ Arthralgia	Pos	Prob	None	MOD	-2	12	Intermittent L knee and ankle pain; usually at night IPSC: joint problem vs. growing pains vs. muscle cramps	RES
			ABNORMAL GAIT/ Difficulty walking			None	MILD	-2	10		RES
15059/M/3	US	YES[2]	ARM PAIN/ Arm pain and R elbow pain	Def	NONE	None	MILD	-10	4	Accidental trauma (pt. fell), pre-existing	RES
16011/F/16	US	YES[3]	--/	Def	NONE	None	--	-10	Ongoing	Abnormalities	INSUF

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
			abnormal joint and gait exam (knees, ankles, feet)							noted at baseline, related to pre-existing conditions; Pt lost to F/u	F/U
23007/F/6	US	NO	ARTHRALGIA/ Bilateral shoulder tenderness	Def	Pos	None	MILD	-7	15	IPSC: possibly reactive arthritis	RES
			ARTHRALGIA/ L knee pain			None	MILD	8	22	Eval by orthopedist: possible inflammatory arthritis	RES
26001/F/12	US	YES[4]	ARTHROSIS/ L ankle swelling	Def	NONE	None	MILD	-6	15	Accidental trauma (soccer injury); pre-existing	RES
			ARTHRALGIA/ R ankle pain			None	MILD	7	33	Sports activity	RES
27006/F/9	US	NO	ARM PAIN/ L forearm soreness	Pos	Pos	None	MILD	5	28	Not related to sports, may be soft tissue (and not joint) soreness	RES
40003/F/6	US	NO	ARTHRALGIA/ ankle pain; guarding in foot and stance	Prob	Prob	None	MILD	-7	15		RES
			ARTHRALGIA/ Bilateral hip			None	MILD	7	18	Noted when running;	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
			pain							possible growing pains	
102002/F/17	CAN	YES[5]	--/ bilateral ankle redness	Def	NONE	None	--	-11	Ongoing	Pre-existing deformity, wears KAFOs	UNCH
204016/M/2	SA	YES[6]	-- L shoulder warmth, pain, tenderness, and bruising	Def	Pos	None	--	-9	19	Accidental trauma (pt. fell from a chair)	RES
301089/F/7	ARG	NO	TENDON DISORDER/ R Achilles tendon ache	Pos	Pos	None	MILD	6	2	No history of trauma	RES
301090/F/7	ARG	NO	PAIN/ dorsal feet ache	Pos	Pos	None	MILD	3	2	No swelling or redness noted; IPSC: unusual complaint, may be joints in mid-foot	RES
301224/F/8	ARG	NO	LEG PAIN/ L thigh pain	Pos	Pos	None	MILD	24	4	IPSC: doubt arthropathy, since lasted only 3 days	RES
301297/M/12	ARG	YES[7]	--/ worsening pubic pain	Pos	Pos	RDT: diclofenac	--	40	Ongoing	Worsening of pre-existing condition; IPSC: could remotely be tendonitis	UNCH
307003/M/6	ARG	YES[8]	ARTHRALGIA/ Bilateral knee	Pos	Pos	None	MILD	0	1	Sporadic episodes of	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
			pain							knee pain prior to study	
307020/F/9	ARG	YES[9]	ARTHRALGIA/ Wrist pain	Def	Pos	None	MILD	-8	2	Ehlers Danlos Syndrome is pre-exisitng	RES
309015/F/8	ARG	NO	MYALGIA/ Quadriceps pain	Pos	Pos	None	MILD	8	25	Possibly related to excessive playing; IPSC: hip pain often referred to thigh, could also be quadriceps tendonitis	RES
401047/F/8	PERU	NO	ARTHRALGIA/ Mechanical gonalgia	Pos	Pos	RDT: topical diclofenac Other: articular protection	MILD	20	25	Dx by rheumatologist	RES
			ARTHRALGIA/ Oligoarthraligia			RDT: topical diclofenac, APAP Other: articular protection measures	MILD	136	15		RES
			ARTHRALGIA/ R ankle arthralgia			None	MILD	257	1	Dx by rheumatologist	RES
			ARTHRALGIA/			None	MILD	357	16	Dx by	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
			Mechanical arthralgia							rheumatologist	
402012/F/12	PERU	YES[12]	PAIN/ Worsening of non-specific growing pains	Pos	Pos	RDT: topical analgesic	MILD	31	22	Worsening of pre-existing condition	RES
402027/F/13	PERU	NO	MYALGIA/ myalgia	Prob	Prob	None	MILD	-6	3	Pain in R lower rib muscles	RES
			MYALGIA/ Coxalgia			None	MILD	2	6	Pain in both "coxfemoral joints"; IPSC: coxalgia is arthropathy	RES
504005/F/5	GER	YES[14]	--/ L hip pain	Pos	NONE	None	--	10	99	Pre-existing condition	RES

KEY for Table 25 (Study 100169)

Pos= possible; prob=probable; def = definite
Arg = Argentina; US = United States; Mex = Mexico; SA = South Africa; Ger = Germany; CR = Costa Rica; CAN = Canada;
Unk = unknown; Hosp = hospitalization; RDT = remedial drug therapy;
Mod = Moderate; Sev = servere
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

[2]R elbow painful on baseline exam(patient fell a few days prior to enrollment)
[3]Spina bifida; meningomyelocele; bilateral ankle and knee swelling; wears KAFOs
[4]History of fractured hand; R ankle swelling at baseline (soccer tournament prior to enrollment)
[5]Spina bifida; bilateral deformity of hips, knees, and ankles
[6]Gait abnormal (possibly due to developmental delays)
[7]History of pubic pain
[8]History of sporadic knee pain
[9]History of generalized ligamentous laxity and sporadic mild joint pain; Ehlers Danlos Syndrome
[12]History of growing pains (ankles)
[14] hip pain

TABLE 27
Ciprofloxacin Cases of Arthropathy as Assessed by the IPSC Occurring between Day 42 and 1 Year of Follow-Up
N=21 (5 patients had events occurring before Day 42)
ARTHRALGIA as the Event occurring after Day 42
Patients with an Arthropathy Event (any type of event, not just arthralgia) both pre-Day 42 and after Day 42

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
301213/M/1	ARG	NO	ABNORMAL GAIT/ R leg limp	Pos	Pos	Other: hip x-ray (normal)	MILD	91	13	Eval by traumatologist was normal	RES
302026/F/9	ARG	YES[1]	ARTHRALGIA/ Hip pain	Pos	Pos	RDT: ibuprofen	MILD	158	22		RES
306054/F/5	ARG	NO	BACK PAIN/ Lumbar pain	Def	NONE	Other: lumbosacral films (negative) RDT: ibuprofen	MILD	158	22		RES
			PYOGENIC ARTHRITIS/ Septic arthritis in R knee due to trauma			Hosp RDT: antibiotics	MOD	53	21	Serious event; trauma due to nail wound	RES
307004/M/16	ARG	YES[2]	BONE PAIN/Cervical spine pain	Prob	Pos	None	MILD	92	UNK	Intermittent back pain possibly related to kyphosis (pre-	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										existing)	
			BACK PAIN			Other: x-ray of hips (negative), x-ray of "spinal cord" (negative)	MILD	7	1		
			BACK PAIN/ Thoracolumbar pain			None	MILD	404	UNK	RES	
			BONE PAIN/Thoracic spine pain			None	MILD	92	UNK		
309014/F/11	ARG	NO	PAIN/ Growing pains (legs, ankle, knee)	Pos	NONE	Other: x-rays of ankle, knee, and feet (all normal)	MILD	199	72	RES One dose of ciprofloxacin; IPSC: too remote to be drug-related RES	RES
			MYASTHENIA/ Muscle weakness			None	MILD	199	72		
103001/F/5	CAN	YES[6]	--/ bilateral knee pain	Def	NONE	None	--	368	UNK	Also pain in L hip and L ankle (pre-existing) RES	INSUF F/U
701014/F/11	MEX	NO	LEG PAIN	Pos	NONE	None	MILD	335	29	Eval by physiotherapist (no inflammation problems);	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										IPSC: may be related to toting heavy backpack	
			BACK PAIN			None	MILD	335	30		
			MUSCULO-SKELETAL CONGENITAL ANOMALY/ R foot deformity			None	MILD	335	29	RES	RES
			HYPOTONIA/ Poor lumbar tone			None	MILD	335	29	Poor posture	RES
707033/F/4	MEX	YES[7]	--/ bilateral ankle and foot tenderness on joint exam	Pos	NONE	None	--	150	273	IPSC: history of ankle pain while running – growing pains or bony abnormality	RES
402052/F/11	PERU	YES[8]	ACCIDENTAL INJURY/ worsening articular hypermotility	Pos	NONE	None	MILD	215	39	Eval by rheuma-tologist: episodic pain in knees lasting for < 1 hour, related to articular hypermotility	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
1001/F/5	US	NO	--/ bilateral knee redness and warmth on joint exam	Def	Pos	None	--	-10	14	IPSC: transient arthralgia during infection is not unusual	RES
			--/ bilateral ankle warmth			None	--	4	35		RES
			ARTHRALGIA/ Joint pain, non-specific, generalized			None	MILD	229	10	Pt doing increased physical activity prior to joint pain; normal joint exam	RES
1021/F/10	US	NO	ARTHRALGIA/ Bilateral wrist tenderness	Def	Pos	RDT: APAP	MILD	5	3	Associated with wrestling event	RES
			ARTHRALGIA/ L wrist discomfort			None	MILD	9	1		RES
			LEG CRAMPS/ change in knee flexion (stiffness)			RDT: APAP	MILD	5	3		RES
			ARTHRALGIA/ Bilateral wrist discomfort			None	MILD	70	14	Hyper-extended wrists during volleyball	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										game	
1031/F/10	US	NO	LEG PAIN/ R foot arch pain and collapse	Def	NONE	Other	MILD	87	6	Accidental trauma (twisted ankle)	RES
2015/F/7	US	YES[10]	ARTHRALGIA/ L hip arthralgia	Def	Pos	Other	SEV	45	5		RES
			ARTHRALGIA/ Bilateral knee pain			Other	SEV	186	52		RES
			MYALGIA/ Fibromyalgia			RDT	MOD	202	Ongoing		RES
			ACCIDENTAL INJURY/joint hypermobility (wrists/elbows/hips/etc.)			None	MILD	66	Ongoing	Diagnosis performed by rheuma-tologist	UNCH
8001/F/5	US	NO	--/ L ankle swelling noted on joint exam	Def	NONE	None	--	125	242	Accidental trauma (pt. tripped and rolled ankle)	RES
11002/F/3 (Stratum II)	US	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	0	3		RES
			ARTHRALGIA/ Bilateral wrist pain			None	MILD	215	19		RES
			ARTHRALGIA/			None	MILD	215			RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			Bilateral elbow pain						19		
13047/F/9 (Stratum II)	US	NO	ARTHRALGIA/ Bilateral knee pain	Prob	NONE	RDT: ibuprofen	MILD	199	UNK	Accidental trauma (pt. fell on stairs); lost to follow-up	INSUF F/U
16014/F/12	US	YES[11]	ARTHRALGIA/ Bilateral intermittent ankle pain	Def	Pos	None	MILD	14	32	Pt. active in sports	RES
			ACCIDENTAL INJURY/ L foot trauma			None	MOD	102	3	Accidental trauma (horse stepped on pt. foot during an equestrian event)	RES
			PAIN/ Bilateral intermittent foot pain			None	MILD	14	32	Pt. active in sports	RES
			ACCIDENTAL INJURY/ Lateral-collateral ligament injury			None	MOD	246	217	Accidental trauma (soccer injury)	RES
			ACCIDENTAL INJURY/ R ankle injury			None	MILD	522	1	Accidental trauma (soccer injury)	RES
			ARTHRALGIA/ R knee pain			None	MILD	74	31	Accidental trauma	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										(soccer injury)	
			LEG PAIN/ Plantar surface heel pain (sports injury)			None	MILD	23	23	Accidental trauma (sports injury)	RES
26018/F/7	US	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	None	MILD	89	93	2 days of ciprofloxacin; IPSC: pain attributed to growing pains; not usually found in knees	RES
44036/F/7	US	YES[14]	ARTHRALGIA/ Bilateral ankle pain	Pos	NONE	None	MILD	370	UNK	2 days of ciprofloxacin; intermittent pain (few times per week and worse after increased activity); IPSC: abnormal spinal cord terminus may be reason for asymmetry on ROM, ankle pain	INSUF F/U

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
204033/F/8	SA	YES[15]	ARTHRALGIA/ Bilateral painful knees	Def	Pos	Other: Patellar tap (negative)	MILD	331	66	Painful knees at night and after walking long distances	RES
205010/F/4	SA	NO	MOVEMENT DISORDER/ Hip rotation decreased	Pos	NONE	None	MILD	368	UNK	No pain, normal waling pattern; IPSC: not considered significant, baseline values suggest improper positioning	UNCH

KEY for Table 27 (Study 100169)

Pos= possible; prob=probable; def = definite
Arg = Argentina; US = United States; Mex = Mexico; SA = South Africa; Ger = Germany; CR = Costa Rica; CAN = Canada;
Unk = unknown; Hosp = hospitalization; RDT = remedial drug therapy;
Mod = Moderate; Sev = servere
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

[1]History of R thigh pain
[2]Kyphosis
[6] pain in L hip at quadriceps area and L ankle
[7] History of ankle pain when running
[8] Articular hypermotility
[10] History of pain in leg, back, knee, hip, which was diagnosed as “growing pains”; myelomeningocele
[11]Abnormal gait (decreased hip extension bilaterally); swelling of R and L knees
[14] Abnormal spinal cord terminus @ T12
[15]L shoulder pain

TABLE 28
Comparator Cases of Arthropathy Occuring between Day 42 and 1 Year of Follow-Up as Assessed by the IPSC
N=13 (one patient also had events occurring before Day 42)
ARTHRALGIA as the Event occurring after Day 42
Patients with an Arthropathy Event (any type of event, not just arthralgia) both pre-Day 42 and after Day 42

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
12001/F/14	US	YES[1]	ARTHRALGIA/ Intermittent L knee pain	Def	Pos	RDT: ibuprofen, APAP	MILD	160	Ongoing	Possible retropatellar syndrome	INSUF F/U
13011/F/7 (Stratum II)	US	NO	ARTHRALGIA/ R knee soreness and R ankle warmth	Prob	NONE	None	MILD	363	81	Accidental trauma (pt. fell); Pre-existing condition	RES
2012/F/9	US	NO	MYALGIA/ fibromyalgia	Def	NONE	RDT: APAP, Flexeril	SEV	326	Ongoing	Eval by rheumatologist, dx fibromyalgia	UNCH
33025/M/9	US	NO	ARTHRALGIA/ Bilateral hip pain	Prob	Pos	None	MILD	99	15	Anterior pain with extension; gluteal pain when sitting 30 min	RES
37001/F/4	US	NO	ARTHRALGIA/ L ankle pain	Pos	Pos	Other: x-ray (neg)	MILD	85	12	Noted when running	RES
103015/F/6	CAN	NO	--/ on caregiver questionnaire noted difficulty walking, bending, kneeling, and	Pos	NONE	None	--	192	169	Bilateral knee pain, and ankle/foot pain on joint exam; possibly related to obesity	RES

			stooping; trouble climbing stairs								
306004/F/5	ARG	NO	ARTHRALGIA/ Shoulder pain	Pos	NONE	None	MILD	364	Ongoing		INSUF F/U
			ARTHRALGIA/ Knee pain			None	MILD	364	Ongoing		INSUF F/U
309018/F/9	ARG	YES[10]	--/ elbow pain and weakness in forearm	Pos	NONE	None	--	93	4	Pre-existing	RES
401047/F/8	PERU	NO	ARTHRALGIA/ Mechanical gonalgia	Pos	Pos	RDT: topical diclofenac Other: articular protection	MILD	20	25	Dx by rheumatologist	RES
			ARTHRALGIA/ Oligoarthraligia			RDT: topical diclofenac, APAP Other: articular protection measures	MILD	136	15		RES
			ARTHRALGIA/ R ankle arthralgia			None	MILD	257	1	Dx by rheumatologist	RES
			ARTHRALGIA/ Mechanical arthralgia			None	MILD	357	16	Dx by rheumatologist	RES

402007/F/6	PERU	YES[11]	MYALGIA/ Myalgia	Pos	Pos	None	MILD	124	69	Growing pains pre-existing; IPSC: possible myalgia vs. arthralgia	RES
402037/F/12	PERU	YES[13]	ACCIDENTAL INJURY/ Worsening of articular hypermotility	Pos	NONE	None	MOD	159	31	Worsening of pre-existing condition	RES
502008/F/9 (Stratum II)	GER	NO	--/ R ankle pain on joint exam	Pos	NONE	None	--	363	Ongoing	Pt. played soccer on the day prior	INSUF F/U
506009/F/2 (Stratum II)	GER	NO	MOVEMENT DISORDER/ Reduced hip movement	Pos	NONE	Other: ultrasound of both hips (WNL)	MILD	271	Ongoing	IPSC: would have expected fluid on US if arthropathy	INSUF F/U

KEY for Table 28 (Study 100169)

Pos= possible; prob=probable; def = definite
Arg = Argentina; US = United States; Mex = Mexico; SA = South Africa; Ger = Germany; CR = Costa Rica; CAN = Canada;
Unk = unknown; Hosp = hospitalization; RDT = remedial drug therapy;
Mod = Moderate; Sev = servere
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

[1]Spina bifida occulta; baseline stiff knees and L ankle swelling; gait abnormal
[10]L elbow pain
[11]History of growing pains
[13] articular hypermotility

TABLE 53
Serious Adverse Events by Patient and Treatment Group
Patients Valid for Safety

TREATMENT GROUP	PATIENT	COSTART TERM	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	OUTCOME OF EVENT
CIPROFLOXACIN	1003	OVERDOSE	INCORRECT DOSE OF ST	1	1	RESOLVED
CIPROFLOXACIN	1040	URINARY INCONTINENCE	REPAIR OF NEUROGENIC	11	50	RESOLVED
CIPROFLOXACIN	14001	PYELONEPHRITIS	PYELONEPHRITIS	2	7	RESOLVED
CIPROFLOXACIN	15028	UROGENITAL SURGERY	LEFT PYELOPLASTY	38	38	RESOLVED
CIPROFLOXACIN	16001	PYELONEPHRITIS	PYELONEPHRITIS	43	45	RESOLVED
CIPROFLOXACIN	16001	CONVULSION	ACUTE ONSET SEIZURES	311	316	RESOLVED
CIPROFLOXACIN	16001	OVERDOSE	DILANTIN TOXICITY	329	331	RESOLVED
CIPROFLOXACIN	36002	CONSTIPATION	WORSENING CONSTIPATI	28	118	RESOLVED
CIPROFLOXACIN	36002	ABDOMINAL PAIN	CHRONIC ABDOMINAL DI	28	118	RESOLVED
CIPROFLOXACIN	36002	ASPIRATION PNEUMONIA	ASPIRATION PNEUMONIA	29	33	RESOLVED
CIPROFLOXACIN	201005	UROGENITAL SURGERY	URETHROTOMY	13	16	RESOLVED
CIPROFLOXACIN	301100	MYOPATHY	DUCHENNE DISEASE.	19	.	UNCHANGED
CIPROFLOXACIN	301100	CONVULSION	SEIZURE	112	112	RESOLVED
CIPROFLOXACIN	301100	MYOPATHY	DUCHENNE DISEASE	133	135	UNCHANGED
CIPROFLOXACIN	301213	CONVULSION	SEIZURE ASSOCIATED W	212	212	RESOLVED
CIPROFLOXACIN	303010	HYDROURETER	RIGHT URETER STENOSI	14	33	RESOLVED
CIPROFLOXACIN	303033	ACCIDENTAL INJURY	CRANIUM TRAUMA	46	46	RESOLVED
CIPROFLOXACIN	304001	HYDRONEPHROSIS	HYDRONEFROSIS	28	33	RESOLVED
CIPROFLOXACIN	304004	HYDRONEPHROSIS	HYDRONEFROSIS	49	58	RESOLVED
CIPROFLOXACIN	305007	HYPERTENSION	HYPERTENSION	4	46	RESOLVED
CIPROFLOXACIN	306003	PYELONEPHRITIS	PYELONEPHHRITIS(NEPH	5	8	RESOLVED
CIPROFLOXACIN	306005	PYELONEPHRITIS	PIELONEPHRITIS WORSE	2	5	RESOLVED
CIPROFLOXACIN	306005	HEPATITIS	HEPATITIS A	8	37	RESOLVED
CIPROFLOXACIN	306054	PYOGENIC ARTHRITIS	ARTHRITIS SEPTIC ON	63	83	RESOLVED
CIPROFLOXACIN	306056	RESPIRATORY DISORDER	THROAT CUT	24	24	DEATH
CIPROFLOXACIN	307006	INFECTION VIRAL	SYNDROME WITH FEVER,	3	8	RESOLVED
CIPROFLOXACIN	309014	PYELONEPHRITIS	PYELONEPHRITIS	1	5	RESOLVED
CIPROFLOXACIN	505010	URTICARIA	URTICARIA	28	30	RESOLVED
CIPROFLOXACIN	601079	VOMITING	VOMITING	37	41	RESOLVED
CIPROFLOXACIN	601079	PYELONEPHRITIS	PYELONEPHRITIS	37	41	RESOLVED
CIPROFLOXACIN	701032	ACCIDENTAL INJURY	LEFT FEMUR FRACTURE	220	470	RESOLVED
CIPROFLOXACIN	704006	PYELONEPHRITIS	PYELONEPHRITIS	13	18	RESOLVED
CIPROFLOXACIN	707021	CARCINOMA	PINEAL GERMINOM	6	264	IMPROVED
CEFTAZIDIME	15060	SEPSIS	UROSEPSIS	12	16	RESOLVED
CEFTAZIDIME	44030	URINARY TRACT INFECTION	UTI	51	54	RESOLVED
CEFTAZIDIME	303001	PYELONEPHRITIS	ACUTE PYELONEPHRITIS	20	22	RESOLVED
CEFTAZIDIME	303001	URINARY TRACT INFECTION	ASYMPTOMATIC BACTERI	57	61	RESOLVED
CEFTAZIDIME	303046	PYELONEPHRITIS	PYELONEPHRITIS WORSE	3	5	RESOLVED
CEFIXIME	13031	ACCIDENTAL INJURY	CLOSED FRACTURE OF L	53	488	RESOLVED
CEFIXIME	13031	ACCIDENTAL INJURY	CLOSED FRACTURE L FI	53	488	RESOLVED
CEFIXIME	16009	URINARY TRACT INFECTION	BREAKTHROUGH URINARY	10	17	RESOLVED
CEFIXIME	16009	PYELONEPHRITIS	PYELONEPHRITIS	38	43	RESOLVED
CEFIXIME	27005	URINARY TRACT DISORDER	BILATERAL URETERAL R	31	36	RESOLVED
CEFIXIME	28009	HYPERTONIA	HYPERTONIA	120	.	UNCHANGED

TABLE 53 (continued)
Serious Adverse Events by Patient and Treatment Group
Patients Valid for Safety

TREATMENT GROUP	PATIENT	COSTART TERM	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	OUTCOME OF EVENT
CEFIXIME	28009	URINARY INCONTINENCE	INCREASING URINARY I	120	238	RESOLVED
CEFIXIME	28009	NEUROPATHY	TETHERED SPINAL CORD	218	218	RESOLVED
CEFIXIME	301080	ACCIDENTAL INJURY	RIGHT ORBIT FRACTURE	228	234	RESOLVED
CEFIXIME	301080	SUBDURAL HEMATOMA	SUBDURAL HEMATOMA.	228	234	RESOLVED
CEFIXIME	301089	PURPURA	SCHONLEIN-HENOCH PUR	275	282	RESOLVED
CEFIXIME	301297	UROGENITAL ANOMALY	BLADDER EXTROPHY REP	12	14	RESOLVED
CEFIXIME	301297	ACCIDENTAL INJURY	LEFT TOE PHALANXÀS F	79	191	RESOLVED
CEFIXIME	301297	ACCIDENTAL INJURY	LEFT TIBIAL FRACTURE	79	191	RESOLVED
CEFIXIME	306024	PENIS DISORDER	PHIMOSIS	24	25	RESOLVED
CEFIXIME	306072	CONVULSION	FEBRILE SEIZURE	205	207	RESOLVED
CEFIXIME	307024	URINARY TRACT DISORDER	URETEROCELE WITH VES	8	26	RESOLVED
CEFIXIME	401098	CEREBRAL HEMORRHAGE	INTRACRANIAL HEMATOM	78	100	RESOLVED
CEFIXIME	401098	CONVULSION	SEIZURES DUE TO HEAD	79	79	RESOLVED
CEFIXIME	402031	CELLULITIS	LEFT SUBMANDIBULAR C	45	52	RESOLVED
CEFIXIME	601009	HYDRONEPHROSIS	RIGHT HYDRONEPHROSIS	14	18	RESOLVED
CEFIXIME	601039	MENINGOMYELOCELE	WORSENING OF MYELOME	273	280	RESOLVED
CEFIXIME	706051	URINARY TRACT INFECTION	URINARY INFECTION RE	21	30	RESOLVED
TMP/SMX 160/800 MG BID	105002	URINARY TRACT INFECTION	PSEUDOMONAS UTI	20	31	RESOLVED

12. APPENDIX 2 - REVIEW OF STUDY 100201 (INTERIM REPORT 100225)

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

Study Number: 100225 (an interim analysis of Study 100201 of all data collected as of June 30, 2003)
Date of the Study Report: September 12, 2003
Study centers: This study was conducted at 67 study sites in the US and one in Canada.

Period of study (first patient's first visit to last patient's last visit):
April 25, 2000 to June 30, 2003 (interim analysis cut-off date)

12.1 Ethical Conduct of the Study

This study was conducted in accordance with Good Clinical Practice (GCP) regulations and all applicable US FDA regulations, including the archiving of required documents. These practices included the following areas: IRB procedures; informed consent; protocol adherence; administrative documents (Form FDA-1572, etc); drug supply accountability; data collection; subject records (source documents); adverse event recording and reporting; inspection and audit preparation; and records retention. The investigators were made aware that FDA and Bayer representatives could inspect the documents and patient records at any time.

This study was monitored by a contract research organization (CRO), (b) (4) in accordance with GCP guidelines and Standard Operating Procedures (SOP) for Bayer (b) (4)

12.2 Study Objectives

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 (i.e., pathology of the joint) and other musculoskeletal sequelae (i.e., articular cartilage, tendon and ligament), if any, of IV, sequential (IV→ PO), and purely oral ciprofloxacin therapy or non-quinolone antibiotic therapy in pediatric patients with various infectious conditions. A co-primary objective was to determine the short- and long-term neurological system tolerability of courses of ciprofloxacin or non-quinolone antibiotic therapy.

12.3 Study Design

This observational study was planned to be a prospective, open-label, non-randomized, multi-center, North American pediatric clinical trial to assess long-term musculoskeletal and neurological system health in infants and younger children (i.e., ≤6 years of age at trial entry) for up to 5 years post-exposure to ciprofloxacin or a non-quinolone antibiotic for pre-pubescent and pubescent children and for 1 year post-exposure to ciprofloxacin or non-quinolone antibiotic for post-pubescent children. There were 4 amendments to the original protocol, which are summarized

in the following section. Originally, the study protocol was not designed for a control group. However, a non-quinolone treatment arm was added to this study at the request of the FDA in Amendment 4.

The decision to treat with either ciprofloxacin or a non-quinolone antibiotic was made prior to a patient's enrollment in the study and was based on the particular infection, type of patient, medical history and the clinical evaluation by the prescribing physician. After the investigator determined that a particular infant or child with an eligible infection was suitable for treatment with ciprofloxacin or a non-quinolone antibiotic, the selection of study unit dose, total daily dose, duration of therapy, route of administration, and formulation (i.e., ciprofloxacin IV, ciprofloxacin oral suspension or ciprofloxacin tablets) was left to the discretion of the pediatric investigator.

Similarly, after the investigator determined that a particular infant or child with an eligible infection was suitable for a non-quinolone antibiotic therapy, the selection of that agent and its unit dose, total daily dose, duration of therapy, route of administration, and formulation (i.e., whether IV, PO tablets or suspension) was left to the discretion of the pediatric investigator.

12.4 Summary of Amendments

There were 4 amendments made to the original protocol dated July 22, 1999 and a summary of the changes accounted for in each amendment are summarized below.

Amendment 1 (December 15, 1999)

- Clarified the timing interval between ciprofloxacin and infant formula (i.e., feeding two hours before or after dosing)
- Corrected discrepancies among the referred to age groups
- Deleted a reference to a data collection instrument other than a CRF
- Provided clarification on performance of required gait/joint examinations and the category of professional evaluator required to perform the exams (physical therapist or rheumatologist)
- Specified the type of intervention (i.e., imaging) to evaluate cases presenting with signs and/or symptoms suggestive of arthropathy
- Added a cap on enrollment of patients in the adolescent age group (a single center should not have enrolled more than 2 patients aged 12 to 16 years of age)
- Clarified the categorization and reporting of adverse events during the long term follow-up

Amendment 2 (July 20, 2000)

- Replaced Joseph Barone, MD (Bayer) with [redacted] (b) (4) as the Medical Monitor;
- Extended the permissible window for a patient's pre-therapy gait/joint examination from 48 hours prior to initiation of study drug therapy up to 24 hours after receipt of the first dose of study drug. This permitted study enrollment in the overnight hours when children presented through the emergency department and qualified physical therapy personnel might not have been available.
- Allowed for enrollment of children reliant on infant formula provided they were treated with IV medication only;
- Corrected a typographical error in the dose strength of the 5% suspension;

- Clarified the exclusion of all children with a diagnosis of cystic fibrosis whether or not this current infection was an exacerbation of the underlying disease;
- Clarified that patients enrolled into Study 100169 (complicated UTI study) could be enrolled into the observational study provided informed consent was provided to allow for retrospective collection of the data from the initial year

Amendment 3 (January 23, 2001)

- Allowed for enrollment of patients up to 72 hours after initiation of study drug treatment;
- Specified provisions for performance of the gait/joint examination when a certified physical therapist was not available;
- Clarified the expectation for documentation of the ROM examination within the CRF;
- Allowed for enrollment of children with febrile neutropenia receiving ciprofloxacin prophylaxis pending recovery of white blood cell (WBC) count to ≥ 500 cells per mm^3;
- Clarified the exclusion of children with cystic fibrosis from the protocol;
- Provided a gait/joint examination flow diagram

Amendment 4 (October 20, 2001)

- Added a non-quinolone arm to the present study. The objective was to obtain information (i.e., assess the "background noise") on musculoskeletal adverse events that could have occurred in this pediatric population had they received treatment with a non-quinolone antibiotic and to monitor these adverse events for the same duration as the ciprofloxacin-treated patients.
- Shortened the long-term follow-up period from 5 to 10 years to 1 to 5 years. Pre-pubescent and pubescent children were to be followed for 5 years and post-pubescent children were to be followed for 1 year. Patients who experienced a musculoskeletal adverse event during therapy were to be followed for 5 years regardless of their stage of pubescence.
- Revised downward the total number of patients to be enrolled from 3,000 to approximately 900 patients. Approximately half (450) of these 900 patients were to be in the ciprofloxacin arm and approximately half (450) in the non-quinolone antibiotic arm. This sample size would provide 95% probability of seeing at least one event that had the event rate of 1 in 250. This is based on combining these 900 patients with at least 600 patients available from another pediatric ciprofloxacin trial (Study 100169).
- Specified demographic and baseline characteristics were to be summarized by treatment group as well as type of ciprofloxacin treatment (IV versus oral), age group (≥ 2 months to < 24 months; 2 years to < 6 years; ≥ 6 years to < 12 years; ≥ 12 years to < 17 years).

The decision to treat with ciprofloxacin or a non-quinolone antibiotic was made prior to a patient's enrollment in the study and was based on the particular infection, type of patient, medical history and the clinical evaluation by the prescribing physician.

This amendment was not intended to change any treatment decisions to be made by the prescribing physician, but merely to add a comparator group of patients who were treated with anon-quinolone antibiotic over the same 1 to 5 year time period as

the treatment group and to document the musculoskeletal and CNS adverse events in both groups.

12.5 Inclusion Criteria

Patients in the age range of 2 months through 16 years of age (i.e., had not reached their 17th birthday) were eligible for enrollment in the study.
A parent/caregiver must have signed an informed consent form, and the patient must have provided assent, as appropriate, based on local IRB guidelines.
Low-risk febrile patients with neutropenia during cancer chemotherapy could be enrolled provided their neutropenia was expected to resolve (>=500 cells per mm^3) within 10 days after the onset of fever. Neutropenic patients with abdominal pain, nausea and vomiting, or diarrhea (passage of 6 loose stools daily) could be enrolled provided they were treated with IV medication and did not meet any of the exclusion criteria.

12.6 Exclusion Criteria

Patients meeting any of the following criteria were not to be enrolled in this study:

- Low-risk patients with febrile neutropenia during cancer chemotherapy who were unstable hemodynamically, had neurological or mental status changes, intravascular catheter infection, catheter tunnel infection, or a new pulmonary infiltrate.
- Underlying diagnosis of or acute exacerbation of cystic fibrosis (CF);
- Acute or chronic meningitis;
- Brain abscess;
- Acute or subacute bacterial endocarditis (ie, ABE or SBE);
- Ciprofloxacin as antimicrobial prophylaxis (except for cases of low-risk febrile neutropenia during cancer chemotherapy);
- Bone and joint infections (e.g., septic arthritis);
- A medical history of one or more of the following conditions:
- Arthritis, not further categorized
- Juvenile rheumatoid arthritis (JRA)
- Rheumatoid arthritis (RA)
- Systemic lupus erythematosis (SLE)
- Spondylitis, of any etiology
- History of rheumatic fever
- Psoriasis
- Inflammatory bowel disease
- Behcet's syndrome
- Chondromalacia
- Hypermobility
- Osteoarthritis (OA);
- Sustained broken bones including small and large bone fractures within 90 days prior to their course of study drug;
- Known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy. Patients with conditions precluding the performance of a reliable series of musculoskeletal examinations were to be excluded from trial participation.

- Patients with any pretreatment baseline musculoskeletal abnormalities on examination;
- Infants and children with spina bifida with: total or near total paralysis of the lower extremities (i.e., motor strength of 0/1+ in the major muscle groups of both lower extremities), and/or who could ambulate only with the recruitment of the upper extremity muscle groups, and/or have associated significant congenital or acquired neuro-orthopedic structural pathology of the lower extremities (i.e., bilateral neuropathic joints, hip dysplasias or dislocations, or arthrogryposis) were to be excluded from trial participation. Enrollment of children with an underlying diagnosis of spina bifida was not to exceed 20% of the target enrollment. [The applicant was to notify centers at the time enrollment of spina bifida patients was to be stopped.]
- Known risk of experiencing seizures, a history of any convulsive disorders or head injury/trauma, current use of anti-seizure medication or within 2 months post-stroke;
- Concomitant systemic antibacterial agents known to have arthropathic effects. Patients could not receive additional quinolone therapy during the observational period during which they received ciprofloxacin for the trial.
- Participation in any industry-sponsored clinical drug development study within one month prior to this study. An exception was infants, children and adolescents enrolled into the ciprofloxacin pediatric complicated UTI study (Study 100169). These patients did not receive treatment with a second course of ciprofloxacin or a new course of a non-quinolone antibiotic; rather they could be enrolled into the observational trial at any time during the initial year of the study since the musculoskeletal information collected for the 100169 study was identical to that required by Protocol 100201. Informed consent was to be provided to allow for retrospective collection of data from the initial year.
- Known significant liver impairment (ALT or AST and/or baseline bilirubin >3 times the upper limit of the normal range);
- Known significant renal insufficiency (calculated creatinine clearance of <30 mL/min/1.73 m^2);
- Pregnant or lactating, or sexually active with unreliable contraception. Sexually active females were to use reliable contraception or abstinence during exposure to study drug. Reliable contraception could include barrier methods (e.g., condoms, diaphragms, intra-uterine devices, implants). Patients taking oral contraceptives were to use barrier contraception with spermicidal foam or abstinence during study drug exposure.
- Reliant on infant formula for nutrition such that dosing of study medication two hours before or after a feeding would not be possible. Patients reliant on formula feedings were eligible for enrollment provided they received IV antibiotics for the entire course of treatment.
- For those patients in the non-quinolone antibiotic arm, there could not be a previous history of quinolone use, or a known allergy to the non-quinolone antibiotic (or related class of non-quinolone antibiotic) being prescribed or treatment with Ceclor® (cefaclor).
- No single center could enroll more than 2 patients aged 12 through 16 years.

12.7 Removal of Patients from Therapy or Assessment

If the patient did not show improvement within 2 to 5 days (therapeutic failure), or if a serious allergic reaction occurred or a superinfection developed, ciprofloxacin or non-quinolone antibiotic therapy was to be discontinued and other appropriate therapy initiated.

All patients who discontinued therapy prematurely, including those who received only one dose of study drug, continued to undergo prospective musculoskeletal and neurological system safety assessments (i.e., periodic examination of the weight-bearing joints and shoulder girdle, gait, and other neurological assessments and caregiver questionnaires).

12.8 Treatments Administered

Investigators were to consider the child's age and renal functional status in the selection of a ciprofloxacin dosing regimen. When administered as an oral formulation, the recommended dose of ciprofloxacin was 5 to 20 mg/kg every 12 hours (q12h), depending upon the severity of infection. When administered as an IV formulation, the recommended dose of ciprofloxacin was 6 mg/kg q12h or 12mg/kg q8h, depending on the severity of infection. The maximum permissible doses in this study were 750 mg twice daily orally (i.e., total daily dose 1500 mg) or 400 mg 3 times daily intravenously (i.e., total daily dose 1200 mg) and were not to be exceeded. Investigators were referred to the approved product labeling (i.e., package insert for US sites or product monograph for Canadian sites) for the dosages and frequency of administration of ciprofloxacin within a 24-hour period.

When treatment was with a non-quinolone antibiotic, investigators were to adhere to the prescribing and dosing information found in the approved package label (i.e., package insert for US sites or product monograph for Canadian sites) or the Physicians. Desk Reference (US sites) or Compendium of Pharmaceuticals and Specialties (Canadian sites). In all cases, the maximum daily dose for the prescribed non-quinolone antibiotic was not to be exceeded.

In general, ciprofloxacin therapy was to be administered for a minimum duration of 7 days and a maximum duration of 21 days, and similarly, the non-quinolone-treated patients were to have comparable treatment durations.

Supplies of the study drug ciprofloxacin (ciprofloxacin IV, ciprofloxacin oral tablets and ciprofloxacin oral suspension) or non-quinolone antibiotics were not provided by the sponsor; study supplies were provided by the clinical sites. Medication was dispensed in commercial packaging.

12.9 Prior and Concomitant Therapy

Efforts were to be made to minimize the total number of concomitant drugs (of any kind) administered to the patient during the duration of ciprofloxacin or non-quinolone antibiotic medication administration. All concomitant medications were recorded on the CRF.

Antibacterial agents were not to be administered concomitantly with study medication. Investigators were to avoid the use of fluoroquinolone antibiotics (including ciprofloxacin) or a non-quinolone antibiotic in all study patients following termination or completion of their prescribed drug regimen through completion of the long term follow-up, insofar as clinically feasible, and provided that a fluoroquinolone or non-quinolone antibiotic were not absolutely clinically indicated at any time during the follow-up period.

Prohibited drugs are listed in the package labeling for ciprofloxacin, which recommends cautious use of concomitant administration of sulfonylurea glyburide, fenbufen, and probenecid. If concomitant administration of theophylline and ciprofloxacin could not be avoided, serum levels of theophylline were to be monitored and dosage adjustments made as appropriate. If oral anticoagulants were administered concomitantly with ciprofloxacin, prothrombin time (PT) or other suitable coagulation tests were to be closely monitored. In rare instances, some quinolones, including ciprofloxacin, have been reported to interact with phenytoin leading to altered levels of serum phenytoin concentrations. Concurrent administration of antacids (containing magnesium, aluminum or calcium), sucralfate, iron supplements, and zinc-containing vitamins with ciprofloxacin were to be avoided. Likewise, the administration of infant formula with ciprofloxacin oral suspension was to be avoided. Should concurrent administration be necessary, ciprofloxacin oral suspension was to be given 2 hours before or after a formula feeding. Quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine.

The investigators were referred to approved package inserts (US sites) or product monographs (Canadian sites) or full prescribing information as found in The Physicians. Desk Reference (US sites) or Compendium of Pharmaceuticals and Specialties (Canadian sites) for non-quinolone antibiotics and their distinctive drug interactions and warnings.

12.10 Treatment Compliance

In the case of hospitalized patients, medication administration record (MAR) sheets were to be reviewed to determine whether patients were compliant with the prescribed dosing regimen. For those outpatients treated with ciprofloxacin tablets or oral suspension or for those in the non-quinolone antibiotic group, caregivers were instructed to report both the number of days and doses of oral ciprofloxacin or non-quinolone antibiotic which their infant or child received. This information was collected at the required one-month follow-up visit (Day +28 to +42).

All patients who received at least one dose of the prescribed study regimen (regardless of the initially intended duration and frequency of dosing) were considered valid for safety and were to be followed as per protocol.

12.11 Efficacy and Safety Variables

The incidence of arthropathy as a musculoskeletal system adverse event was specifically evaluated. In addition, neurological system adverse event incidence rates were documented. 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. This definition was seen as broad and inclusive of such phenomena as bursitis, enthesitis and tendonitis.

The Independent Pediatric Safety Committee (IPSC) 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 study. Their assessments of arthropathy classification, relationship of arthropathy to study drug therapy, and possible pre-existing conditions were used for the statistical analyses described in this study.

Parent-reported musculoskeletal and neurological system adverse event incidence rates as documented on the questionnaires initially and later through telephone interviews at 3 months, 6 months, 9 months, and 12 months for the first year post-exposure and were performed quarterly as well for up to one year for post-pubescent children or five years for pre-pubescent and pubescent children. Patients who experienced a musculoskeletal adverse event during therapy were to be followed for 5 years regardless of their stage of pubescence.

12.11.1 Efficacy and Safety Measurements

To fulfill the primary objective of the study and to determine the clinical safety of ciprofloxacin or non-quinolone antibiotic in pediatric patients, two structured assessments for general, neurological and musculoskeletal safety, i.e., evaluations of the joints (especially all weight-bearing joints) and gait, were required. These were to be conducted within 72 hours of initiation of ciprofloxacin or non-quinolone antibiotic administration, which was considered a patient's baseline, and at the 1-month follow-up (Day +28 to +42).

Baseline Visit
Patients had a routine physical examination including neurological assessment performed at the time of study enrollment. If patients started ciprofloxacin therapy or non-quinolone antibiotic 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 CRF. Patients also had a gait/joint examination to assess the range of motion (ROM) of the weight-bearing joints (in particular, the hip, knee and ankle) as well as the shoulder girdle. Parents/caregivers were also 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.

Follow Up Visit (Day +28 to +42)
Patients were seen again approximately 4 to 6 weeks (Day +28 to +42) following the course of ciprofloxacin or non-quinolone antibiotic therapy in the office to assess whether there had been any changes in gait, ROM, or

neurological exam. On completion of this visit, the role of the enrolling clinical site was completed, unless a problem was detected during telephone interviews in which case the child was referred back to the clinical site.

Telephone Contact

Patients/caregivers then were interviewed by telephone at 3, 6, 9, and 12 months (of the first year) and quarterly each year thereafter for the purpose of long-term follow-up of musculoskeletal and neurological system status checks.

During the treatment phase, the 1-month follow-up, and the long-term surveillance period, parents/caregivers were provided with a phone number to call in the event their child developed musculoskeletal or neurological symptoms. A triage specialist, who was to assess such events and recommend appropriate follow-up, including specialist referrals, was assigned to answer these calls. The primary focus of this trial was assessment of the musculoskeletal and neurological safety of ciprofloxacin or non-quinolone antibiotics in pediatric patients.

12.11.2 Follow-Up for Musculoskeletal Adverse Events

All serious adverse events reported spontaneously or by the investigator, were reported through the 1-month follow-up visit (Day +28 to +42, inclusive). The reporting of all non-serious and serious adverse events beyond the structured 1-month follow-up visit during the long-term surveillance (i.e., registry) phase of the child's participation was primarily the responsibility of the parent or caregiver.

The musculoskeletal safety assessments were carried out primarily through objective evaluations of joint appearance, structure and function (i.e., ROM testing) and of gait conducted by either rheumatologists or trained physical therapists experienced in musculoskeletal examinations. If the physical therapist and rheumatologist were unavailable at the time of enrollment, the examination could have been conducted by a physician trained in gait/joint examination conduct. This training was to include the review of a videotape provided by the applicant which demonstrated proper passive ROM measurements for each of the joints of interest.

Formal physical examination of all joints was performed; however, special care and attention were given to the weight-bearing joints (i.e., knees, hips, and ankles) and to the shoulder girdle. Joints were examined for pain/tenderness, evidence of inflammation (i.e., redness, warmth, swelling or ballotable fluid), loss of function (to the extent this could be assessed in younger children and infants) and any restrictions to expected active/passive ROM. Both active and passive ROM were always to be assessed. Passive ROM was recorded in the CRF. For shoulders, knees, hips and ankles, the motions tested and their normal ranges recorded were as follows:

- Shoulder: extension, flexion, abduction, internal and external rotation
- Hip: extension, flexion, adduction, abduction, internal and external rotation
- Knees: extension and flexion
- Ankles/feet: plantar flexion, dorsiflexion

Any post-baseline abnormal finding noted on the clinical joint or gait assessment was followed up by a pediatric rheumatology consultation as appropriate. Pending a determination of objective clinical findings by the pediatric rheumatologist, further diagnostic procedures, including performance of an MRI on clinically affected joint(s) (as well as of contralateral non-affected joints, potentially), could be recommended and offered to the patient's parent or guardian based upon the pediatric rheumatologist's recommendations.

During the study, subjective complaints spontaneously volunteered by both patients and by their parents or caregivers, especially those attributable to the musculoskeletal and neurological systems, were carefully recorded and followed up with additional objective clinical assessments as warranted. In addition, telephone interviews completed by the patient's parent or caregiver were performed at 3, 6, 9, and 12 months during the first year post-exposure and, thereafter, performed quarterly as well for up to 1 year for post-pubescent children (older children) or 5 years for prepubescent and pubescent children. Patients who experienced a musculoskeletal adverse event during therapy were to be followed for 5 years regardless of their stage of pubescence. Primary responsibility for documenting and reporting the child's health throughout the post-exposure follow-up rested with the child's parent or caregiver, to ensure continuity of assessment over a long time span of observation.

The study flow chart is presented in Figure 1.

FIGURE 1
Study Flow Chart

	Pre-treatment	Post-treatment		
	(Within 48 hours of dosing)	Day +28 to +42 after end of treatment (first follow-up visit)	First Year Post-Exposure Follow-up (ie, Day +355 to +375) Quarterly Modular Assessments	Long-term Follow-up (Years 2 to 5)[a] Quarterly Modular Assessments
Informed consent	I			
Check of inclusion/exclusion criteria	I			
Patient demography	I			
Medical History	I			
Physical examination	I	I	< ---------- I[b] ---------- >	
Gait/joint exam	I	I[c]	< ---------- I[b] ---------- >	
Pediatric or Adolescent Neurological System Exam	I	I	< ----------I[b] ---------- >	
Pregnancy Test: urine/serum[d]	I	I	< ----------I[b] ---------- >	
Parental Assessment (Data Module) Completion			C	C
Telephone Contacts			< ---------- C ---------- >	
Adverse event monitoring[e]		I/C[f]	< ----------(I,C)[g] ---------- >	
Serious AE monitoring[e]		I/C[h]	< ---------- (I, C)[g] ---------- >	
Documentation of concomitant therapy and procedures[e]			< ---------- (I, C)[g] ---------- >	

The symbol "I" represents assessments primarily carried out by the investigator.
The symbol "C" represents assessments carried out by the patient's parent or caregiver.

[a] Prepubescent and pubescent children were to be followed for 5 years and post-pubescent children were to be followed for 1 year. (Amendment 4, dated October 30, 2001)

[b] To be performed by the investigator, as warranted and practicable.

[c] See gait/joint diagram in Figure 9-2. In case of complaints/abnormal findings, appropriate intervention was to be initiated.

[d] Older female children and female adolescent patients of childbearing potential could be enrolled based upon a negative urine pregnancy test performed in the clinic. In this group, a serum pregnancy test was also performed at the pre-treatment baseline and was repeated at the follow-up visit (Day +28 to +42).

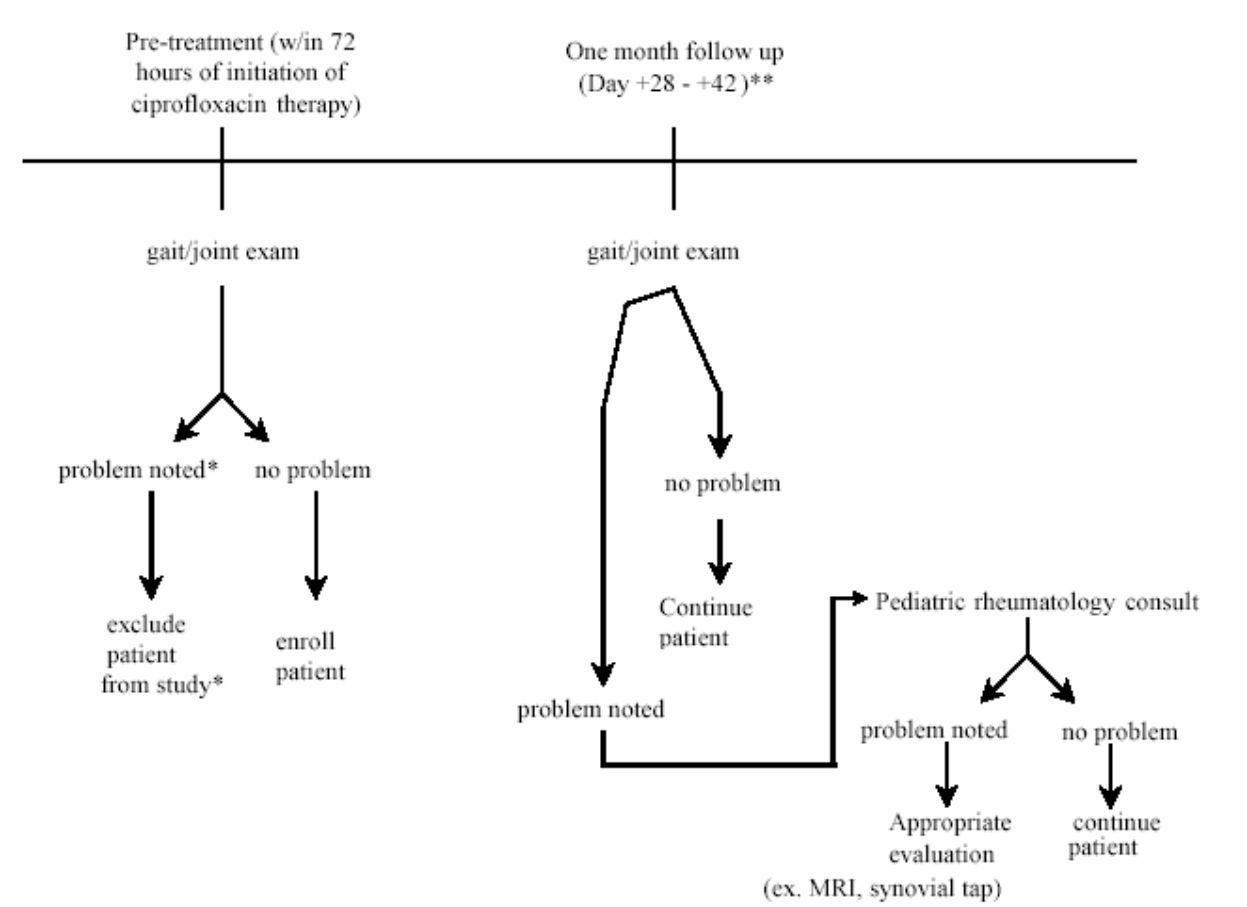
[e] Beyond the Day +28 to +42 investigative site visit, assessments of both serious (SAEs) and non-serious adverse events referable to either the musculoskeletal or CNS body system, and of all SAEs only (not routine adverse events) referable to other body systems, were performed primarily by the infant's or child's parent or guardian, and were supplemented by data and documentation from local investigative sites and other non-study affiliated physicians, as warranted and practical.

[f] Adverse events were collected through study Day +42

[g] A conjoint responsibility of the patient's parent or caregiver, and the investigator (if notified).

[h] Serious adverse events were reported up until and including the late follow-up visit (Day +28 to +42 after the end of study drug administration).

FIGURE 2
Gait/Join Examination Flow Diagram



* If the patient has already received ciprofloxacin prior to the gait/joint examination, and a problem is noted on exam follow-up as per the 1-month follow-up should be conducted.
** If an adverse event related to the musculoskeletal system occurs throughout the long-term follow-up period (1-5 years, per Amendment 4), intervention should occur.

12.12 Statistical and Analytical Plans

The primary objective of the trial was to determine the musculoskeletal and neurological system safety profile of ciprofloxacin in a long-term safety surveillance study. The primary population was to be patients considered valid for safety. The primary outcomes of interest were the incidence of musculoskeletal and CNS adverse events occurring by Day +28 to +42.

Since this was planned as a noncomparative trial, no formal statistical tests were planned.

Demographic and baseline characteristics were summarized for all patients valid for safety using means and standard deviations (for continuous variables) and frequency counts (for categorical variables). Medical conditions were tabulated using ICD-9 codes and concomitant medications using ATC codes.

A summary of incidence rates of serious adverse events (including both serious and non-serious CNS and musculoskeletal events) documented by Day +28 to +42 was presented. Events were to be tabulated by type (according to the COSTART glossary) and frequency, for all events and for those considered by the investigator to have a possible or probable relationship to drug treatment. The tables for musculoskeletal and CNS events were to be further summarized by age groups.

Kaplan-Meier survival curve estimates for the probability of not having any new musculoskeletal events were to be calculated through Day +42. Similar curves were planned for the probability of not having any new CNS event. These curves were also planned to be presented by age groups and by type of treatment (IV versus PO). Life-table estimates were to be used for events occurring after Day +28 to +42, since the exact dates for events occurring after this timepoint were not expected to be available.

12.13 Determination of Sample Size

The protocol specified that 3,000 ciprofloxacin patients would be enrolled into the study (changed as per Amendment 4 to 900 patients; 450 ciprofloxacin and 450 non-quinolone). This sample size was selected by the applicant because it provides a 95% probability of seeing at least one rare event (as defined by an event rate of 1 in 1,000, changed to 1 in 250 as per Amendment 4) using the binomial distribution. This is based on combining the 900 patients from this study with at least 600 patients available from the pediatric complicated UTI trial (Study 100169).

12.14 Independent Pediatric Safety Committee (IPSC)

The purpose of the IPSC was to review musculoskeletal and neurological adverse events. The mission of the IPSC was to determine 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 IPSC was formed in September 1999 with 2 members, a pediatric infectious disease specialist and a pediatric rheumatologist. By October 2001, it consisted of 4 members, including a pediatric neurologist and a pediatric orthopedic surgeon. They participated in 7 meetings, scheduled by the applicant, from June 2003 through September 2003.

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. This definition was seen as broad and inclusive of such phenomena as bursitis, enthesitis and tendonitis.

Evidence of arthropathy was characterized as either physical or historical evidence.

Physical evidence of arthropathy may have included but was not necessarily limited to: warmth, redness, joint effusion, tenderness, synovial thickness, abnormal gait or limp, weakness, and/or limited joint mobility/motion.

Since these objective findings may not alone have provided an adequate range of symptoms, a broader range of events to include all COSTART terms in the musculoskeletal system was added. See Table 1 in Appendix 1.

Historical evidence included joint and/or periarticular tissue pain and/or stiffness.

Diagnostic imaging demonstrating structural damage or change was also accepted as evidence of arthropathy.

Evidence of arthropathy may have been further categorized as weak or strong evidence. Historical data was considered weak evidence; joint effusion, synovial thickness, limited motion and diagnostic imaging findings were examples of strong evidence.

Relevant modifiers of evidence included severity, duration, and the presence of concurrent factors such as trauma, infection, and other confounding diseases (e.g. cerebral palsy causing abnormal gait). In addition, concurrence of parameters or change in parameters over time was given greater weight (e.g. increased joint stiffness with swelling).

Overall evidence for arthropathy was classified by the IPSC as none; possible; probable; or definite.

If a case was identified as possible, probable or definite arthropathy by the IPSC, the Committee also assessed the relationship to study drug as none; possible; probable; or definite.

In making the determination of relationship to study drug, multiple factors were considered. The 3 major considerations were any pre-existing conditions, conditions with clear alternative etiology (i.e., septic arthritis, trauma), and/or timing of the event in relationship to study drug administration. Generally, conditions that began more than 1 year after the administration of study drug were not considered related to study drug.

Statistical testing was used to determine whether the ciprofloxacin treatment group was non-inferior to the control group with regard to the incidence rate of arthropathy, as determined by the IPSC. For this analysis, all classification categories of drug relatedness were combined. It should be noted that arthritis was summarized in a descriptive fashion with other adverse events.

A SAS program was developed to help identify patients with potential cases of arthropathy. Patients who met any one of 5 conditions were identified, and then reviewed by the IPSC to determine whether arthropathy was present. Before the blind was broken, the IPSC reviewed all potential cases of arthropathy as identified by the following algorithm:

- Patients with any musculoskeletal adverse events, as identified by the COSTART coding system (COSTART codes between 7000000 and 7999999).
- 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.

- Patients with abnormal gait/joint appearances, as determined by the investigators.
- Patients with abnormal stance or swing, as determined by the investigators.
- Patients with a 10 degree or greater decrease from baseline on any range of motion (ROM) exam. (Note: If ROM was the only finding, the case was not reviewed, as the IPSC did not believe that this, as an isolated finding, would warrant consideration as indicative of arthropathy.)

Clinical Reviewer's Comment: At the end of the study, 128 patients were identified using the arthropathy algorithm. One patient did not appear on the algorithm at the end of the study. The patient had arthralgia as an initial event, which was later clarified as an event of neck pain. The patient is included for completeness. In total 141 cases were reviewed by the IPSC. See safety results section of the review.

12.15 SAFETY RESULTS

12.15.1 Disposition of Patients

Sixty-eight centers (67 from the United States, 1 from Canada) enrolled 1029 patients into the study. Of the 1,029 patients, 510 were in the ciprofloxacin group, and 519 were in the control group. Table 2 in Appendix 1 summarizes patient enrollment by center.

Since the control group was added 2 years after the study started, and since the enrollment process was not randomized, the patient distribution within centers was highly variable. Most of the centers enrolled all or nearly all of their patients into the same treatment group, and very few centers had similar numbers of patients in the two groups. Of the 68 centers, 35 enrolled only ciprofloxacin patients, 30 enrolled patients into both groups, and 3 enrolled only control patients. Most centers enrolled between 1 and 40 patients (only 4 centers enrolled more than 40). Center 7 enrolled 223 control patients, accounting for 43% of the control group population, while only enrolling 14 (3%) ciprofloxacin patients.

As shown in Table 3, 63 ciprofloxacin and 26 control patients did not complete the study drug as planned. The ciprofloxacin patients prematurely discontinued treatment more often than the control patients did (12% versus 5%). The reason for discontinuation with the largest difference between groups was adverse event (3% for ciprofloxacin patients, <1% for control patients), but in all categories there were more ciprofloxacin patients than control patients.

TABLE 3
Number of Patients and Reasons for Premature Discontinuation from Study Treatment

	Ciprofloxacin (N=510)	Control (N=519)
Any reason	63 (12%)	26 (5%)
Adverse event	13 (3%)	3 (<1%)
Patient non-compliance	11 (2%)	6 (1%)
Consent withdrawn	11 (2%)	6 (1%)
Insufficient therapeutic effect	5 (<1%)	2 (<1%)
Patient lost to follow-up	18 (4%)	8 (2%)
Investigator decision	4 (<1%)	1 (<1%)
Death	1 (<1%)	0 (0%)

Efficacy evaluations were not included in this trial, so there is no valid for efficacy population.

12.15.2 Protocol deviations

Overall, 54 patients did not have pages in the CRF completed for study drug schedule. Of those 54, information obtained by the applicant for 19 patients suggested they indeed had received study drug. However, for these 19 patients, information regarding treatment duration, formulation, and dosage was not available. Therefore, for 35 patients (23 ciprofloxacin and 12 control), it could not be confirmed (by the study drug schedule page, end of study page, or additional information page of the CRF), that the patients received any dose of study drug. These patients were excluded from the safety analysis, leaving 487/510 (95%) in the ciprofloxacin group and 507/519 (98%) valid for safety.

Known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy were to be excluded from the study. However, 7% (32/487) of ciprofloxacin patients and 5% (24/507) control patients were enrolled with a medical history of any abnormal musculoskeletal or connective tissue finding. In addition, at study entry 7% (36/487) of ciprofloxacin patients and 0.8% (4/507) of control patients had an abnormal gait assessment at baseline and 5% (23/487) of ciprofloxacin patients and 2% (9/507) of control patients had an abnormal joint appearance at baseline. These patients were included in the applicant's valid for safety population.

Clinical Reviewer's Comment: The differences in baseline abnormalities and medical histories may make it difficult to assess any potential drug effect on gait or joint appearance and will be taken into consideration when reviewing musculoskeletal adverse event rates and arthropathy rates for the two treatment groups.

One ciprofloxacin patient (380008) had a baseline history of paraplegia so interpretations of gait assessment were limited.

In total, 21 patients had a history of seizures and should have been excluded as per protocol. In theory, these patients could have been placed at potential risk for a convulsion during the treatment phase. Patient 70203 (control group) had a seizure on Day +38. Patient 9930010 (ciprofloxacin group) with a history of Arnold-Chiari, insertion of a ventriculo-peritoneal shunt, and recurrent seizures (not on baseline anticonvulsant) had a seizure on Day +1.

No other substantial protocol deviations were observed.

By June 30, 2003, 404 ciprofloxacin patients and 315 control patients would have been eligible for 1-year post-treatment follow-up. Of these, it could be verified through phone call records kept by the CRO (b) (4) that 355 (88%) ciprofloxacin patients and 267 (85%) control (non-quinolone) patients had been contacted at least through the 1-year follow-up timepoint and beyond.

12.15.3 Control Group – Treatments Administered

In the control group, amoxicillin monotherapy was the most commonly used regimen; 273 of the 507 (54%) control patients received this therapy. Other commonly used monotherapies in the control group included Augmentin® (7%; 34/507), Zithromax® (6%; 30/507), Keflex® (6%;28/507) and Omnicef® (6%; 29/507).

12.15.4 Demographic and Other Baseline Characteristics

Descriptive statistics for some of the key demographic and baseline variables for the population of patients valid for safety are provided in Table 4.

Clinical Reviewer's Comment: Table 4 was expanded by the reviewer to include more variables than the applicant's original table.

TABLE 4
Selected Demographic and Infection Characteristics for Patients Valid for Safety

	Ciprofloxacin N=487	Control N=507
Sex		
% Female	269 (55%)	242 (48%)
Race		
% Caucasian	292 (60%)	330 (65%)
% Black	33 (7%)	27 (5%)
% Hispanic	138 (28%)	128 (25%)
% Asian	16 (3%)	8 (2%)
% Not Coded	8 (2%)	13 (3%)
% American Indian	0	1 (<1%)
Mean ± SD Age at Enrollment in years (range)	6.2 ± 4.3 (0 to 16 years)	5.3 ± 3.5 (0 to 16 years)
Mean ± SD Age in years for Patients ≥ 2 years (range)	7.3 ± 3.7 (2 to 16 years)	6.5 ± 2.9 (2 to 16 years)
Mean ± SD Age in months for Patients < 24 months (range)	13.6 ± 6.3 (2 to 23 months)	12.7 ± 5.7 (2 to 23 months)
Infection Type		
% UTI	105 (22%)	12 (2%)
% Pyelonephritis	24 (5%)	8 (2%)
% Otitis Media	143 (29%)	207 (41%)
% Pharyngitis/Tonsillitis	39 (8%)	148 (29%)
% Sinusitis	39 (8%)	47 (9%)
% Pneumonia	12 (2%)	17 (3%)
% Cellulitis	16 (3%)	11 (2%)
% External Otitis	10 (2%)	1 (<1%)
% Other Infections	99 (21%)	56 (12%)
Patient Prematurely Born		
% Yes	62 (13%)	57 (11%)
% No	386 (79%)	447 (88%)
% Unknown	39 (8%)	3 (<1%)
Country of Enrollment		
Canada	11 (2%)	4 (<1%)
United States	476 (98%)	503 (99%)

There were also more females (55%) in the ciprofloxacin group compared to the control group (48%). The race distribution and percentage of patients born prematurely were very similar in the two groups. The distribution of infections, which led to enrollment in the trial, was very different in the two groups. In the ciprofloxacin group, 27% of patients were enrolled due to a UTI or pyelonephritis, while only 4% of control patients were enrolled due to these infections. In the control group, 70%

of patients were enrolled due to otitis media orpharyngitis/tonsillitis, while only 37% of ciprofloxacin patients were enrolled due to these infections.

The age groups and distributions of patients in each age group that were studied are shown in Table 5. Of the patients ≤ 5 years of age, 48% (235/487) were in the ciprofloxacin group and 52% (265/507) were in the control group. More ciprofloxacin patients (12%; 58/487) were 12 years to <17 years of age compared to control patients (4%; 19/507).

TABLE 5
Age Distribution
Patients Valid for Safety

	Ciprofloxacin N = 487	Control N = 507
2 months, <24 months	85 (17.5%)	100 (19.7%)
2 years, < 6 years	150 (30.8%)	165 (32.5%)
6 years, < 12 years	194 (39.8%)	223 (44.0%)
12 years, <17 years	58 (11.9%)	19 (3.7%)

There was a large difference between groups in the use of previous antimicrobials. Among ciprofloxacin-treated patients, 17% (81/487) had used a previous antimicrobial, while among control patients, less than 1% (3/507) had used a previous antimicrobial. Ciprofloxacin and Bactrim® were the most commonly used previous antimicrobials in the ciprofloxacin group.

Clinical Reviewer's Comment: Ofloxacin was used previously in 9/487 (2%) of ciprofloxacin patients and none of the control patients.

The overall rate of any medical history for patients treated with ciprofloxacin was 84% and 83% in the control group. There were many individual conditions for which the percentages differed greatly between groups. Table 6 shows all classes of conditions for which the difference between groups was at least 2%.

The medical history results were consistent with the infections causing patients to be entered into the trial. Many more ciprofloxacin patients had histories in the genitourinary system, and many more control patients had histories in the respiratory infections. The ciprofloxacin group also had many more patients with histories of various types of operations.

TABLE 6
Medical Histories for Conditions with ≥ 2% Difference Between the Treatment Groups

	Ciprofloxacin (N=487)	Control (N=507)
Any History	406 (84%)	422 (83%)
Neoplasms	23 (5%)	5 (<1%)
Endocrine, Nutritional, Metabolic, and Immunity	36 (7%)	12 (2%)
Blood and Blood-Forming Organs	44 (9%)	29 (6%)
Nervous System and Sense Organs	150 (31%)	270 (53%)
Respiratory System	181 (37%)	315 (62%)
Digestive System	81 (17%)	43 (8%)
Genitourinary System	114 (23%)	41 (8%)
Musculoskeletal and Connective Tissue	32 (7%)	24 (5%)
Congenital Abnormalities	58 (12%)	22 (4%)
Symptoms, Signs, Ill-Defined Conditions	128 (26%)	93 (18%)
Injury and Poisoning	85 (17%)	205 (40%)
Operations on the Nervous System	11 (2%)	0 (0%)
Operations on the Ear	74 (15%)	30 (6%)
Operations on the Nose, Mouth, and Pharynx	43 (9%)	21 (4%)
Operations on the Cardiovascular System	17 (3%)	1 (<1%)
Operations on the Digestive System	33 (7%)	11 (2%)
Operations on the Urinary System	31 (6%)	0 (0%)
Operations on the Integumentary System	23 (5%)	7 (1%)

12.15.5 Concomitant Medication Use

Prevalence rates of concomitant medication use (at the time of enrollment) were 76% (369/487) for ciprofloxacin patients and 68% (347/507) for control patients (data not shown). Antimicrobial use was much more common among ciprofloxacin patients (41%; 201/487) than control patients (17%; 88/507). Ciprofloxacin patients also had higher use of vitamins (8% [40/487] versus 2% [11/507]), antacids (6% [27/487] versus 2% [11/507]), antifungals for dermatologic use (4% [20/487] versus 1% [7/507]), urologicals (5% [24/487] versus 0% [0/507]), antimycotics for systemic use (3% [13/487] versus <1% [1/507]), analgesics (23% [112/487] versus 14% [72/507]), and anti-asthmatics (14% [70/487] versus 11% [55/507]).

The incidence rate of treatment-emergent concomitant medication use (i.e., medications started for the first time after enrollment) was 58% (284/487) in the ciprofloxacin group and 60% (303/507) in the control

group (data not shown). There was a difference between groups in the number of patients using general anti-infectives for systemic use (31% [152/487] for ciprofloxacin-treated patients, 17% [84/507] for control patients). The ciprofloxacin group also had higher incidence rates of treatment-emergent use of alimentary tract and metabolism medications (9% [45/487] versus 4% [19/507]), nervous system medications (19% [93/487] versus 14% [71/507]), and sensory organ medications (10% [40/487] versus 7% [34/507]). The control group had a higher incidence rate of treatment-emergent use of respiratory system medications (23% [111/487] versus 34% 170/507]).

When limited to antimicrobials being used at the same time as study drug therapy, there were more ciprofloxacin patients using concomitant antimicrobials than control patients (16% [77/487] versus 3% [13/507]).

12.15.6 Compliance with Study Drug

Tables 7 and 8 display the treatment duration and dosing information, respectively. The mean duration of treatment was one day longer for the ciprofloxacin patients than for the control patients (12.4 days versus 11.3 days). Ciprofloxacin-treated patients had higher mean durations of both oral therapy (12.3 days versus 11.1 days) and IV therapy (5.8 days versus 5.1 days). The maximum duration of ciprofloxacin treatment was 88 days, while the maximum duration of control therapy was 70 days.

Clinical Reviewer's Comment: Tables 7 and 8 were created by the reviewer.

TABLE 7
Mean (± SD) Duration of Study Drug Administration
Patients Valid for Safety

	Ciprofloxacin N=487	Control N=507
Total treatment duration (days)	12.4 ± 7.9 [1 to 88] N=468	11.3 ± 6.7 [3 to 70] N=503
Duration of oral therapy (days)	12.3 ± 7.5 [1 to 88] N=455	11.1 ± 5.8 [3 to 56] N=499
Duration of IV therapy (days)	5.8 ± 4.9 [2 to 21] N=41	5.1 ± 2.8 [1 to 14] N=30

TABLE 8
Mean (± SD) Number of Doses of Study Drug Administered
Patients Valid for Safety

	Ciprofloxacin N=487	Control N=507
Total number of doses	23.4 ± 15.0 [1 to 20] N=464	23.9 ± 16.5 [2 to 139] N=504
Number of oral capsules	23.2 ± 14.1 [1 to 20] N=450	23.4 ± 14.6 [2 to 119] N=500
Number of IV doses	11.0 ± 11.3 [2 to 42] N=41	10.5 ± 7.5 [1 to 37] N=30

Clinical Reviewer's Comment: The safety results of this study should be interpreted with caution for the reasons outlined below. The applicant acknowledges the limitations in interpreting the data based up the same reasons identified by the reviewer.

The study was not blinded or randomized and enrollment into the comparator arm was not temporal to the ciprofloxacin arm (i.e., the comparator arm was added to the study 2 years after it had been initiated).

Differences in the reasons for treatment. The distribution of infections, which led to enrollment in the trial, was very different in the two groups. In the ciprofloxacin group, 27% of patients were enrolled due to a UTI or pyelonephritis, while only 4% of control patients were enrolled due to these infections. In the control group, 70% of patients were enrolled due to otitis media orpharyngitis/tonsillitis, while only 37% of ciprofloxacin patients were enrolled due to these infections.

Differences in Age. The most notable difference was in the patient age group of 12 years to < 17 years (12%; (58/487) of ciprofloxacin patients compared to 4% (12/507) control patients.

Differences in previous antimicrobial use. There was a large difference between groups in the use of previous antimicrobials. Among ciprofloxacin-treated patients, 17% (81/487) had used a previous antimicrobial, while among control patients, only 1% (3/507) had used a previous antimicrobial. Ciprofloxacin and Bactrim® were the most commonly used previous antimicrobials in the ciprofloxacin group.

Differences in medical history and concomitant medical conditions. Notable differences (>2% differences) were observed in medical history (ICD-9 class) between the two treatment groups. The conditions with the greatest discrepancy between the groups are as follows. Ciprofloxacin-

treated patients had a higher incidence of genitourinary system (23% [114/487] versus 8% [41/507]) and digestive system disorders (17% [81/487] versus 8% [43/507]) compared to the control group. The control group had a higher incidence of medical histories of conditions in the nervous system and sense organs (53% [270/507] control versus 31% [150/487] ciprofloxacin; mainly attributed to a higher incidence of otitis media), respiratory system (62% [315/507] control versus 37% [181/487] ciprofloxacin; mainly attributed to differences in upper respiratory infections, pharyngitis, and chronic sinusitis), and injury and poisoning (40%[205/507] control versus 17% [85/487] ciprofloxacin; mainly attributed to allergy).

Differences in baseline abnormalities or medical histories of musculoskeletal adverse events. Known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy were to be excluded from the study. However, 7% (32/487) of ciprofloxacin patients and 5% (24/507) control patients were enrolled with a medical history of any abnormal musculoskeletal or connective tissue finding. In addition, at study entry 7% (36/487) of ciprofloxacin patients and 0.8% (4/507) of control patients had an abnormal gait assessment at baseline and 5% (23/487) of ciprofloxacin patients and 2% (9/507) of control patients had an abnormal joint appearance at baseline.

Differences in concomitant medications. Prevalence rates of concomitant medication use (at the time of enrollment) were 76% (9369/487) for ciprofloxacin patients and 68% (347/507) for control patients (data not shown). Antimicrobial use was much more common among ciprofloxacin patients (41%) than control patients (17%). Ciprofloxacin patients also had higher use of vitamins (8% [40/487] versus 2% [11/507]), antacids (6% [27/487] versus 2% [11/507]), antifungals for dermatologic use (4% [20/487] versus 1% [7/507]), urologicals (5% [24/487] versus 0% [0/507]), antimycotics for systemic use (3% [13/487] versus <1% [1/507]), analgesics (23% [112/487] versus 14% [72/507]), and anti-asthmatics (14% [70/487] versus 11% [55/507]).

The differences between treatment groups outlined above should be considered when reviewing adverse event rates for the two treatment groups and the population of ciprofloxacin patients should not be directly compared to the population of control patients.

12.15.7 Overview of Adverse Events Through Day +42

Table 9 displays a brief summary of the rates of death, any adverse event, any drug-related adverse event, any serious adverse event, and premature discontinuations due to adverse events, for ciprofloxacin and control patients valid for safety through the 42-day follow-up time point.

TABLE 9
Summary of Adverse Events by Day +42
Ciprofloxacin (N=487) and Control (N=507) Patients

	Ciprofloxacin	Control
Deaths	1 (<1%)*	0 (0%)
Adverse Events	210 (43%)	134 (26%)
Drug-Related Adverse Events	70 (14%)	20 (4%)
Serious Adverse Events	22 (5%)	5 (1%)
Premature Discontinuations due to Adverse Events	13 (3%)	3 (<1%)

* One ciprofloxacin-treated patient died (Patient 49-0055) due to right atrial thrombosis with deterioration in cardiac function during the Day +42 follow-up period.

The 13 patients who were premature discontinuations in the ciprofloxacin group had:

- Arthralgia – shoulder pain (mild); jaw pain (moderate); and R wrist pain [one patient each]
- Dizziness – (one moderate one mild) [2 patients]
- Headache (mild)
- Tachycardia (moderate)
- Rash (mild)
- Injection site reaction (mild)
- Allergic reaction (mild)
- Vomiting (mild) [2 patients]
- Otitis media, worsening (severe)
- Bacteremia (moderate)
- Sinusitis (one moderate one mild) [2 patients]
- Infected abdominal wounds (one moderate, one severe) [2 patients]
- Urticaria, hives (severe)

All ciprofloxacin patients had resolution of their events.

The 3 patients who were premature discontinuations in the comparator group had: vomiting (mild) and rash (moderate) in one patient each who received amoxicillin; and abdominal pain (mild) in a patient who received cefzil. All events resolved.

12.15.8 Serious Adverse Events Through Day +42

Patients who experienced serious adverse events through 42 days after the end of therapy are summarized in Table 10. Overall, 5% of ciprofloxacin patients experienced serious adverse events. The most frequent serious adverse events were fever and sepsis (4 patients each). Two patients experienced serious musculoskeletal events; one patient reported osteomyelitis, and one reported arthralgia.

Overall, 5/507 (<1%) of control patients experienced serious adverse events by Day 42. The five events, which all occurred in different patients were: vertigo, acute asthma (2 patients), peritonisllar abcess, and increasing pleural effusion (pt. 470048). All events were severe in intensity and all resolved. The patients with vertigo and pleural effusion were hospitalized. The patients with asthma and the peritonsillar abcess received remedial drug therapy.

TABLE 10
Incidence Rates of Serious Adverse Events by Body System
by Day +42 After Treatment
Ciprofloxacin Treated Patients Valid for Safety (N=487)

Event	Number Experiencing Event in Ciprofloxacin Group (%)
Any Body System – Any Event	22 (5%)
Body as a Whole	
Any Event	11 (2%)
Fever	4 (<1%)
Sepsis	4 (<1%)
Abscess	2 (<1%)
Back Pain	1 (<1%)
Congenital Anomaly	1 (<1%)
Infection	1 (<1%)
Cardiovascular	
Any Event	2 (<1%)
Heart Arrest	1 (<1%)
Heart Failure	1 (<1%)
Thrombophlebitis	1 (<1%)
Thrombosis	1 (<1%)
Digestive	
Any Event	4 (<1%)
Pseudomembranous enterocolitis	2 (<1%)
Intestinal obstruction	1 (<1%)
Gastroenteritis	1 (<1%)
Nausea	1 (<1%)
Vomiting	1 (<1%)
Hemic and Lymphatic	
Any Event	4 (<1%)
Leukopenia	3 (<1%)
Acute Leukemia	1 (<1%)
Metabolic and Nutritional	
Any Event	1 (<1%)
Dehydration	1 (<1%)
Musculoskeletal	
Any Event	2 (<1%)
Osteomyelitis	1 (<1%)
Arthralgia	1 (<1%)

Event	Number Experiencing Event in Ciprofloxacin Group (%)
Respiratory	
Any Event	1 (<1%)
Bronchitis	1 (<1%)
Special Senses	
Any Event	2 (<1%)
Otitis Media	2 (<1%)
Urogenital	
Any Event	5 (1%)
Acute Kidney Failure	1 (<1%)
Kidney Function Abnormal	1 (<1%)
Pyleonephritis	1 (<1%)
Uremia	1 (<1%)
Urinary Incontinence	1 (<1%)
Urinary Tract Disorder	1 (<1%)
Urinary Tract Infection	1 (<1%)

Serious adverse events for ciprofloxacin believed to be drug related occurred in two patients, both in the digestive body system. There were 2 patients with pseudomembranous enterocolitis (270024 and 500011); one of these patients also had gastroenteritis (270024).

12.15.9 Musculoskeletal and CNS Adverse Events Through Day +42

The incidence rates of musculoskeletal or CNS events occurring in ≥1% of ciprofloxacin patients, including arthropathy, through the 42-day follow-up period for ciprofloxacin and control patients valid for safety are shown in Table 11. The overall rate of any musculoskeletal or CNS event for ciprofloxacin was 13%, with a corresponding 95% confidence interval of (10.5%, 16.7%) and 4% with a corresponding 95% confidence interval of (2.1%, 5.6%) for control. The incidence rate of arthropathy (assessed by the IPSC) for ciprofloxacin was 8%, with a 95% confidence interval of (5.4%, 10.3%) and 2%, with a 95% confidence interval of (0.8%, 3.3%) for control.

TABLE 11
Musculoskeletal or CNS Events by Day +42 Occurring in ≥1% of Ciprofloxacin Patients
Ciprofloxacin (N=487) and Control (N=507) Patients

	Ciprofloxacin	95% Confidence Interval	Control	95% Confidence Interval
Any Musculoskeletal or CNS Event	65 (13%)	(10.5%, 16.7%)	18 (4%)	(2.1%, 5.6%)
Any Musculoskeletal Event	42 (9%)	(6.3%, 11.5%)	9 (2%)	(0.8%, 3.3%)
Arthropathy (assessed by IPSC)	37 (8%)	(5.4%, 10.3%)	9 (2%)	(0.8%, 3.3%)
Arthralgia	26 (5%)	(3.5%, 7.7%)	3 (<1%)	(0.1%, 1.7%)
Any CNS Event	28 (6%)	(3.9%, 8.2%)	9 (2%)	(0.8%, 3.3%)
Insomnia	17 (3%)	(2.1%, 5.5%)	3 (<1%)	(0.1%, 1.7%)

Clinical Reviewer's Comment: Tables 12 and 13 Appendix 1 were created by the reviewer and list the ciprofloxacin and comparator patients, respectively, with arthropathy occurring by Day +42, as assessed by the IPSC. Of these, 7/35 ciprofloxacin patients and none (0/9) of the comparator patients had an event(s) occurring by Day +42 as well as an event(s) occurring between Day +42 and one year.

Clinical Reviewer's Comment: DSI audit was performed February 17, 2004. Form 483 was issued March 18, 2004. During the FDA inspection of Site 25 (Dr. Corazon Oca; Irvine, California), the following was noted by the inspector on the form:

Failure to report Adverse Events:
Subject #33 developed right wrist pain three days after starting the study drug. An MRI of the right wrist performed (b) (6) to evaluate this complaint demonstrated an intrasubstance tear of the right ulnar fibrocartilage. The subject was seen for follow up on February 28, 2001, with this visit recorded as a Module 2 visit. However, the MRI findings were not reported in any case report forms for this subject. The case report forms listed only right and left wrist pain and left lower back pain.

The Division requested the applicant include a description of the patient with fibrocartilage tear in the Adverse Reactions section of the package insert. The following is a narrative of the patient cited on Form 483: Patient 250033 was a 13 year old female who was enrolled in the observational study on November 6, 2000 and prescribed ciprofloxacin for "sinus problems" (sinusitis and cervical adenitis). Patient history is significant for back pain. She was active in gymnastics in the summer of 2000, but quit because of the back pain. At that time an MRI showed swollen discs. She was also active in volleyball from September to November 2000. The patient reported mild right wrist pain on the third day of taking ciprofloxacin (November 9, 2000). Study drug was discontinued due to the adverse event on November 13, 2000, after 7 days of treatment. The wrist pain improved, but did not completely resolve. An MRI performed (b) (6) showed an intrasubstance tear of the triangular fibrocartilage in the right wrist (21 days following treatment with ciprofloxacin). The patient was referred for physical therapy and prescribed anti-inflammatory medication (prescribed Relafen®, but subsequent note says that she only took acetaminophen) and braces (both wrists) by an orthopedic surgeon. Patient was lost to follow-up for about 2 months. She did not respond to two telephone messages asking her to come back for a follow-up visit. On February 28, 2001 the patient was seen by a rheumatologist and had complaints of pain in the left wrist and left lower back. No pain in the right wrist. The rheumatologist diagnosed the patient with "probable tenosynovitis versus overuse syndrome secondary to gymnastics" and "no evidence of inflammatory arthritis." The patient was advised to take NSAIDs (ibuprofen) as needed. On (b) (6) the patient returned to the clinic.

She complained of a pain in her tail bone. X-ray showed inflamed tissue near the spinal cord. The patient was told to discontinue (or take time off) from gymnastics. No mention of wrist pain at this visit.

In order to understand the cases of arthralgia better, as this category of musculoskeletal events comprises the greatest proportion of the musculoskeletal events, the FDA Clinical Reviewer looked in greater detail at these patients. Table 14 lists the patients with arthralgia events occurring by Day +42 for ciprofloxacin and comparator, respectively,

TABLE 14
ARTHRALGIA Cases Occurring by Day +42

Ciprofloxacin			Comparator		
27 patients (38 events)/56 = 48%			3 patients (3 events)/13 = 23%		
Pt. #/Sex/Age in years	Description	Duration	Pt. #/Sex/ Age in years	Description	Duration
80006/F/14	Shoulder pain	8	70085/M/11	R wrist pain	5
90014/F/4	L knee pain	1	70101/M/11	R knee pain	88
170001/M/2	L ankle tenderness	9	70104/F/5	Knee pain	236
	L knee tenderness	9			
210005/M/2 [2 additional events after Day 42]	Intermittent jaw pain	633			
290023/F/3	Bilateral knee pain	ongoing			
350022/F/11 [1 additional event after Day 42]	Bilateral elbow pain	Unknown			
	Bilateral wrist pain	unknown			
350023/M/8	Ankle pain	Ongoing			
	Knee pain	Ongoing			
	Shoulder pain	Ongoing			
380006/F/10	Jaw pain	5			
400049/F/11	Intermittent L shoulder pain	6			
610001/M/8 [1 additional event after Day 42]	Knee pain	2			
760005/F/14	Hip pain	unknown			
920005/F/9	L knee pain	2			
220001/F/2	Elbow pain	7			
250003/M/9*	L wrist pain	3			

Ciprofloxacin			Comparator		
27 patients (38 events)/56 = 48%			3 patients (3 events)/13 = 23%		
Pt. #/Sex/Age in years	Description	Duration	Pt. #/Sex/ Age in years	Description	Duration
250033/F/13	R wrist pain	Unknown			
	L wrist pain	unknown			
270017/F/8 [2 additional events after Day 42]	Bilateral knee pain	66			
	Bilateral ankle pain	66			
290007/F/13	L shoulder pain	23			
400033/M/11	R knee pain	22			
460001/F/10	L wrist pain	8			
	R knee pain	8			
870056/M/5	Aching in knees	16			
80003/F/9*	L ankle pain	8			
210004/F/11**	L elbow pain	3			
	L shoulder pain	2			
	L elbow pain	7			
	L elbow pain	3			
30001/M/6	L elbow pain	1			
320002/F/11	Soreness in knees	1			
350015/F/12**	R ankle pain	3			
	R ankle pain	6			
370010/M/3*	R knee pain	7			
790011/M/16**	R knee pain	12			

* associated with “accidental trauma”
** IPSC inadvertently unblinded to study drug

The incidence rates of drug-related musculoskeletal or CNS events occurring in > 1% of patients, through the 42-day follow-up period for ciprofloxacin and control are shown in Table 15. The incidence rates of any drug-related musculoskeletal or CNS events were 8% for ciprofloxacin and 2% for control, and the incidence rate of drug-related arthropathy was 6% for ciprofloxacin and 2% for control.

TABLE 15
Drug-Related Musculoskeletal or CNS Events by Day +42 Occurring in ≥1% of Ciprofloxacin Patients
Ciprofloxacin (N=487) and Control (N=507) Patients

	Ciprofloxacin	95% Confidence Interval	Control	95% Confidence Interval
Any Musculoskeletal or CNS Event	37 (8%)	(5.4%, 10.3%)	9 (2%)	(0.8%, 3.3%)
Any Musculoskeletal Event	28 (6%)	(3.9%, 8.2%)	8 (2%)	(0.7%, 3.1%)
Arthropathy (assessed by IPSC)	27 (6%)	(3.7%, 8.0%)	8 (2%)	(0.7%, 3.1%)
Any CNS Event	9 (2%)	(0.8%, 3.5%)	1 (<1%)	(< 0.1%, 1.1%)
Insomnia	5 (1%)	(0.3%, 2.4%)	1 (<1%)	(< 0.1%, 1.1%)

12.15.10 All Adverse Events Through Day +42

Tables 16 and 17 shows adverse events, for all adverse events and those related to study drug, respectively, for all body systems through the Day +42 follow-up period for ciprofloxacin and control patients. The results for events, regardless of relationship to study drug that occurred in at least 2% of patients are shown in Table 14.

TABLE 16
Incidence Rates of Adverse Events by Body System Through Day +42
Ciprofloxacin (N=487) and Control (N=507) Patients

Body System	Ciprofloxacin		Control	
Any event	210	(43%)	134	(26%)
Body as a Whole	89	(18%)	50	(10%)
Cardiovascular	11	(2%)	1	(<1%)
Digestive	44	(9%)	17	(3%)
Endocrine	1	(<1%)	0	(0%)
Hemic and Lymphatic	11	(2%)	3	(<1%)
Metabolic & Nutritional	6	(1%)	2	(< 1%)
Musculoskeletal	42	(9%)	9	(2%)
Nervous	28	(6%)	9	(2%)
Respiratory	68	(14%)	50	(10%)
Skin & Appendages	27	(6%)	22	(4%)
Special Senses	35	(7%)	27	(5%)
Urogenital	18	(4%)	4	(<1%)

Through the 42-day follow-up period, 43% of ciprofloxacin patients experienced at least one adverse event. Most of the events were in the

Body as a Whole and Respiratory body systems (18% [89/487] and 14% [68/487] incidence rates, respectively). The most common events (other than musculoskeletal events) were otitis media and pharyngitis (5% each [25/487] and [24/487], respectively).

Through 42-day follow-up period, 26% (134/507) of control patients experienced at least one adverse event. Most of the events were in the Body as a Whole and Respiratory body systems (10% each [50/507] and [50/507], respectively). The most common event was pharyngitis (4% [20/507]).

TABLE 17
Incidence Rates of Drug-Related Adverse Events by Body System Through Day +42
Ciprofloxacin (N=487) and Control (N=507) Patients

Body System	Ciprofloxacin		Control	
Any event	70	(14%)	20	(4%)
Body as a Whole	16	(3%)	4	(<1%)
Cardiovascular	1	(<1%)	0	(0%)
Digestive	21	(4%)	3	(<1%)
Musculoskeletal	28	(6%)	8	(2%)
Nervous	9	(2%)	1	(<1%)
Respiratory	1	(<1%)	0	(0%)
Skin & Appendages	4	(<1%)	6	(1%)
Special Senses	1	(<1%)	0	(0%)
Urogenital	2	(<1%)	0	(0%)

Most of the adverse events reported through the 42-day follow-up period were not considered drug-related. The incidence rate of any drug-related adverse event was 14% (70/487) in the ciprofloxacin group and 4% (20/507) in the control group. Specific drug-related adverse events (other than musculoskeletal events) with drug-related incidence rates of 1% or higher for ciprofloxacin were abdominal pain (2%; 8/487), diarrhea (2%; 9/487), and vomiting (2%; 9/487). All events (other than musculoskeletal events) with drug-related incidence rates were 1% or less in the control group.

Specific adverse events reported through the 42-day follow-up period, other than those affecting the musculoskeletal and central nervous systems, are shown in Table 18, if incidence was at least 2% of patients in either group.

TABLE 18
Incidence Rates of Adverse Events Through Day +42 (Other than Musculoskeletal and CNS) Occurring in at Least 2% of Patients (Regardless of Relationship to Study Drug) in Either Group Ciprofloxacin (N=487) and Control (N=507) Patients

Adverse Event	Ciprofloxacin		Control	
Any event	210	(43%)	134	(26%)
Otitis Media	25	(5%)	14	(3%)
Pharyngitis	24	(5%)	20	(4%)
Fever	21	(4%)	7	(1%)
Accidental Injury	18	(4%)	14	(3%)
Vomiting	18	(4%)	5	(<1%)
Rhinitis	18	(4%)	15	(3%)
Asthenia	17	(3%)	0	(0%)
Rash	17	(3%)	13	(3%)
Abdominal Pain	15	(3%)	6	(1%)
Headache	14	(3%)	4	(<1%)
Cough Increased	14	(3%)	3	(<1%)
Diarrhea	14	(3%)	2	(<1%)
Leg Pain	8	(2%)	4	(<1%)
Sinusitis	8	(2%)	7	(1%)

12.15.11 Severe Adverse Events Through Day +42

Severe adverse events were experienced by 7% (33/487) of ciprofloxacin patients and 3% (15/507) of control patients through the 42-day follow-up period. The most common severe adverse events in the ciprofloxacin group were sepsis and fever (4 patients each). Three ciprofloxacin patients experienced severe musculoskeletal events; 2 had severe arthralgia, and 1 had severe osteomyelitis. There were no severe nervous system events in the ciprofloxacin group.

The most common severe adverse event in the control group was asthma (2 patients). No other event was considered severe in more than one control patient. No control patient experienced a severe musculoskeletal event. Two control patients experienced severe nervous system events (1 convulsion and 1 vertigo).

12.15.12 Outcomes for Adverse Events Through Day +42

Outcomes for adverse events through the 42-day follow-up period for ciprofloxacin patients were reported as follows: 135 patients had events that resolved, 11 improved, 24 were unchanged, 5 patients worsened (2 patients with rash, 1 with heart failure, 1 with thrombosis, and 1 with asthma), and 24 patients had insufficient follow-up to assess resolution.

Outcomes for adverse events through the 42-day follow-up period for control patients were reported as follows: 95 patients had events that

resolved, 3 improved, 25 were unchanged, 2 patients worsened (1 patient with infection, and 1 with pharyngitis and rhinitis) and 3 had insufficient follow-up to assess resolution.

12.15.13 Overview of Adverse Events Through One Year

Table 19 displays a brief summary of the rates of death, any adverse event, any drug-related adverse event, any serious adverse event, and premature discontinuations due to adverse events, for ciprofloxacin patients valid for safety through the on year follow-up time point. No additional patients died between Day +42 and the 1-year follow-up time point.

TABLE 19
Summary of Adverse Events by Day +42
Ciprofloxacin Treated Patients (N=487)

	Ciprofloxacin
Deaths	1 (<1%)*
Adverse Events	252 (52%)
Drug-Related Adverse Events	88 (18%)
Serious Adverse Events	22 (5%)
Premature Discontinuations due to Adverse Events	14 (3%)

* One ciprofloxacin-treated patient died (Patient 49-0055) due to right atrial thrombosis with deterioration in cardiac function during the Day +42 follow-up period.

12.15.14 Serious Adverse Events Through One Year

Only one additional serious adverse event was reported after the 42-day follow-up period (fever). This event was not thought to be drug-related. Therefore, there were no serious drug-related adverse events reported after the initial 42-day follow-up period.

12.15.15 Musculoskeletal and CNS Adverse Events Through One Year

The incidence rates of musculoskeletal or CNS events occurring in $\geq$ 1% of ciprofloxacin patients, including arthropathy, through the 1-year follow-up period for ciprofloxacin and control patients valid for safety are shown in Table 17. The overall rate of any musculoskeletal or CNS event through the 1-year follow-up period for ciprofloxacin was 21%, with a corresponding 95% confidence interval of (17.8%, 25.3%) and 5%, with a corresponding 95% confidence interval of (3.2%, 7.2%) for control. The incidence rate of arthropathy for ciprofloxacin was 11%, with a 95% confidence interval of (8.8%, 14.7%) and 3%, with a corresponding 95% confidence interval of (1.4%, 4.3%) for control.

The only musculoskeletal event occurring in $\geq$1% of ciprofloxacin patients was arthralgia (9%; 46 patients). Arthrosis occurred in 3 patients (0.6%) and myalgia in 2 patients(0.4%). Tendon disorder was reported in one

patient (0.3%). The incidence of convulsions was the same in both treatment arms (3 patients each, 0.6%).

TABLE 20
Musculoskeletal or CNS Events Through One Year of Follow-Up
Occurring in ≥1% of Ciprofloxacin Patients
Ciprofloxacin (N=487) and Control (N=507) Patients

	Ciprofloxacin	95% Confidence Interval	Control	95% Confidence Interval
Any Musculoskeletal or CNS Event	104 (21%)	(17.8%, 25.3%)	25 (5%)	(3.2%, 7.2%)
Any Musculoskeletal Event	64 (13%)	(10.3%, 16.5%)	14 (3%)	(1.5%, 4.6%)
Arthropathy (assessed by IPSC)	56 (11%)	(8.8%, 14.7%)	13 (3%)	(1.4%, 4.3%)
Arthralgia	46 (9%)	(7.0%, 12.4%)	6 (1%)	(0.4%, 2.6%)
Any CNS Event	56 (11%)	(8.8%, 14.7%)	11 (2%)	(1.1%, 3.9%)
Insomnia	21 (4%)	(2.7%, 6.5%)	4 (<1%)	(0.2%, 2.0%)
Dizziness	9 (2%)	(0.8%, 3.5%)	1 (<1%)	(<0.1%, 1.1%)
Abnormal Dreams	6 (1%)	(0.5%, 2.7%)	0	--
Anxiety	5 (1%)	(0.3%, 2.4%)	0	--
Abnormal Gait	5 (1%)	(0.3%, 2.4%)	0	--

Clinical Reviewer's Comment: Tables 21 and 22 Appendix 1 were created by the reviewer and list the ciprofloxacin and control patients, respectively, with arthropathy occurring between Day +42 and 1-year of follow-up, as assessed by the IPSC. Of these, 7 ciprofloxacin patients and none of the control patients had an event(s) occurring between Day +42 and one year as well as an event(s) occurring by Day +42.

In order to understand the cases of arthralgia better, as this category of musculoskeletal events comprises the greatest proportion of the musculoskeletal events, the FDA Clinical Reviewer looked in greater detail at these patients. Table 23 lists the patients with arthralgia events occurring between Day +42 and 1-year of follow-up for ciprofloxacin and control, respectively.

TABLE 23
ARTHRALGIA Cases Occurring between
Day +42 and 1 Year of Follow-up

Ciprofloxacin		Comparator	
15 patients (22 events)/56 = 27%		2 patients (2 events)/13 = 15%	
Pt. #/Sex/Age in years	Description	Pt. #/Sex/ Age in years	Description
210005/M/7 [2 events prior]	Unable to bend second toe on R foot	320036/F/8	Bilateral knee pain
	Intermittent bilateral knee pain (back of knees)	830028/F/9	R knee pain
300001/M/12	R knee pain		
	L knee pain		
310011/F/4	Bilateral knee pain		
	Hip pain		
310016/F/4	R ankle pain		
	R knee pain		
320004/F/3	Joint pains in knees		
320032/F/11	Knee pain		
350022/F/11 [2 earlier events]	R hip pain		
610001/M/8 [1 earlier event]	Knee pain		
630005/F/10	Pain in fingers and back		
640008/F/5	Bilateral knee pain		
270017/F/8 [2 earlier events]	Pains on ankles		
	Knee pains		
270024/M/5**	Knee pain		
320029/M/11	Joint pain in knees		
	Joint pain		
	Bilateral joint pain in knees		
210015/M/11**	Jaw pain		
9930010/M/8	Hip pain		

** IPSC inadvertently unblinded to study drug

Table 24 displays the incidence rates of drug-related musculoskeletal or CNS events occurring in ≥1% of ciprofloxacin patients through the 1-year follow-up period for ciprofloxacin and control patients valid for safety. The incidence rate of any drug-related musculoskeletal or CNS event at this time point was 11% for ciprofloxacin and 3% for control. The incidence rate of drug-related arthropathy was 8% for ciprofloxacin and 2% for control.

TABLE 24
Drug-Related Musculoskeletal or CNS Events
Through One Year of Follow-Up
Occurring in ≥1% of Ciprofloxacin Treated Patients (N=487)

	Ciprofloxacin 95% Confidence Interval		Control 95% Confidence Interval	
Any Musculoskeletal or CNS Event	53 (11%)	(8.3%, 14.0%)	10 (3%)	(1.0%, 3.6%)
Any Musculoskeletal Event	41 (8%)	(6.1%, 11.2%)	9 (2%)	(0.8%, 3.3%)
Arthropathy (assessed by IPSC)	40 (8%)	(5.9%, 11.0%)	9 (2%)	(0.8%, 3.3%)
Arthralgia	8 (2%)	(0.7%, 3.2%)	0	--
Any CNS Event	12 (2%)	(1.3%, 4.3%)	1 (<1%)	(<0.1%, 1.1%)
Insomnia	6 (1%)	(0.5%, 2.7%)	1 (<1%)	(<0.1%, 1.1%)
Dizziness	9 (2%)	(0.8%, 3.5%)	0	--

12.15.16 Analysis of Arthropathy Adverse Events Through One Year

At the end of the study (i.e., through one year of follow-up) there were 128 patients identified using the arthropathy algorithm. Of note, 1 patient (60001) did not appear on the algorithm at the end of the study. The patient had arthralgia as an initial adverse event, which was later clarified as an adverse event of neck pain. The patient's case was also reviewed by the IPSC.

Of the 129 patients reviewed by the IPSC, 70 patients were deemed by the IPSC to have possible, probable, or definite arthropathy. The information for these cases, with one exception, was included in the applicant's statistical analyses for the study. One patient (350008) was not considered to be valid for safety by the applicant and thus was not included in the statistical analyses.

Clinical Reviewer's Comment: It could not be confirmed by the applicant that Patient 350008 received at least one dose of study drug, therefore the reviewer agrees with the removal of this patient from the statistical analyses. A breakdown of the remaining 69 cases by treatment received can be found in Tables 25 and 26 in Appendix 1. There were 56 cases of arthropathy in the ciprofloxacin arm and 13 in the comparator arm by one year of follow-up.

The incidence rates of arthropathy increased with increasing age. Among ciprofloxacin patients less than 6 years old, the incidence rate of arthropathy was 5% (12/235); for patients ages 6 to 11 years, the incidence rate was 15% (29/194); for patients ages 12 to 16, the incidence rate was 26% (15/58). Among control patients less than 6 years old, the incidence rate of arthropathy was 1.5% (4/265); for patients ages 6 to 11 years, the incidence rate was 4% (8/223); for patients ages 12 to 16, the incidence rate was 5% (1/19).

Rates of arthropathy were slightly higher among patients who received IV or sequential ciprofloxacin therapy (18%; 7/39) than among those who received oral therapy (11%; 48/487). Rates of arthropathy were higher in the IV or sequential therapy groups (8%; 2/26) than among those that received oral therapy (2%; 11/474).

In order to understand the arthropathy cases further, additional analyses were performed by the FDA Clinical Reviewer.

Of Note: The IPSC was inadvertently unblinded to the results of 7 patients in the ciprofloxacin arm: 870053/M/7; 270024/M/5; 350014/M/6; 210004/F/11; 210015/M/11; 350015/F/12; and 790011/M/16.

Clinical Reviewer's Comment: Tables 27 through 36 were created by the reviewer.

Table 27 shows the arthropathy rates by sex of the patient. Overall enrollment into the study was about 51% female (55% for ciprofloxacin and 48% for control). The incidence of arthropathy in the overall valid for safety population for the ciprofloxacin group was 12.3% (33/269) in females and 10.5% (23/218%) in males.

TABLE 27
Sex Distribution of Patients with Arthropathy

	Ciprofloxacin N= 56	Control N= 13
Females	33 (59%)	5 (38%)
Males	23 (41%)	8 (62%)

Table 28 shows the age distribution of patients with arthropathy. In both groups, the about 38% of cases of arthropathy occurred in patients between 9 to 12 years of age.

Clinical Reviewer's Comment: The age breakdown in Table 28 is similar, but not identical to the applicant's grouping of patients by age.

TABLE 28
Age Distribution of Patients with Arthropathy

	Ciprofloxacin N= 56	Control N= 13
$\leq$ 2 years	2 (4%)	3 (23%)
3 to 5 years	10 (18%)	1 (8%)
6 to 8 years	11 (20%)	3 (23%)
9 to 12 years	21 (37%)	5 (38%)
13 to 17 years	12 (21%)	1 (8%)

The breakdown of the arthropathy assessment by the IPSC (i.e., definite, probable, or possible arthropathy) is shown in Table 29 for ciprofloxacin

and control. In addition, for each arthropathy classification, it is noted the number of cases which were probably, possibly, or not related to study drug. The arthropathy cases in the both groups were predominantly possible arthropathies.

TABLE 29
Arthropathy Classification and Corresponding Relationship to Study Drug (as determined by IPSC)

Classification	Ciprofloxacin N= 56	Control N= 13
Definite	13 (23%) 1 probable association with study drug, 6 possible, and 6 not related	2 (15%) both were not related to study drug
Probable	13 (23%) 4 probable associations with study drug, 7 possible, and 2 not related	1 (8%) probable association with study drug
Possible	30 (54%) no probable associations with study drug, 22 possible, and 8 not related	10 (77%) 8 were possibly related to study drug and 2 were not related

Table 30 shows the reverse relationship as shown in Table 23. In Table 24 the cases for ciprofloxacin and control are grouped by relationship to study drug (i.e., probably, possibly, or not related) and then the corresponding arthropathy classification is given (i.e., definite, probable, or possible arthropathy). The majority of cases in each treatment group were possibly related to study drug.

TABLE 30
Relationship to Study Drug and Corresponding Arthropathy Classification (as determined by IPSC)

Relationship	Ciprofloxacin N= 56	Control N= 13
Probable	5 (9%) 1 was a definite arthropathy, and 4 were probable	1 (8%) probable arthropathy
Possible	35 (63%) 6 were definite arthropathies, 7 were probable, and 22 were possible	8 (61%) all possible arthropathies
None	16 (28%) 6 were definite arthropathies, 2 were probable, and 8 were	4 (31%) 2 definite arthropathies and 2 possible

Relationship	Ciprofloxacin N= 56	Control N= 13
	possible	

The severity of arthropathy events is shown in Table 31. Since many patients had more than one event, they were classified by the reviewer based upon the most severe event.

TABLE 31
Severity of Arthropathy Events

Severity of Event	Ciprofloxacin N= 56	Control N= 13
Mild	29 (52%)	3 (23%)
Moderate	16 (29%)	4 (31%)
Severe	4 (7%) 70062/M/14: myalgia, bilateral knee pain and bilateral shoulder muscle pain (associated with exercising in the pool) 210005/M/7:arthralgia, intermittent jaw pain and intermittent bilateral knee pain (back of knees) 760005/F/14: arthralgia, hip pain; back pain [serious event, resulted in hospitalization] 210015/M/11: arthralgia, jaw pain	1 (8%) 830028/F/9: arthralgia, R knee pain (patient doesn't stretch before running)
No information	7 (12%)	5 (38%)

* a patient may have had more than one event

There was only one serious arthropathy which occurred in a ciprofloxacin patient, as shown in Table 32. The event was classified by the IPSC as a possible arthropathy. The patient was being treated with chemotherapy (vincristine) and the IPSC thought the event could possibly be related to the vincristine.

TABLE 32
Serious Arthropathy Adverse Events

Ciprofloxacin N= 56	Control N= 13
One patient	No patients
760005/F/14: arthralgia, hip pain; back pain [serious event, resulted in hospitalization] IPSC: myopthy or neuropathy, could be related to vincristine toxicity	

There were two tendon disorders noted in the study, one in each treatment group, as shown in Table 33. Patient 350011 in the ciprofloxacin group had a pre-existing tendonitis in his right elbow which continued during the study and was exacerbated by pitching baseball. The IPSC classified the event as a possible arthropathy with no relationship to study drug.

TABLE 33
Tendon-Related Adverse Events

Ciprofloxacin N= 56	Control N= 13
One patient	One patient
350011/M/13: R elbow tendonitis, present at baseline, exacerbated by pitching baseball possible arthropathy, no relationship to study drug	280018/F/14: bilateral Achillean tendonitis IPSC: not warming up in sports, spondyloarthritis Probable arthropathy, probable relationship to study drug

Table 34 shows the arthropathy events which developed while the patient was still receiving study medication. Of the patients with arthropathy, similar percentages (37% for ciprofloxacin and 38% for control) developed arthropathy before the end of treatment with study drug.

TABLE 34
Patients with Arthropathy Developing During Study Drug Administration

Ciprofloxacin N= 56		Control N= 13	
21/56 (37%)		5/13 (38%)	
Pt. Number	COSTART term /Description	Pt. Number	COSTART term/ Description
80006/F/14	Arthralgia/shoulder pain	500026/M/1	--/R hip pain and tenderness on joint exam
170001/M/2	Arthralgia/L ankle tenderness	500032/M/15	--/R hip pain and tenderness on joint exam
	Arthralgia/L knee tenderness		

Ciprofloxacin N= 56		Control N= 13	
21/56 (37%)		5/13 (38%)	
Pt. Number	COSTART term /Description	Pt. Number	COSTART term/ Description
210005/M/7	Arthralgia/intermittent jaw pain	870025/M/2	--/bilateral knee tenderness on joint exam
350012/M/15	--/bilateral ankle and foot swelling	280018/F/14	Tendon disorder/bilateral Achillean tendonitis
350013/F/9	Peripheral edema/bilateral ankle swelling		
350020/F/7	--/L shoulder pain		
380006/F/10	Arthralgia/jaw pain		
400049/F/11	Arthralgia/intermittent L shoulder pain		
490054/F/15	--/L shoulder pain and tenderness on joint exam		
	--/R ankle and foot pain on joint exam		
580001/F/6*	--/R shoulder tenderness on joint exam		
9930001/F/10	--/bilateral hip pain on joint exam (pre-existing)		
220001/F/2	Arthralgia/elbow pain		
250033/F/13	Arthralgia/R wrist pain		
270017/F/8	Arthralgia/bilateral knee pain		
	Arthralgia/bilateral ankle pain		
460001/F/10	Arthralgia/L wrist pain		
	Arthralgia/R knee pain		
210004/F/11**	Arthralgia/L elbow pain		
	Arthralgia/L shoulder pain		
	Arthralgia/L elbow pain		
210015/M/11**	Joint disorder/stiffness in hands and fingers		
30011/M/6	Arthralgia/L elbow		

Ciprofloxacin N= 56		Control N= 13	
21/56 (37%)		5/13 (38%)	
Pt. Number	COSTART term /Description	Pt. Number	COSTART term/ Description
	pain		
350015/F/12**	Arthralgia/R ankle pain		
9930010/M/8	--/bilateral foot and ankle swelling on joint exam		

* study drug started prior to the baseline exam being conducted
** IPSC inadvertently unblended to study drug

The reviewer noted that there were many arthropathy events which occurred as a result of "accidental trauma", which for the purposes of this review is defined as a specific traumatic event which caused the patient injury. Of the patients with arthropathy, 9% of ciprofloxacin patients compared to 15% of control patients developed an arthropathy event as a result of a traumatic injury, as shown in Table 35.

TABLE 35
Arthropathy Events Associated with "Accidental Trauma"

Ciprofloxacin N= 56			Control N= 13		
5/56 (9%)			2/13 (15%)		
Pt. #/Sex/Age in years	COSTART term/Description	Rel Start to End of Tx	Pt. #/Age (yrs) /Country	COSTART term/Description	Rel Start to End of Tx
250003/M/9	Arthralgia/L wrist pain (pt. wrestling with brother)	42	70152/M/7	Sprained hip (pt. playing football)	92
60003/F/9	Arthralgia/L ankle pain (pt. cheerleading and playing on the trampoline)	38	870034/F/11	Abnormal gait (Pt. hurt hip while playing)	36
270046/M/10	Accidental injury/ L wrist sprain (pt. fell off bike)	27			
370010/M/3	Arthralgia/R knee pain; arthralgia/ R knee injury (Pt. drove into a house on his battery-operated moped)	28			
300001/M/12	Accidental injury/L knee sprain;				

Ciprofloxacin N= 56			Control N= 13		
5/56 (9%)			2/13 (15%)		
Pt. #/Sex/Age in years	COSTART term/Description	Rel Start to End of Tx	Pt. #/Age (yrs) /Country	COSTART term/Description	Rel Start to End of Tx
	accidental injury/R wrist sprain (no info)				

In addition to the events related to traumatic injury, the reviewer also noted that events were associated with strenuous physical activity (PA) or physical exercise (PE). Table 36 shows the cases for ciprofloxacin and control. Of the patients with arthropathy, there was approximately an equal distribution of events associated with PA or PE in both groups (i.e., 11% vs. 15%).

TABLE 36
Arthropathy Events Associated with
Physical Activity (PA) or Exercise (PE)

Ciprofloxacin N= 56		Control N= 13	
6/56 (11%)		2/13 (15%)	
Pt. Number/Sex/Age in years	COSTART term /Description	Pt. Number	COSTART term/ Description
80006/F/14	Arthralgia/shoulder pain (associated with exercising in the pool)	280018/F/14	Tendon disorder/bilateral Achillean tendonitis (pt. not warming up in sports)
80006/F/14	Arthralgia/shoulder pain (associated with swimming)	830028/F/9	Arthralgia/R knee pain (pt. doesn't stretch before running)
170001/M/2 (pt. rolling around on the ground with a ball)	Arthralgia/ L ankle tenderness		
	Arthralgia/ L knee tenderness		
	Arthralgia/ L knee swelling		
350011/M/13	Tendon disorder/ R elbow tendonitis (present at baseline, exacerbated by pitching baseball)		
250033/F/13	Arthralgia/ L wrist pain (associated with gymnastics)		
350021/F/11	Accidental injury/R		

Ciprofloxacin N= 56		Control N= 13	
6/56 (11%)		2/13 (15%)	
Pt. Number/Sex/Age in years	COSTART term /Description	Pt. Number	COSTART term/ Description
	knee injury (associated with dancing and soccer)		

12.15.17 Time to Musculoskeletal Events

Ciprofloxacin

Figure 1 in Appendix 1 shows the Kaplan-Meier estimates of time to any musculoskeletal event for ciprofloxacin patients valid for safety, through the Day +42 time point. Figures 2 and 3 in Appendix 1 show the same curves by age group and treatment type, respectively. Figures 4 through 6 in Appendix 1 provide these estimates through the 1-year follow-up time point.

Note: In all the curves, the last day of treatment is shown as Day 1 on the x-axis with each day afterwards representing the relative time from end of treatment to musculoskeletal adverse event or arthropathy. For this reason, any events that occurred during therapy (and therefore had a negative start day relative to the end of treatment) were considered to have occurred at Day +1 so as not to be excluded from the analysis. In addition, for events that were documented but were missing relative day information, the mean time of musculoskeletal event or arthropathy for that patient's treatment group was used.

Figures 1 and 4 reinforce the results from the tables that show that approximately 70% of the musculoskeletal events reported had been reported by Day +42. Many events were reported during therapy (evidenced by the sharp drop in the curve at Day +1), then fairly uniformly through Day +42 post-therapy (evidenced by the fairly constant slope from Day +42).

Figures 2 and 5 show that the age group differences seen in the incidence rates of any musculoskeletal event were defined very early in the treatment regimen. Within 10 days after the end of therapy, the ordering of the age groups (increasing incidence with increasing age group) had been established, and remained this way throughout the 42-day and 1-year follow-up periods. This is evidenced by the fact that the age-specific survival curves do not cross beyond 10 days.

Figures 3 and 6 indicate that the only constant difference in time to musculoskeletal event or arthropathy according to treatment type (oral, IV or sequential) was that the oral group had the lowest event rate. This was due to the fact that although the treatment-specific survival curves for IV and sequential therapy cross, the oral therapy curve remains above them. This was seen over the Day +42 and one year periods.

Control

Figure 7 in Appendix 1 shows the Kaplan-Meier estimates of time to any musculoskeletal event for ciprofloxacin patients valid for safety, through the Day +42 time point. Figures 8 and 9 in Appendix 1 show the same curves by age group and treatment type, respectively. Figures 10 through 12 in Appendix 1 provide these estimates through the 1-year follow-up time point.

Note: In all the curves, the last day of treatment is shown as Day 1 on the x-axis with each day afterwards representing the relative time from end of treatment to musculoskeletal adverse event or arthropathy. For this reason, any events that occurred during therapy (and therefore had a negative start day relative to the end of treatment) were considered to have occurred at Day +1 so as not to be excluded from the analysis. In addition, for events that were documented but were missing relative day information, the mean time of musculoskeletal event or arthropathy for that patient's treatment group was used.

Figures 7 and 10 reinforce the results from the tables that show that approximately 70% of the musculoskeletal events reported had been reported by Day +42. Many events were reported during therapy (evidenced by the sharp drop in the curve at Day +1), then fairly uniformly through Day +42 post-therapy (evidenced by the fairly constant slope from Day +42).

Figures 8 and 11 show that as in the ciprofloxacin group, the oldest age group had the highest event rate by Day +42 post-therapy and continuing to Day +365 post-therapy.

Figures 9 and 12 show that the IV control group had the lowest event rate until approximately Day +32 post-therapy, and the highest event rate afterwards.

12.15.18 Parental Questionaire – Adverse Musculoskeletal or CNS Events

Adverse musculoskeletal or CNS events were reported infrequently for ciprofloxacin using the parental questionnaire at 3, 6, 9, and 12 month periods (data not shown). Incidence rates of any musculoskeletal or CNS event reported were 5% or below at each time point and for each subgroup except patients 12-16 years of age at 9 and 12 months (10%).

In the control group, musculoskeletal or CNS events reported using the parental questionnaire were also infrequent and were reported below 5% at each time point and for each subgroup. (data not shown). Only 5 events were reported through the 12-month follow-up period. Three of these events were arthralgia, all from patients in the 6 to 11 age group.

12.15.19 All Adverse Events Through One Year

Table 37 shows adverse events, for all adverse events and those related to study drug, respectively, for all body systems through the one year

follow-up period for ciprofloxacin and control patients. The results for events, regardless of relationship to study drug that occurred in at least 2% of patients in either group are shown in Table 38. The most common events for ciprofloxacin (other than musculoskeletal events) were accidental injury (7% incidence rate), otitis media, pharyngitis, and headache (6% each). The most common events for control (other than musculoskeletal events) were pharyngitis and accidental injury (4% each).

TABLE 37
Incidence Rates of Adverse Events by Body System
Through One Year
Ciprofloxacin (N=487) and Control (N=507) Patients

Body System	Ciprofloxacin		Control	
Any Event	252	(52%)	141	(28%)
Body as a Whole	131	(27%)	60	(12%)
Cardiovascular	11	(2%)	1	(<1%)
Digestive	46	(9%)	17	(3%)
Endocrine	2	(<1%)	0	(0%)
Hemic and Lymphatic	14	(%)	5	(<1%)
Metabolic & Nutritional	6	(%)	2	(<1%)
Musculoskeletal	64	(13%)	14	(3%)
Nervous	56	(11%)	11	(2%)
Respiratory	75	(15%)	52	(10%)
Skin & Appendages	27	(6%)	23	(5%)
Special Senses	41	(8%)	29	(6%)
Urogenital	19	(4%)	4	(<1%)

TABLE 38
Incidence Rates of Adverse Events Through One Year (Other than Musculoskeletal and CNS) Occurring in at Least 2% of Patients (Regardless of Relationship to Study Drug) in Either Group
Ciprofloxacin (N=487) and Control (N=507) Patients

Adverse Event	Ciprofloxacin		Control	
Any event	252	(52%)	141	(28%)
Accidental Injury	34	(7%)	21	(4%)
Allergic Reaction	1	(<1%)	9	(2%)
Otitis Media	28	(6%)	15	(3%)
Pharyngitis	27	(6%)	22	(4%)
Headache	27	(6%)	7	(1%)
Rhinitis	22	(5%)	15	(3%)
Fever	22	(5%)	7	(1%)
Leg Pain	18	(4%)	5	(<1%)
Vomiting	18	(4%)	5	(<1%)
Asthenia	18	(4%)	0	(0%)

Rash	17	(3%)	13	(3%)
Abdominal Pain	17	(3%)	7	(1%)
Cough Increased	15	(3%)	3	(<1%)
Diarrhea	14	(3%)	2	(<1%)
Sinusitis	8	(2%)	7	(1%)

Most of the adverse events reported in either group were not considered drug-related. The incidence rate of any drug-related adverse event in the ciprofloxacin group was 18% and 5% in the control group. The only events with drug-related incidence rates of 1% or higher (other than musculoskeletal or CNS events) in the ciprofloxacin group were abdominal pain (8 patients, 2%), diarrhea (9 patients, 2%), vomiting (10 patients, 2%), and headache (5 patients, 1%); and rash (6 patients, 1%) in the control group.

12.15.20 Deaths

There was one death in the study. Patient narrative is provided below.

Patient 490055
Patient is a 5-month old male was treated with ciprofloxacin 100 mg IV bid for the indication of bacteremia and sepsis due to *Morganella morganii* (b) (6) (for a total of 32 doses).

The patient was a critically ill full-term infant who had been hospitalized since birth. He had a history of VACTERL syndrome (vertebral, anal, cardiac, tracheal, esophageal, renal, and limb pattern of congenitial anomalies), Hirschsprung's disease, (congenital megacolon), primary pulmonary hypertension, hemivertebra, imperforate anus/colostomy, duodenal atresia/ end to end repair anastomosis, hyposadias, and patent ductus arteriosis since birth. He also had a history of RSV (b) (6) respiratory failure requiring intubation (b) (6) hepatomegaly (b) (6) sepsis from central venous catheter infections with isolates of *S. homins*, *Enterococcus faecalis*, and *E. coli* (b) (6) anemia/decreased oxygen carrying capacity (b) (6) small bowel obstruction/ileostomy (b) (6) electrolyte abnormalities (b) (6) post-operative wound dehiscence/cellulitis (b) (6) feeding intolerance (b) (6) and fungemia sepsis (*Malassezia furfur*, since (b) (6)). The patient was receiving multiple concomitant medications.

The serious adverse event of deterioration in cardiac function began on (b) (6) (ciprofloxacin treatment (b) (6)). The ongoing respiratory failure and electrolyte abnormalities most likely contributed to this event. The patient was hyperkalemic and acidotic with decreased oxygenation and perfusion. Widening of QRS complex, hypotension and bradycardia were noted. The patient responded well to electrolyte correction, diuresis, and increased ventilatory settings. The

investigator considered the event to have no association to the study drug.

The patient was stable in the morning (b) (6) and by afternoon (b) (6) was noted to have low blood pressure, no peripheral pulses, and low oxygen saturation. An ECG was done which showed abnormally narrow QRS complexes. CPR was initiated with chest compressions and epinephrine, sodium bicarbonate, calcium chloride were given. Patient returned to normal sinus rhythm after 20 minutes. An echocardiogram showed a right atrial thrombus/vegetation with extension from the inferior vena cava. The patient was then started on heparin. Cardiac pressors as drips were initiated (epinephrine, dopamine and dobutamine). At (b) (6) the patient's blood pressure dropped. The patient again was dosed with epinephrine, sodium bicarbonate, calcium chloride. Despite all of the above, patient became pulseless and expired (b) (6)

Information from the death certificate considered cardiac arrest as the immediate cause of death and pulmonary hypertension as a contributory cause of death. As per the death certificate, other significant conditions that contributed to the patient's death were VACTERL syndrome, Hirschsprung's disease, and sepsis. An autopsy was not performed. The relative day of death to end of treatment was 17 days.

Clinical Reviewer's Comment: The reviewer agrees that ciprofloxacin administration was not directly related to the patient's death, although sepsis, the infection for which ciprofloxacin was being given, did contribute to the patient's death.

12.15.21 Serious Adverse Events

Serious adverse events were reported for 22 patients in the ciprofloxacin group as shown in Table 41. The most commonly reported serious adverse events were fever (5 patients) and sepsis (4 patients). One ciprofloxacin patient died from cardiac arrest 17 days after the end of treatment. In the control arm, there were 5 patients (2 patients with acute asthma exacerbations and one patient each with abscess, vertigo and pleural effusion) with serious adverse events as shown in Table 42.

Two ciprofloxacin patients had serious adverse events considered at least possibly related to study drug. Patient 270024 had acute gastroenteritis and *Clostridium difficile* colitis considered possibly related to study drug. Patient 500011 had *Clostridium difficile* colitis considered probably related to study drug. All other serious adverse events reported in the ciprofloxacin group were judged by the investigators to be unlikely or not related to study drug. Two ciprofloxacin patients had musculoskeletal serious adverse events. Patient 310019 had severe osteomyelitis, which resolved and was considered unlikely related to study drug. Patient 760005 had severe hip pain, which resolved and was not considered related to study drug.

TABLE 41
Serious Adverse Events
Ciprofloxacin Patients Valid for Safety

PATIENT	TREATMENT GROUP	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	OUTCOME	ACTION TAKEN 1	SEVERITY
90025	CIPROFLOXACIN	DEHYDRATION	47	49	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
200008	CIPROFLOXACIN	CENTRAL VENOUS	24	31	RESOLVED	HOSPITALIZATION	SEVERE
210015	CIPROFLOXACIN	NEUTROPENIA	49	78	RESOLVED	HOSPITALIZATION	SEVERE
210015	CIPROFLOXACIN	BACTEREMIA	49	58	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
210015	CIPROFLOXACIN	NEUTROPENIC FEV	61	67	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
210015	CIPROFLOXACIN	BACTEREMIA	63	69	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
220013	CIPROFLOXACIN	RECURRENT URINA	47	52	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
270024	CIPROFLOXACIN	ACUTE GASTROENT	4	9	RESOLVED	HOSPITALIZATION	SEVERE
270024	CIPROFLOXACIN	CLOSTRIDIUM DIF	23	39	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
270024	CIPROFLOXACIN	SEPSIS	27	41	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
290062	CIPROFLOXACIN	FAILURE ACUTE R	23	29	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
290062	CIPROFLOXACIN	HEMOLYTIC UREMI	63	65	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
300002	CIPROFLOXACIN	PERIANAL ABSCES	13	16	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
300004	CIPROFLOXACIN	OTITIS MEDIA (R	54	57	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
300004	CIPROFLOXACIN	OTITIS MEDIA (R	65	68	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
310017	CIPROFLOXACIN	WORSENING OTITI	6	15	RESOLVED	STUDY DRUG DISCONTINUED PERMANENTLY	SEVERE
310019	CIPROFLOXACIN	OSTEOMYELITIS	23	156	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
350014	CIPROFLOXACIN	FEVER	18	27	RESOLVED	REMEDIAL DRUG THERAPY	MODERATE
360002	CIPROFLOXACIN	FEVER	27	30	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
360002	CIPROFLOXACIN	RULE OUT BACTER	27	30	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
420010	CIPROFLOXACIN	ACUTE LYMPHOCYT	22	24	RESOLVED	HOSPITALIZATION	MILD
420010	CIPROFLOXACIN	ACUTE LYMPHOCYT	38	39	RESOLVED	HOSPITALIZATION	MILD
490055	CIPROFLOXACIN	DETERIORATION I	32	34	WORSENED	OTHER	SEVERE
490055	CIPROFLOXACIN	RIGHT ATRIUM TH	34	34	WORSENED	OTHER	SEVERE
490055	CIPROFLOXACIN	CARDIAC ARREST	34	34	DEATH	OTHER	SEVERE
500008	CIPROFLOXACIN	ABDOMINAL WOUND	4	42	RESOLVED	STUDY DRUG DISCONTINUED PERMANENTLY	SEVERE
500011	CIPROFLOXACIN	CLOSTRIDIUM DIF	17	33	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
500011	CIPROFLOXACIN	THROMBUS IN RIG	21	31	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
500011	CIPROFLOXACIN	URETERAL REFLUX	11	13	RESOLVED	OTHER	SEVERE
500011	CIPROFLOXACIN	NEPHROPATHY	11	13	RESOLVED	OTHER	SEVERE
500024	CIPROFLOXACIN	ABDOMINAL WOUND	4	.		. STUDY DRUG DISCONTINUED PERMANENTLY	SEVERE
500024	CIPROFLOXACIN	REHOSPITALIZATI	8	19	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
500024	CIPROFLOXACIN	NAUSEA	32	34	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
500024	CIPROFLOXACIN	VOMITING	32	34	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
510009	CIPROFLOXACIN	STENOTROPHOMONA	19	28	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
760005	CIPROFLOXACIN	HIP PAIN	38	48	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
760005	CIPROFLOXACIN	BACK PAIN	38	48	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
760005	CIPROFLOXACIN	NEUTROPENIA	38	62	RESOLVED	HOSPITALIZATION	SEVERE
760005	CIPROFLOXACIN	FEVER	38	44	RESOLVED	HOSPITALIZATION	SEVERE
770002	CIPROFLOXACIN	PYELONEPHRITIS	.	.	RESOLVED	REMEDIAL DRUG THERAPY	MODERATE
770002	CIPROFLOXACIN	LEFT URETEROPEL	.	.	RESOLVED	OTHER	MODERATE
790011	CIPROFLOXACIN	NEUTROPENIA	44	47	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
790011	CIPROFLOXACIN	FEVER	44	47	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
9930010	CIPROFLOXACIN	NEUROGENIC BLAD	12	12	RESOLVED	HOSPITALIZATION	SEVERE
9930010	CIPROFLOXACIN	SMALL BOWEL OBS	31	31	RESOLVED	HOSPITALIZATION	SEVERE
9930010	CIPROFLOXACIN	SMALL BOWEL OBS	40	40	RESOLVED	HOSPITALIZATION	SEVERE

TABLE 42
Serious Adverse Events
Control Patients Valid for Safety

PATIENT	TREATMENT GROUP	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	OUTCOME	ACTION TAKEN 1	SEVERITY
510013	AMOXICILLIN	VERTIGO	39	43	RESOLVED	HOSPITALIZATION	SEVERE
800051	AMOXICILLIN	ACUTE ASTHMA EX	22	24	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
800016	AUGMENTIN	ACUTE ASTHMA EX	16	17	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
800021	UNASYN	PERITONSILLAR A	29	30	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
470048	AMPICILLIN, CEFOTAXIME, ROCEPHIN	INCREASING PLEU	15	18	RESOLVED	OTHER	SEVERE

12.15.22 Premature Discontinuations

Adverse events caused discontinuation of study drug in 14 ciprofloxacin patients as shown in Table 39. Arthralgia (4 patients), vomiting (2 patients), and rash or urticaria (2 patients) were the most common events causing discontinuation. Adverse events caused discontinuation of study drug in 3 control patients as shown in Table 40. One patient discontinued therapy due to vomiting, one due to rash, and one due to abdominal pain.

TABLE 39
Premature Discontinuations Due to Adverse Events
Ciprofloxacin Patients Valid for Safety

PATIENT	TREATMENT GROUP	COSTART TERM	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	SEVERITY	OUTCOME
80006	CIPROFLOXACIN	ARTHRALGIA	SHOULDER PAIN	13	20	MILD	RESOLVED
90026	CIPROFLOXACIN	DIZZINESS	DIZZINESS	1	7	MODERATE	RESOLVED
90026	CIPROFLOXACIN	DIZZINESS	LIGHTHEADEDNESS	1	7	MILD	RESOLVED
90026	CIPROFLOXACIN	HEADACHE	HEADACHES	1	7	MILD	RESOLVED
90026	CIPROFLOXACIN	TACHYCARDIA	TACHYCARDIA	1	7	MODERATE	RESOLVED
220001	CIPROFLOXACIN	ARTHRALGIA	ELBOW PAIN	11	17	MODERATE	RESOLVED
250027	CIPROFLOXACIN	RASH	ALLERGIC RASH	2	4	MILD	RESOLVED
250033	CIPROFLOXACIN	ARTHRALGIA	WRIST PAIN, RIG	4	.	MILD	IMPROVED
290060	CIPROFLOXACIN	INJECTION SITE	INFUSION SITE R	3	3	MILD	RESOLVED
290060	CIPROFLOXACIN	ALLERGIC REACTI	ALLERGIC REACTI	3	3	MILD	RESOLVED
310012	CIPROFLOXACIN	VOMITING	VOMITING	1	2	MILD	RESOLVED
310017	CIPROFLOXACIN	OTITIS MEDIA	WORSENING OTITI	6	15	SEVERE	RESOLVED
310026	CIPROFLOXACIN	VOMITING	VOMITING	1	1	MILD	RESOLVED
320023	CIPROFLOXACIN	INFECTION BACTE	CHRONIC STREPTO	7	10	MODERATE	RESOLVED
320023	CIPROFLOXACIN	SINUSITIS	CHRONIC SINUSIT	7	10	MODERATE	RESOLVED
320023	CIPROFLOXACIN	SINUSITIS	SINUSITIS	12	25	MILD	RESOLVED
380006	CIPROFLOXACIN	ARTHRALGIA	JAW PAIN	5	9	MODERATE	RESOLVED
500008	CIPROFLOXACIN	INFECTION	ABDOMINAL WOUND	4	42	SEVERE	RESOLVED
500024	CIPROFLOXACIN	ABSCESS	ABDOMINAL WOUND	4	.	SEVERE	.
680001	CIPROFLOXACIN	URTICARIA	HIVES	5	.	.	INSUFFICIENT FOLLOW-UP

TABLE 40
Premature Discontinuations Due to Adverse Events
Control Patients Valid for Safety

PATIENT	TREATMENT GROUP	COSTART TERM	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	SEVERITY	OUTCOME
70194	AMOXICILLIN	VOMITING	VOMITING	1	3	MILD	RESOLVED
760008	AMOXICILLIN	RASH	RASH	7	19	MODERATE	RESOLVED
870039	CEFZIL	ABDOMINAL PAIN	ABDOMINAL PAIN	.	46	MILD	RESOLVED

12.15.23 Clinical Laboratory Evaluation

The study did not require any scheduled laboratory assessments.

12.15.24 Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs
Vital signs were not collected as a routine assessment in this study.

Range of Motion (ROM) Assessments (data not shown)
The mean change in ROM from pre-therapy to post-therapy for ciprofloxacin patients was small (less than 4 degrees), but positive, in all joints; the largest changes were 3.1 degrees extension increase in the right shoulder and 3.0 degrees extension increase in the left shoulder. In the control arm, most mean changes were very small (less than 3 degrees), but positive, in all joints; the largest change post-therapy was 2.6 degrees plantar flexion in the right ankle/foot.

Gait and Joint Assessments (data not shown)
In ciprofloxacin patients, the vast majority had a normal assessment that remained the same from baseline to post-therapy. In the shoulder joint, only one patient's assessment changed from normal to pain. In the hip, one patient changed from normal to pain, and one changed from normal to tenderness. In the left knee, 9 patients changed from normal to swelling, pain, or tenderness. In the right knee, 6 patients changed from

normal to redness, swelling, pain, tenderness, or brace. In the left ankle/foot, 7 patients changed from normal to swelling, pain, or tenderness. In the right ankle/foot, 4 patients changed from normal to redness, swelling, pain, or tenderness.

In control patients, the majority had their assessment remain the same from baseline to post-therapy. In the left hip, one patient's assessment changed from normal to pain. Changes from normal to pain or tenderness were similarly rare in the shoulder, knee, ankle and foot.

Thirty-seven ciprofloxacin patients had joint appearance abnormalities compared to 11 control patients. Of these, 23 ciprofloxacin and 9 control patients had these abnormalities at baseline. Most abnormalities were seen in the knees or ankles. All cases of joint appearance abnormalities, regardless of whether it was a baseline finding or treatment-emergent, were reviewed by the IPSC for possible arthropathy. Of the 14 ciprofloxacin patients with treatment-emergent joint appearance abnormalities, 13 were assessed by the IPSC as having arthropathy. Of the 2 control patients with treatment-emergent joint appearance abnormalities, 1 was assessed by the IPSC as having arthropathy.

Forty-six ciprofloxacin patients had stance/swing abnormalities compared to 8 control patients. Of these, 36 ciprofloxacin patients and 4 control patients had the abnormalities at baseline. All cases of gait abnormality, whether it was a baseline finding or treatment-emergent, were assessed by the IPSC for possible arthropathy. Of the 10 ciprofloxacin patients with treatment-emergent gait abnormalities, 5 were assessed by the IPSC as having arthropathy. Of the 4 control patients with treatment-emergent gait abnormalities, 2 were assessed by the IPSC as having arthropathy.

Of the 10 ciprofloxacin patients with treatment-emergent gait abnormalities, 5 were assessed by the IPSC as having arthropathy. Of the 4 control patients with treatment-emergent gait abnormalities, 2 were assessed by the IPSC as having arthropathy.

X-ray Findings (data not shown)

X-rays were performed 28 times on ciprofloxacin patients and 4 times on control patients (one patient could have had more than one x-ray). Of the 28 x-rays in e ciprofloxacin group, 19 were within normal limits and 3 were abnormal, but with clinically insignificant findings (as per the investigator). There were 2 lower arm, 2 hip, 1 throacic spine, and one lumbar spine x-rays that were abnormal and clinical significant. Three of the 4 x-rays in the control group were within normal limits and one that was considered abnormal, but clinically insignificant in the control group.

Developmental Milestones (data not shown)

At baseline, 95% of ciprofloxacin patients were developmentally on target. By the 1-year follow-up timepoint, only 2 patients were not developmentally on target, with 1 patient being deficient in gross motor skills and one being deficient in language. At baseline, 99% of control

patients were developmentally on target. By the 1-year follow-up timepoint, all patients were developmentally on target.

Electroencephalography (EEG) Findings (data not shown)
In the ciprofloxacin patients 30 EEGs were performed (a patient may have had more than one EEG). One ciprofloxacin patient reported an abnormal clinically significant EEG finding. In the control patients 12 EEGs were performed and one abnormal, clinically significant EEG abnormality was noted.

12.16 Safety Conclusions

In this open-label, non-randomized study involving pediatric patients with a variety of infections, ciprofloxacin was compared to active control. Of the 1029 patients enrolled in the study, 994 (96.6%; 487 ciprofloxacin and 507 non-quinolone controls) were considered to have received at least one dose of study drug and were valid for the safety analysis. Of those 994 patients valid for safety, 21 ciprofloxacin patients and 1 control patient had participated in Study 100169 (complicated urinary tract infection and pyelonephritis trial). By June 30, 2003 (date form the interim analysis cut-off), 355 ciprofloxacin and 267 non-quinolone patients had been contacted by telephone for at least 1-year post-treatment follow-up (all 22 patients that participated in Study 100169 had 1-year follow-up). This is an ongoing clinical study. The data presented is from an interim analysis and additional follow-up information is still being pursued.

In the ciprofloxacin group, 55% (269/487) of the patients were female compared to 485 (242/507) in the control group). Although the majority of the ciprofloxacin patients were Caucasian (60%; 292/487), patients of other racial and ethnic origins were represented (7% [33/487] Black, 3% [16/487] Asian, 28% [138/487] Hispanic, and 2% [8/487] were not codable using the applicant's coding system). The control group had slightly more Caucasians (65%; 330/507) with 5% [27/507] Black, 2% [8/507] Asian, 25% [138/507] Hispanic, <1% [1/507] American Indian, and 3% [13/507] were not codable.

The mean age of ciprofloxacin patients was 6.2 years (range: 2 months to 16 years) while the mean age of control patients was slightly lower (5.3 years with a range of 2 months to 16 years). Of the patients ≤ 5 years of age, 48% (235/487) were in the ciprofloxacin group and 52% (265/507) were in the control group. More ciprofloxacin patients (12%; 58/487) were 12 years to <17 years of age compared to control patients (4%; 19/507).

The most common (defined as > 2%) baseline infection types for the ciprofloxacin patients were urinary tract (22%; 105/487) and otitis media (29%; 143/487). The most common baseline infections in the control group were otitis media (41%; 207/507) and pharyngitis/tonsillitis (29%; 148/507).

The mean (± standard deviation) total treatment durations were 12.4 ± 7.9 (range 1 to 88 days) and 11.3 ± 6.7 days (range: 3 to 70 days) for the ciprofloxacin and control groups, respectively.

Previous antimicrobial use was 17% (81/487) in the ciprofloxacin group and 1% (3/507) in the control group. Ciprofloxacin and Bactrim® were the most commonly used previous antimicrobials in the ciprofloxacin group.

Notable differences (>2% differences) were observed in medical history (ICD-9 class) between the two treatment groups. The conditions with the greatest discrepancy between the groups are as follows. Ciprofloxacin-treated patients had a higher incidence of genitourinary system (23% [114/487] versus 8% [41/507]) and digestive system disorders (17% [81/487] versus 8% [43/507]) compared to the control group. The control group had a higher incidence of medical histories of conditions in the nervous system and sense organs (53% [270/507] control versus 31% [150/487] ciprofloxacin; mainly attributed to a higher incidence of otitis media), respiratory system (62% [315/507] control versus 37% [181/487] ciprofloxacin; mainly attributed to differences in upper respiratory infections, pharyngitis, and chronic sinusitis), and injury and poisoning (40% [205/507] control versus 17% [85/487] ciprofloxacin; mainly attributed to allergy).

Known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy were to be excluded from the study. However, 7% (32/487) of ciprofloxacin patients and 5% (24/507) control patients were enrolled with a medical history of any abnormal musculoskeletal or connective tissue finding. In addition, at study entry 7% (36/487) of ciprofloxacin patients and 0.8% (4/507) of control patients had an abnormal gait assessment at baseline and 5% (23/487) of ciprofloxacin patients and 2% (9/507) of control patients had an abnormal joint appearance at baseline. These patients were included in the applicant's valid for safety population. However, these baseline abnormalities and medical histories may have rendered it difficult to assess any potential drug effect on gait or joint appearance.

Prevalence rates of concomitant medication use (at the time of enrollment) were 76% for ciprofloxacin patients and 68% for control patients (data not shown). Antimicrobial use was much more common among ciprofloxacin patients (41%; 201/487) than control patients (17%; 88/507). Ciprofloxacin patients also had higher use of vitamins (8% [40/487] versus 2% [11/507]), antacids (6% [27/487] versus 2% [11/507]), antifungals for dermatologic use (4% [20/487] versus 1% [7/507]), urologicals (5% [24/487] versus 0% [0/507]), antimycotics for systemic use (3% [13/487] versus <1% [1/507]), analgesics (23% [112/487] versus 14% [72/507]), and anti-asthmatics (14% [70/487] versus 11% [55/507]).

Due to the demographic and baseline characteristic differences described, and because the study was not blinded or randomized, safety results of this study should be interpreted with caution. These differences should be considered when reviewing adverse event rates for the two treatment groups and the population of ciprofloxacin patients should not be directly compared to the population of control patients.

One patient death was reported during the study. Patient 490055 died 17 days after receiving the last dose of ciprofloxacin. The patient was a 5-month-old male who had multiple congenital anomalies and had been hospitalized since birth. He developed a right atrium thrombus and died of cardiac arrest. The events were not considered related to study drug by the investigator and the reviewer is in agreement.

In the ciprofloxacin group, 22 patients (5%) had a serious adverse event. Two ciprofloxacin patients had serious adverse events considered at least possibly related to study drug. Patient 270024 had acute gastroenteritis and *Clostridium difficile* colitis considered possibly related to study drug. Patient 500011 had *Clostridium difficile* colitis considered probably related to study drug. All other serious adverse events reported in the ciprofloxacin group were judged by the investigators to be unlikely or not related to study drug. Two ciprofloxacin patients had musculoskeletal serious adverse events. Patient 310019 had severe osteomyelitis, which resolved and was considered unlikely related to study drug. Patient 760005 had severe hip pain, which resolved and was not considered related to study drug. In the control arm, there were 5 patients (2 patients with acute asthma exacerbations and one patient each with abscess, vertigo and pleural effusion) with serious adverse events

In the ciprofloxacin group, 14 patients (2.9%) had an adverse event with the action of study drug permanently discontinued. The most common adverse events leading to discontinuation of study drug were arthralgia (4 patients), vomiting (2 patients), and rash or urticaria (2 patients). No other events causing discontinuation of treatment occurred in more than 1 patient. Adverse events caused discontinuation of study drug in 3 control patients. One patient discontinued therapy due to vomiting, one due to rash, and one due to abdominal pain.

The protocol was designed to specifically examine any musculoskeletal or neurological events. The overall rate of any musculoskeletal or CNS event through the 1-year follow-up period for ciprofloxacin was 21% (104/487) [95% CI: 18%, 25%] and 5% (25/507) [95% CI: 3%, 7%] for control. The incidence of any musculoskeletal adverse event alone by the 1-year post-treatment follow-up was 13% (64/487) [95% CI: 10%, 16%] and 3% (14/507) [95% CI: 1%, 5%] in the ciprofloxacin and control groups, respectively.

The incidence of any CNS event alone by the 1-year post-treatment follow-up was 11% (56/487) [95% CI: 9%, 15%] and 2% (11/507) [95% CI: 1%, 4%] in the ciprofloxacin and control groups, respectively. The only neurologic events occurring in at least 2% of patients were insomnia (4.3% [21/487] versus 0.6% [4/507]) and dizziness (1.8% [9/487] versus 0.8% [1/507]). The incidence of convulsions was the same in both treatment arms (3 patients each, 0.6%).

All patients who had a musculoskeletal adverse event, an abnormal joint appearance (at baseline or any time during the trial), or an abnormal gait assessment (at baseline or any time during the trial), were reviewed by an IPSC, without regards to treatment group. The IPSC evaluated each case for any possible evidence of arthropathy.

The incidence rate of arthropathy, as assessed by the IPSC, for ciprofloxacin was 11% (56/487) [95% CI: 9%, 15%] and 3% (13/507) [95% CI: 1.4%, 4.3%] for control at the end of one year of follow-up.

The incidence rates of arthropathy increased with increasing age. Among ciprofloxacin patients less than 6 years old, the incidence rate of arthropathy was 5% (12/235); for patients ages 6 to 11 years, the incidence rate was 15% (29/194); for patients ages 12 to 16, the incidence rate was 26% (15/58). Among control patients

less than 6 years old, the incidence rate of arthropathy was 1.5% (4/265); for patients ages 6 to 11 years, the incidence rate was 4% (8/223); for patients ages 12 to 16, the incidence rate was 5% (1/19).

Thirty-seven ciprofloxacin patients had joint appearance abnormalities compared to 11 control patients. Of these, 23 ciprofloxacin and 9 control patients had these abnormalities at baseline. Most abnormalities were seen in the knees or ankles. All cases of joint appearance abnormalities, regardless of whether it was a baseline finding or treatment-emergent, were reviewed by the IPSC for possible arthropathy. Of the 14 ciprofloxacin patients with treatment-emergent joint appearance abnormalities, 13 were assessed by the IPSC as having arthropathy. Of the 2 control patients with treatment-emergent joint appearance abnormalities, 1 was assessed by the IPSC as having arthropathy.

Forty-six ciprofloxacin patients had stance/swing abnormalities compared to 8 control patients. Of these, 36 ciprofloxacin patients and 4 control patients had the abnormalities at baseline. All cases of gait abnormality, whether it was a baseline finding or treatment-emergent, were assessed by the IPSC for possible arthropathy. Of the 10 ciprofloxacin patients with treatment-emergent gait abnormalities, 5 were assessed by the IPSC as having arthropathy. Of the 4 control patients with treatment-emergent gait abnormalities, 2 were assessed by the IPSC as having arthropathy.

Of the 10 ciprofloxacin patients with treatment-emergent gait abnormalities, 5 were assessed by the IPSC as having arthropathy. Of the 4 control patients with treatment-emergent gait abnormalities, 2 were assessed by the IPSC as having arthropathy.

Incidence rates of adverse events, other than musculoskeletal and CNS) were accidental injury (7%; 34/487), otitis media, pharyngitis, and headache (6% each [28/487], 27/487], and [27/487], respectively). The most common events for control (other than musculoskeletal events) were pharyngitis and accidental injury (4% each; [22/507] and [21/507]).

12.17 APPENDIX – Additional Tables from Study 100201

TABLE 1
List of COSTART Terms for the Musculoskeletal System

COSTART NUMBER	COSTART TERM
7010010	Bone Disorder
7010020	Bone Implant Lysis
7010030	Bone Necrosis
7010040	Bone Neoplasm
7010050	Bone Pain
7010060	Bone Sarcoma
7010070	Epiphysis Closure Delayed
7010080	Fluorosis
7010090	Osteomalacia
7010100	Osteomyelitis
7010110	Osteoporosis Fracture
7010120	Osteoporosis
7010130	Osteosclerosis
7010140	Pathological Fracture
7010150	Periosteal Disorder
7010160	Premature Epiphyseal Closure
7010170	Spina Bifida
7020010	Bursitis
7030010	Chondrodystrophy
7040010	Musculoskeletal Congenital Anomaly
7050010	Arthralgia
7050020	Arthritis
7050030	Arthrosis
7050040	Joint Disorder
7050050	Pyogenic Arthritis
7050060	Rheumatoid Arthritis
7050065	Synovitis
7060010	Extraocular Palsy
7060020	Generalized Spasm
7060030	Hypocalcemic Tetany
7060035	Leg Cramps
7060040	Muscle Atrophy
7060050	Muscle Hemorrhage
7060060	Myalgia
7060070	Myasthenia
7060080	Myopathy
7060090	Myositis
7060100	Ptosis
7060105	Rhabdomyolysis
7060110	Strabismus
7060120	Tetany
7060130	Twitching
7070010	Tendinous Contracture

COSTART NUMBER	COSTART TERM
7070015	Tendon Disorder
7070020	Tendon Rupture
7070030	Tenosynovitis
7999998	Diagnostic Procedure
7999999	Surgery

TABLE 2
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
2	Eck	13OCT00	09MAY02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	1	1	1	1	1
				TOTAL	2	2	2	2	2
3	Jannetti	18AUG00	26MAR03	CIPROFLOXACIN	10	9	9	9	8
				COMPARATOR	0	0	0	0	0
				TOTAL	10	9	9	9	8
5	Deeths	07JUL00	11MAY01	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
6	Congeni	25AUG00	17DEC02	CIPROFLOXACIN	5	5	5	5	5
				COMPARATOR	2	2	2	2	2
				TOTAL	7	7	7	7	7
7	Hedrick	08MAY00	22MAY03	CIPROFLOXACIN	14	14	14	14	14
				COMPARATOR	223	223	223	223	221
				TOTAL	237	237	237	237	235
8	Sumerson	07SEP00	15MAY02	CIPROFLOXACIN	3	2	2	2	1
				COMPARATOR	1	1	1	1	1
				TOTAL	4	3	3	3	2
9	Maguire	24APR00	20MAY03	CIPROFLOXACIN	33	33	33	33	32
				COMPARATOR	0	0	0	0	0
				TOTAL	33	33	33	33	32
10	Tarpay	30JUN01	20MAY02	CIPROFLOXACIN	4	4	4	4	4
				COMPARATOR	0	0	0	0	0
				TOTAL	4	4	4	4	4
13	Harmon	17OCT00	19DEC00	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	1	1
15	Chartrand	30SEP00	11FEB02	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3

TABLE 2 (continued)
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
17	Mulcihy	06DEC00	24OCT02	CIPROFLOXACIN	1	1	1	1	0
				COMPARATOR	4	4	4	4	4
				TOTAL	5	5	5	5	4
18	Paredes	14FEB01	18OCT02	CIPROFLOXACIN	9	9	9	9	9
				COMPARATOR	0	0	0	0	0
				TOTAL	9	9	9	9	9
20	SanJoaquin	20NOV01	12JUL02	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
21	Seto	19MAY01	27NOV02	CIPROFLOXACIN	7	7	7	7	6
				COMPARATOR	0	0	0	0	0
				TOTAL	7	7	7	7	6
22	Murphey	24SEP01	09DEC02	CIPROFLOXACIN	9	7	7	7	6
				COMPARATOR	0	0	0	0	0
				TOTAL	9	7	7	7	6
23	Heilman	29MAY01	16JUL01	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	1	1
25	Oca	19MAY00	07FEB03	CIPROFLOXACIN	43	42	42	42	39
				COMPARATOR	59	58	58	58	57
				TOTAL	102	100	100	100	96
27	Lieberman	23MAY00	21FEB03	CIPROFLOXACIN	24	24	24	24	23
				COMPARATOR	1	1	1	1	1
				TOTAL	25	25	25	25	24
28	Bui	21JUN00	30OCT02	CIPROFLOXACIN	5	4	4	4	4
				COMPARATOR	9	8	8	8	5
				TOTAL	14	12	12	12	9
29	Mitchell	31JUL00	28MAY03	CIPROFLOXACIN	20	18	18	18	17
				COMPARATOR	2	2	2	2	2
				TOTAL	22	20	20	20	19

TABLE 2 (continued)
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
30	Sharma	23FEB01	07APR03	CIPROFLOXACIN	8	8	8	8	8
				COMPARATOR	2	2	2	2	2
				TOTAL	10	10	10	10	10
31	Schechtman	12AUG00	13SEP02	CIPROFLOXACIN	37	37	37	37	32
				COMPARATOR	1	1	1	1	1
				TOTAL	38	38	38	38	33
32	Melamed	21AUG00	03FEB03	CIPROFLOXACIN	33	33	33	33	30
				COMPARATOR	4	4	4	4	4
				TOTAL	37	37	37	37	34
35	Arrieta	18OCT99	03APR03	CIPROFLOXACIN	15	12	12	12	11
				COMPARATOR	0	0	0	0	0
				TOTAL	15	12	12	12	11
36	Rathore	08MAR01	25APR01	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	1	1
37	Slavin	19OCT00	18MAR02	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
38	Stavola	13SEP00	03OCT02	CIPROFLOXACIN	7	6	6	6	5
				COMPARATOR	3	3	3	3	3
				TOTAL	10	9	9	9	8
39	Stolovitzky	29SEP00	26NOV01	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3
40	McKinney, Jr.	11SEP01	24APR02	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3
42	Flynn	28AUG01	01NOV02	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	1	1	1	1	1
				TOTAL	3	3	3	3	3

TABLE 2 (continued)
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
43	Hawa	22AUG00	15JUL02	CIPROFLOXACIN	11	8	8	8	7
				COMPARATOR	0	0	0	0	0
				TOTAL	11	8	8	8	7
44	Bradburn	08AUG00	11DEC00	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
45	Wolff	08SEP00	31JUL02	CIPROFLOXACIN	4	4	4	4	4
				COMPARATOR	0	0	0	0	0
				TOTAL	4	4	4	4	4
46	Griffin	28JUL00	27MAR01	CIPROFLOXACIN	4	4	4	4	4
				COMPARATOR	0	0	0	0	0
				TOTAL	4	4	4	4	4
47	Anderson	15JUN01	08NOV02	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	15	14	14	14	13
				TOTAL	18	17	17	17	16
49	Saiman	26OCT00	17OCT02	CIPROFLOXACIN	7	7	7	7	6
				COMPARATOR	1	1	1	1	1
				TOTAL	8	8	8	8	7
50	Patel	24OCT00	12NOV02	CIPROFLOXACIN	14	14	14	14	9
				COMPARATOR	11	11	11	11	9
				TOTAL	25	25	25	25	18
51	Sindel	27SEP00	23OCT02	CIPROFLOXACIN	11	10	10	10	8
				COMPARATOR	1	1	1	1	1
				TOTAL	12	11	11	11	9
52	Casale	09JUL01	16OCT02	CIPROFLOXACIN	9	9	9	9	9
				COMPARATOR	0	0	0	0	0
				TOTAL	9	9	9	9	9
54	Pollara	02MAY02	10JAN03	CIPROFLOXACIN	4	4	4	4	4
				COMPARATOR	1	1	1	1	1
				TOTAL	5	5	5	5	5

TABLE 2 (continued)
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
56	Johnson	06APR01	26JUN01	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
57	Weisse	25OCT00	15MAY02	CIPROFLOXACIN	9	8	8	8	6
				COMPARATOR	0	0	0	0	0
				TOTAL	9	8	8	8	6
58	Chaudhary	27APR01	10MAY02	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3
59	Norris	26SEP00	15FEB01	CIPROFLOXACIN	3	3	3	3	2
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	2
61	Krieger	28JUL01	04DEC01	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
63	Molina	02NOV00	16DEC02	CIPROFLOXACIN	30	27	27	27	27
				COMPARATOR	0	0	0	0	0
				TOTAL	30	27	27	27	27
64	Phillips	19FEB01	15NOV01	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3
65	Ayoub	01MAY01	21JAN03	CIPROFLOXACIN	4	4	4	4	3
				COMPARATOR	0	0	0	0	0
				TOTAL	4	4	4	4	3
66	Plaire	10AUG01	30OCT02	CIPROFLOXACIN	6	5	5	5	5
				COMPARATOR	1	1	1	1	1
				TOTAL	7	6	6	6	6
67	Nachman	17JUL01	11FEB03	CIPROFLOXACIN	10	10	10	10	10
				COMPARATOR	0	0	0	0	0
				TOTAL	10	10	10	10	10

TABLE 2 (continued)
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
68	Iezzi	12FEB01	12FEB01	CIPROFLOXACIN	1	1	1	1	0
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	1	0
69	Rolston	27MAR02	14OCT02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	1	1	1	1	1
				TOTAL	2	2	2	2	2
70	Alter	27NOV01	10DEC02	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3
73	Abdel-Mageed	07AUG01	05APR02	CIPROFLOXACIN	6	6	6	6	4
				COMPARATOR	0	0	0	0	0
				TOTAL	6	6	6	6	4
76	Lavoie	28MAR02	02DEC02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	9	9	9	9	7
				TOTAL	10	10	10	10	8
77	Diamond	19AUG02	19AUG02	CIPROFLOXACIN	1	1	1	1	0
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	1	0
78	Abughali	27FEB02	18JUL02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	6	6	6	6	6
				TOTAL	7	7	7	7	7
79	Rajan	03APR02	20NOV02	CIPROFLOXACIN	4	4	4	4	3
				COMPARATOR	1	1	1	1	1
				TOTAL	5	5	5	5	4
80	Fennelly	11APR02	19MAR03	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	19	17	17	17	17
				TOTAL	20	18	18	18	18
81	Menendez	11APR02	09OCT02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	3	3	3	3	3
				TOTAL	4	4	4	4	4

FIGURE 1
Survival Curve for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
Ciprofloxacin Treated Patients Valid for Safety

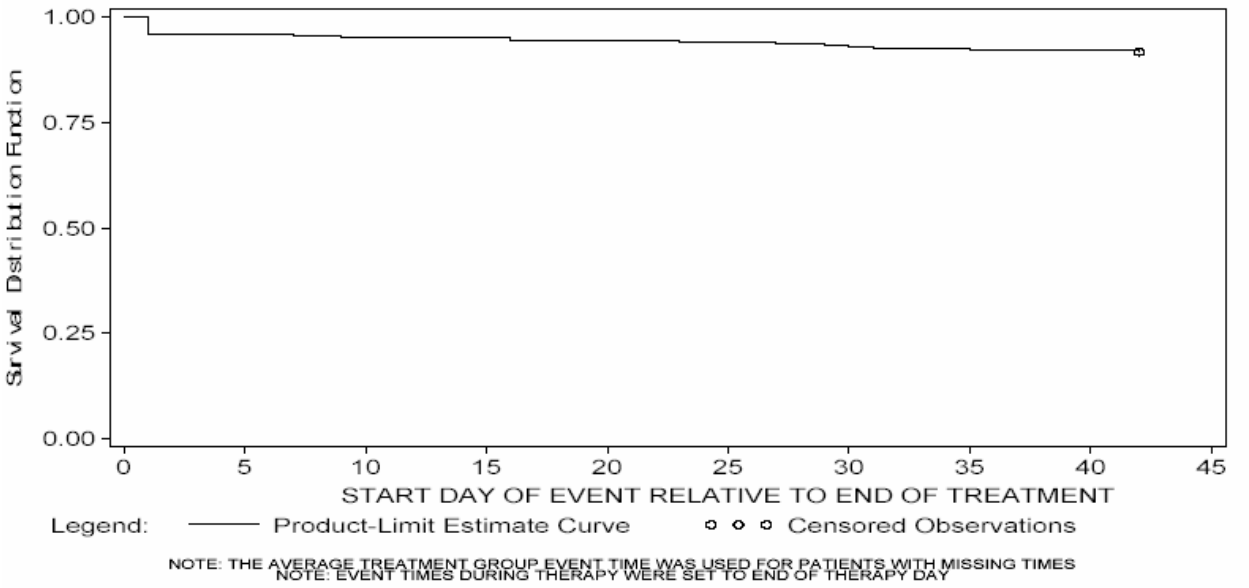


FIGURE 2
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
By Age Group
Ciprofloxacin Treated Patients Valid for Safety

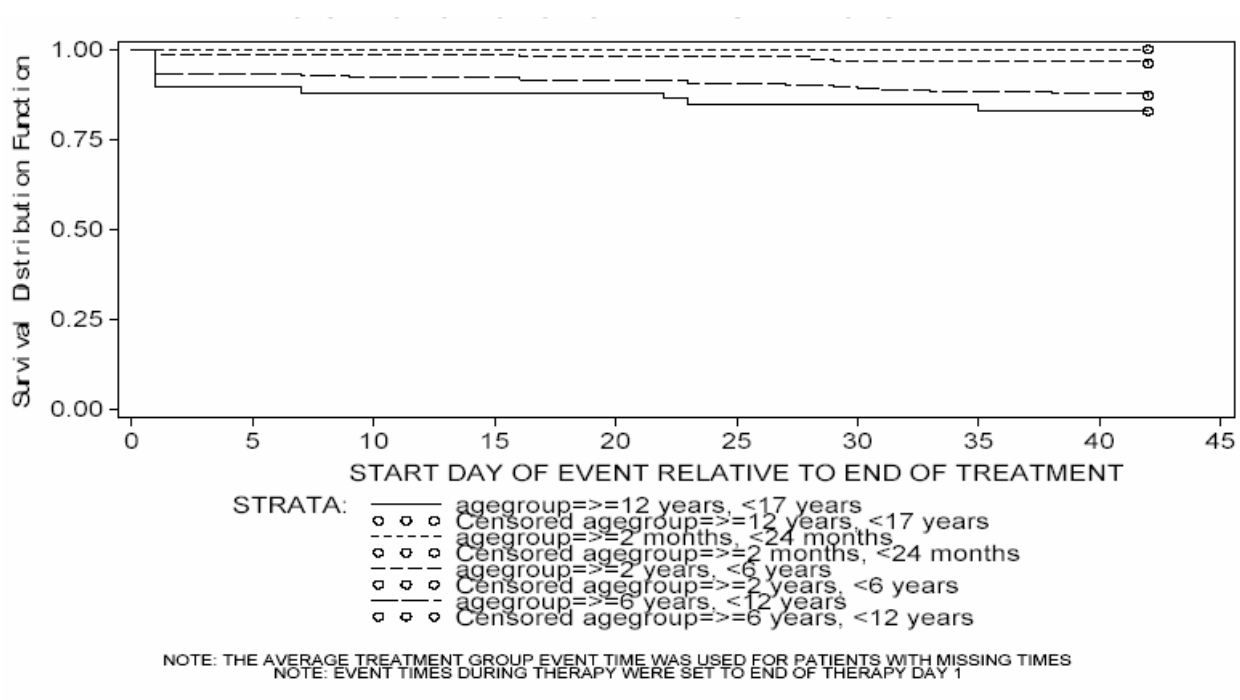
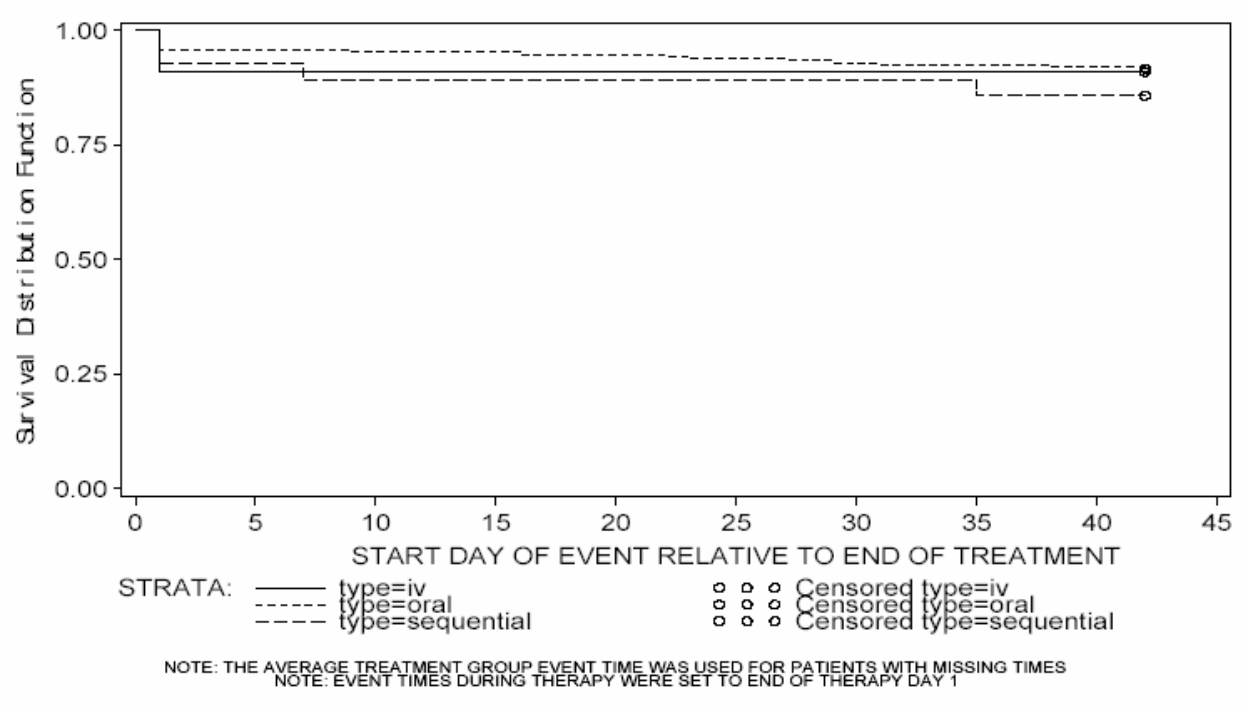


FIGURE 3
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
By Treatment Route (Oral, IV, Sequential)
Ciprofloxacin Treated Patients Valid for Safety



FIGUE 4
Survival Curve for Time to Musculoskeletal Event (Including Arthopathy) by One Year
Ciprofloxacin Treated Patients Valid for Safety

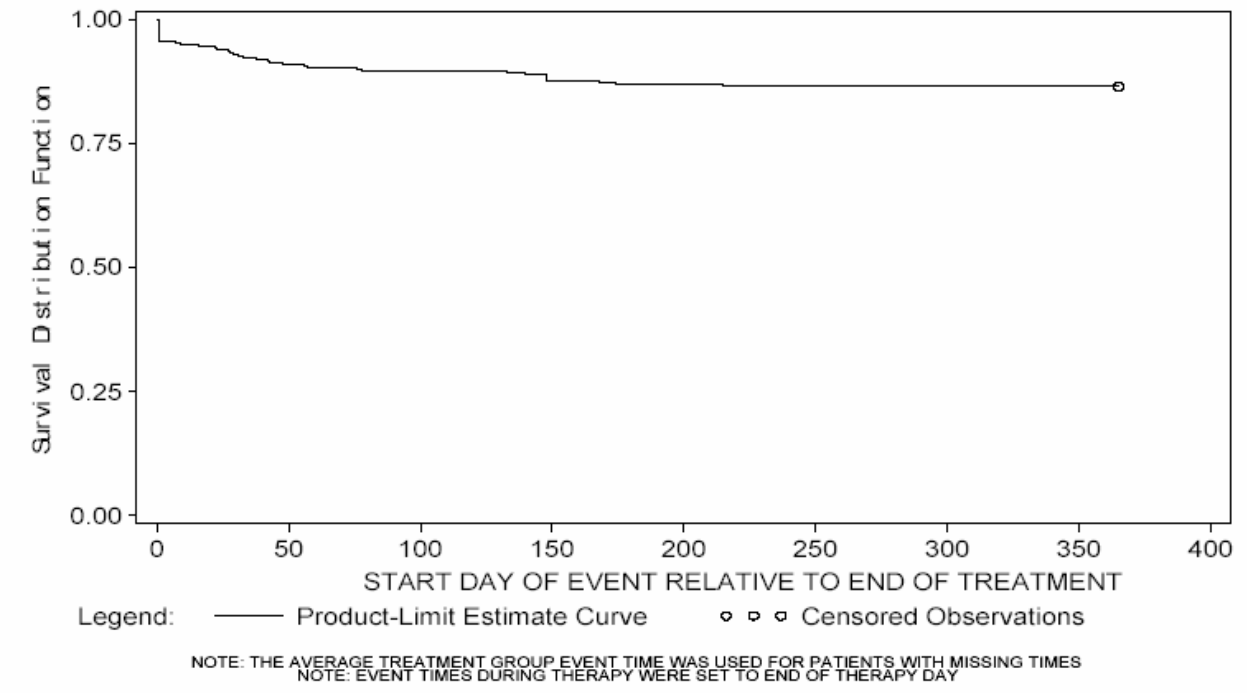
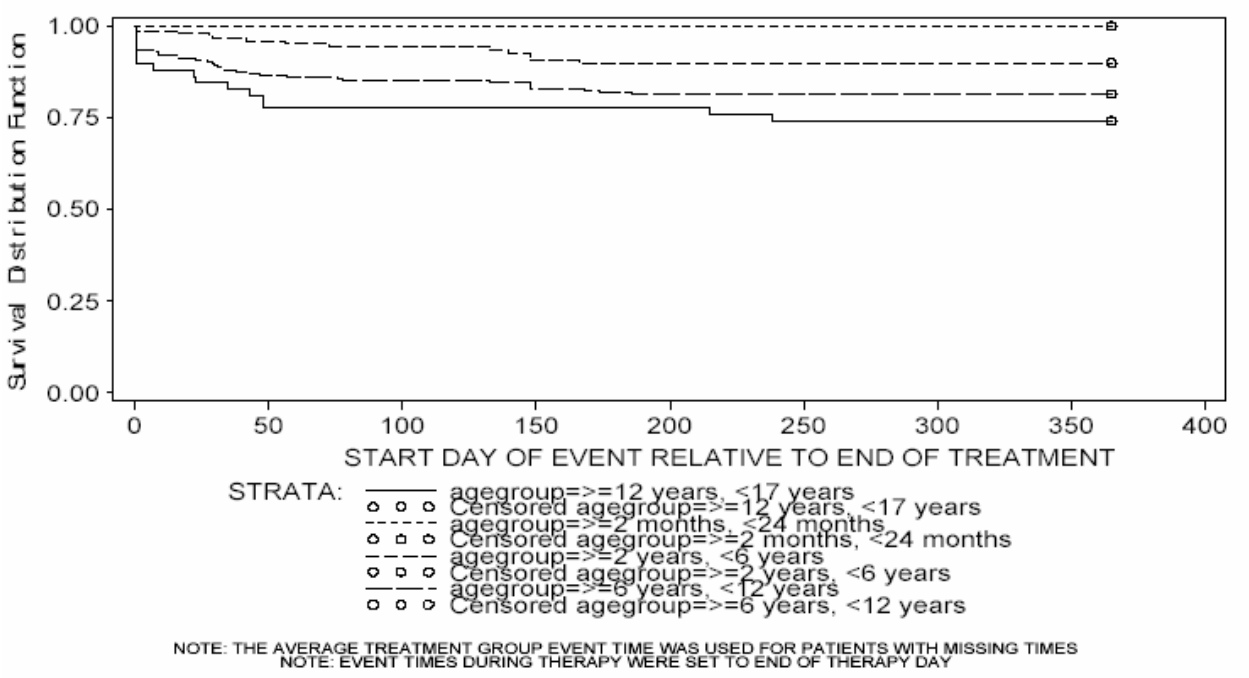


FIGURE 5
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by One Year
By Age Group
Ciprofloxacin Treated Patients Valid for Safety



FIGUE 6
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by One Year
By Treatment Route (Oral, IV, Sequential)
Ciprofloxacin Treated Patients Valid for Safety

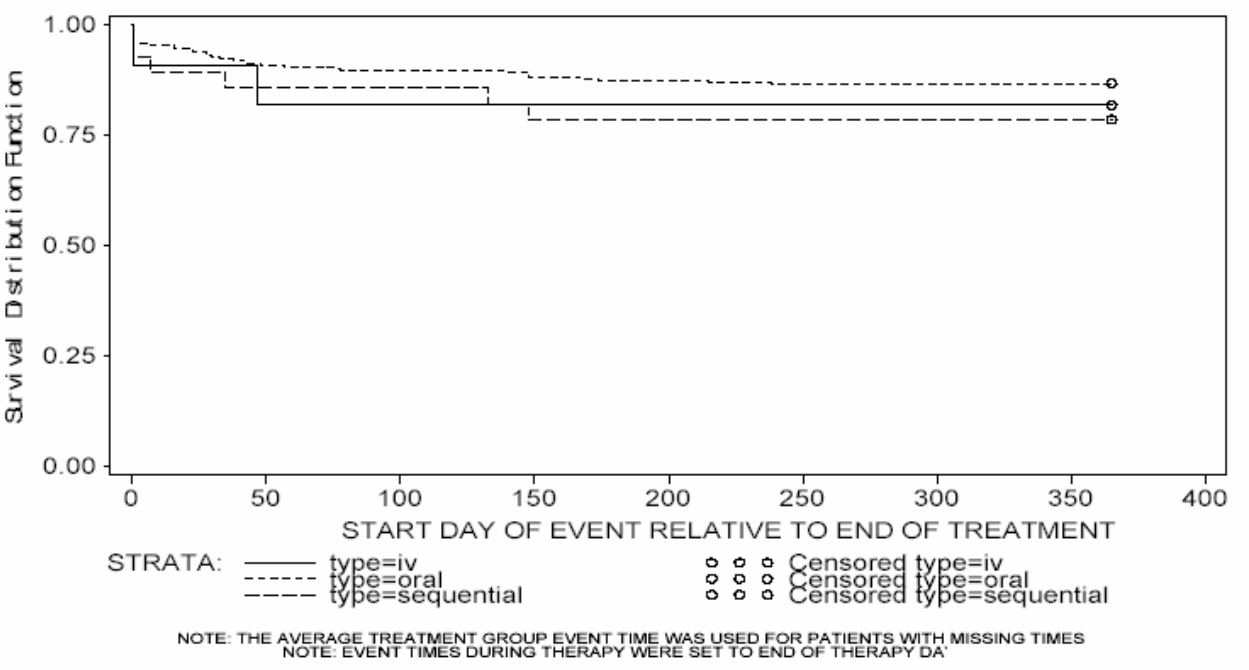


FIGURE 7
Survival Curve for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
Control Treated Patients Valid for Safety

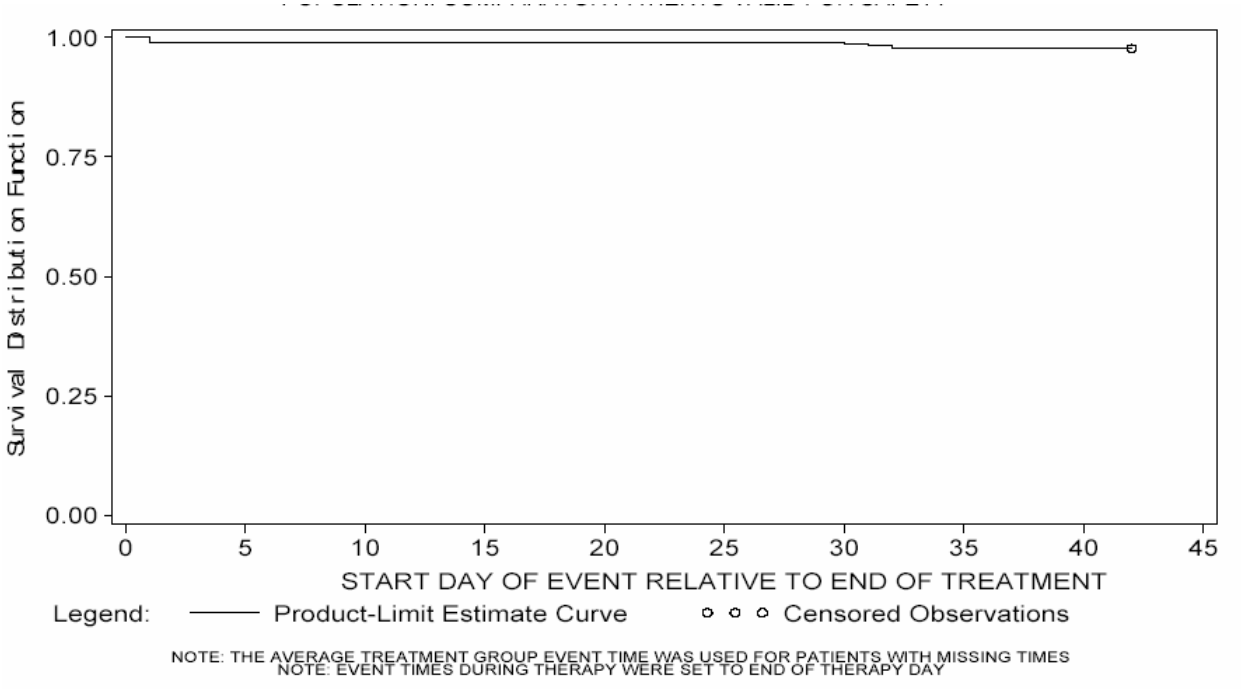


FIGURE 8
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
By Age Group
Control Treated Patients Valid for Safety

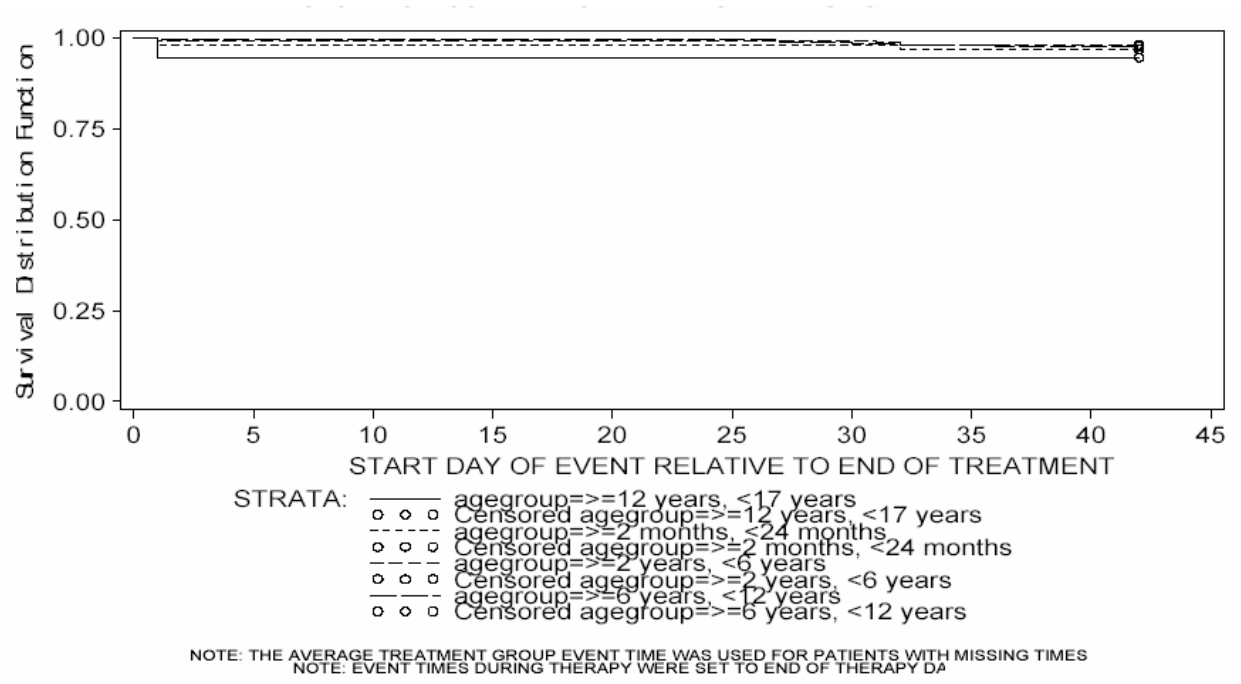


FIGURE 9
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
By Treatment Route (Oral, IV, Sequential)
Control Treated Patients Valid for Safety

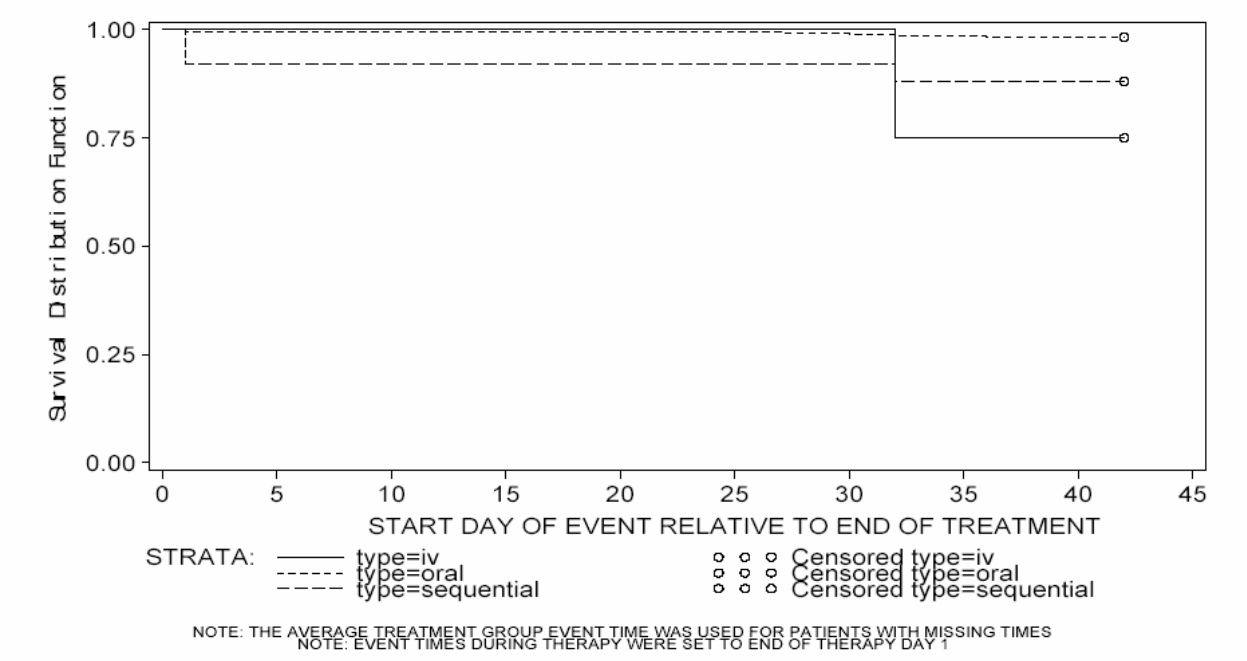


FIGURE 10
Survival Curve for Time to Musculoskeletal Event (Including Arthopathy) by One Year
Control Treated Patients Valid for Safety

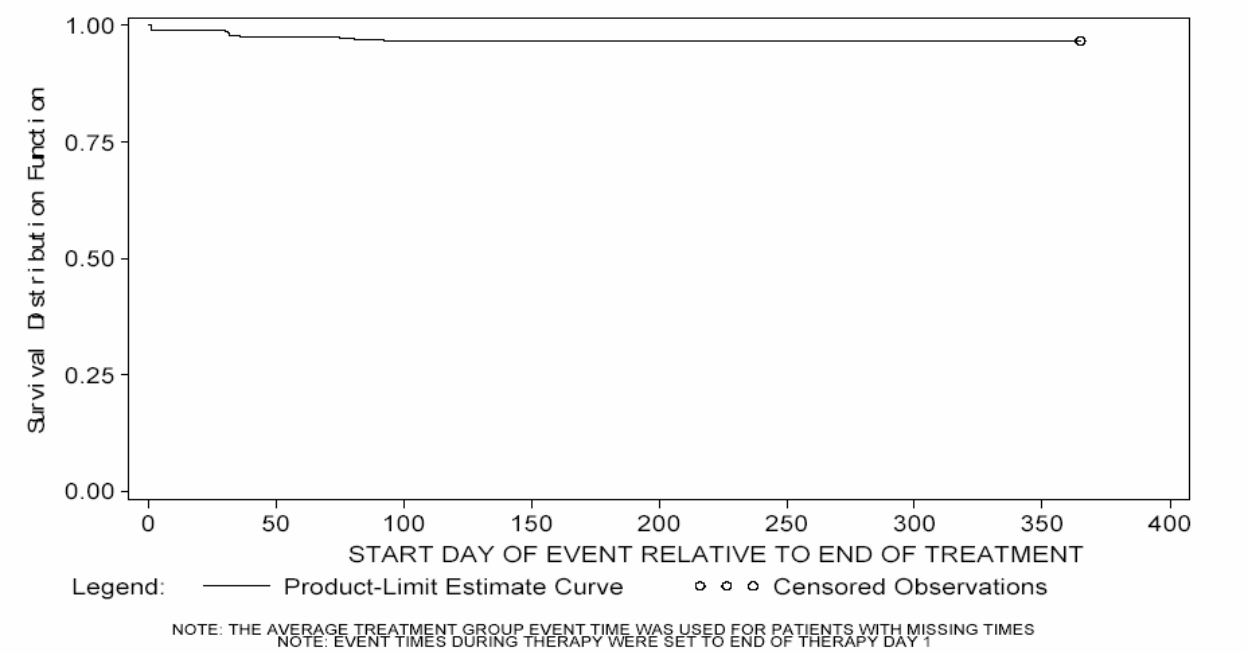


FIGURE 11
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by One Year
By Age Group
Control Treated Patients Valid for Safety

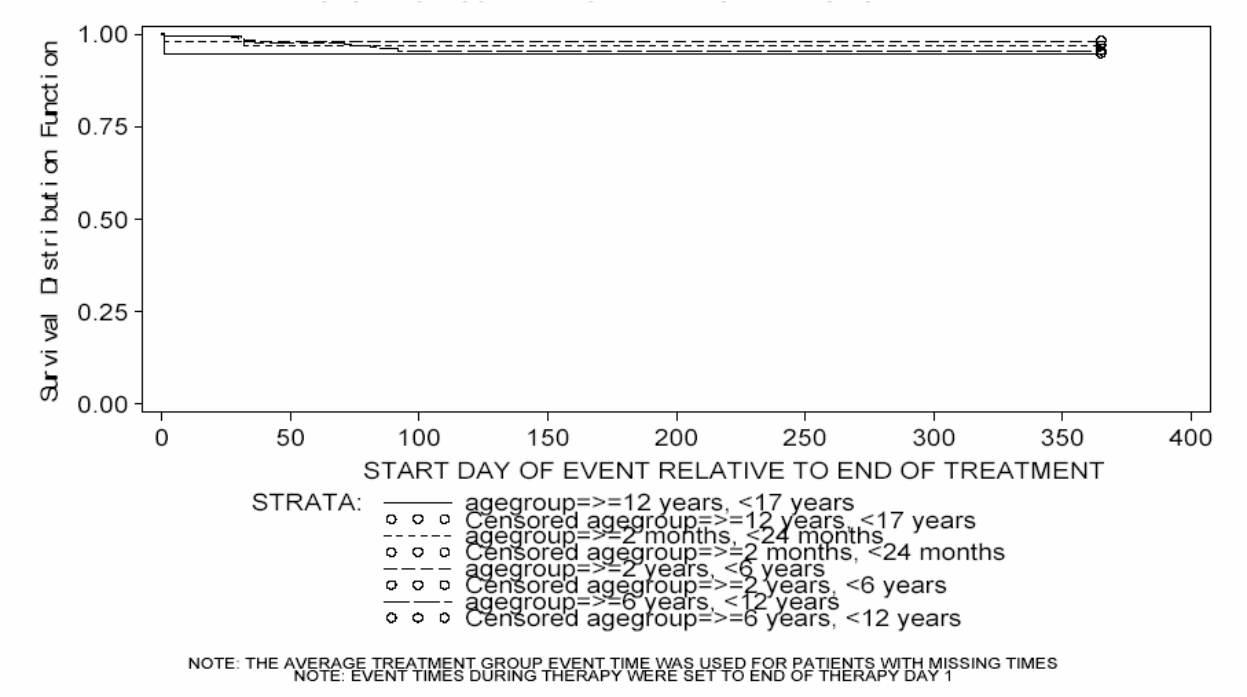


FIGURE 12
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by One Year
By Treatment Route (Oral, IV, Sequential)
Control Treated Patients Valid for Safety

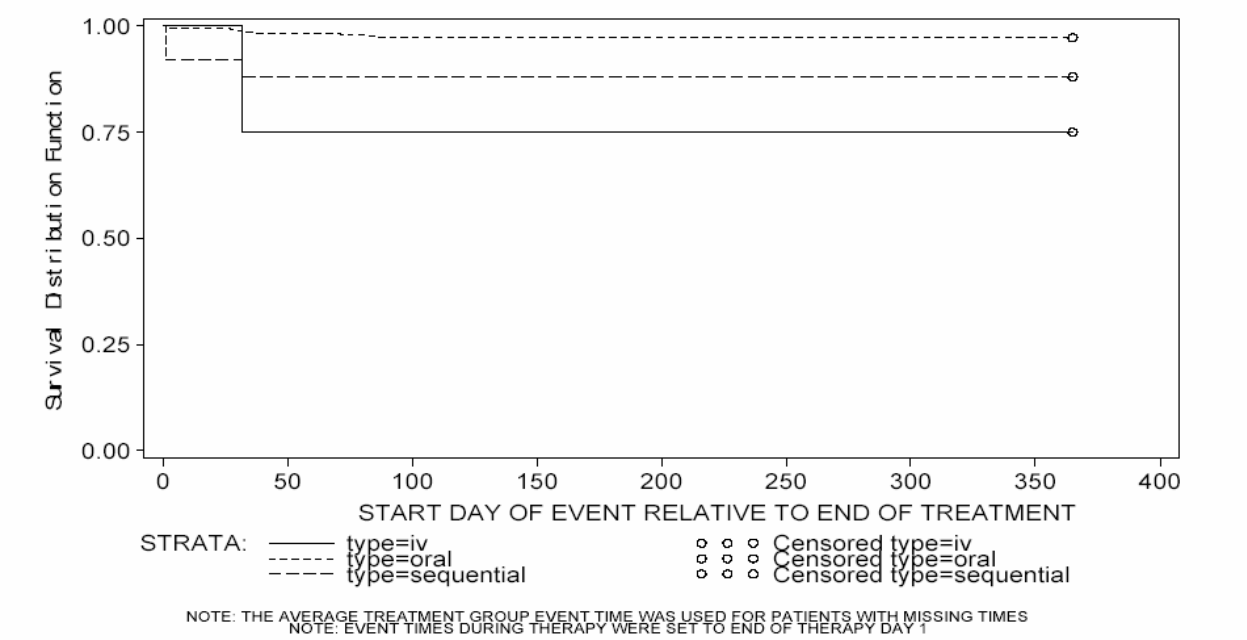


TABLE 12
Ciprofloxacin Cases of Arthropathy Occurring by Day +42
as Assessed by the IPSC
N= 35 patients (7 patients also had events occurring after Day 42)
ARTHRALGIA as the Event occurring by Day +42
Patients with any event (not just arthralgia) both pre-Day 42 and after Day 42

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
80006/F/14	YES[2]	ARTHRALGIA/ Shoulder pain	Pos	Pos	d/c study drug	MILD	-2	8	Associated with swimming; IPSC: paucity of data, in close proximity to study drug, doubt swimming is the only factor	RES
90014/F/4	NO	LEG PAIN/ L thigh pain	Pos	Pos	None	MILD	42	1	Noted on ROM exam, possibly growing pains; IPSC: resolved in one day, unusual for arthropathy, growing pains not usually in thighs	RES
		ARTHRALGIA/ L knee pain			None	MILD	42	1		RES
170001/M/2	NO	ARTHRALGIA/ L ankle tenderness	Pos	Pos	None	MILD	-8	9	Pt. had been playing with siblings and rolling around on the ground with a ball; resolved on therapy IPSC: could be trauma or "reactive arthritis" due infection (not study drug).	RES
		ARTHRALGIA/ L knee tenderness			None	MILD	-8	9		RES
		ARTHROSIS/ L knee swelling			None	MILD	-8	9		RES
210005/M/7	UNK	ARTHRALGIA/ Intermittent jaw pain	Pos	NONE	None	SEV	-12	633	X-ray was normal; IPSC: mastoiditis could have been a factor, diagnosis is TMJ	RES
		ARTHRALGIA/ ~~Unable to bend~~ second toe on R			None	MOD	158	Ongoing		UNCH

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		foot								
		ARTHRALGIA/ Intermittent bilateral knee pain (back of knees)			RDT	SEV	158	Ongoing		IMP
290023/F/3	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	Other: MRI (results unknown)	MOD	29	Ongoing		INSUF F/U
300001/M/12	UNK	ARTHROSIS/ L knee swelling	Def	Pos	None	MILD	8	2		RES
		ACCIDENTAL INJURY/ L knee sprain			None	MILD	-17	5		RES
		ARTHRALGIA/ R knee pain			RDT: x-ray and MRI (normal)	MILD	166	Ongoing	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	UNCH
		ACCIDENTAL INJURY/ R wrist sprain			RDT: x-ray and MRI (normal)	MILD	166	92		RES
		ARTHRALGIA/ L knee pain			RDT	MILD	52	3	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	RES
350011/M/13	YES[3]	PERIPHERAL EDEMA/ L ankle swelling	Pos	NONE	None	MILD	35	339		RES
		TENDON DISORDER/ R elbow tendonitis			Other: MRI (WNL)	MILD	UNK	≈ 2 years	Present at baseline, exacerbated by pitching baseball	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
350012/M/15	YES[4]	--/ bilateral ankle/foot swelling on joint exam	Pos	Pos	None	--	-6	178	IPSC: could be fluid retention from surgery	RES
350013/F/9	UNK	PERIPHERAL EDEMA/ Bilateral ankle swelling	Prob	Prob	None	MILD	-7	115		RES
350020/F/7	YES[5]	--/ L shoulder pain	Pos	NONE			-1	51	IPSC: pre-existing and may have been due to pneumonia and not arthropathy	RES
350022/F/11	YES[6]	ARTHRALGIA/ Bilateral elbow pain	Pos	Pos	None	MILD	1	UNK	Associated with viral illness	RES
		ARTHRALGIA/ Bilateral wrist pain			None	MILD	1	UNK		RES
		ARTHRALGIA/ R hip pain			None	MILD	82	UNK		INSUF F/U
350023/M/8	YES[7]	ARTHRALGIA/ Ankle pain	Pos	NONE	None	MILD	UNK	Ongoing		INSUF F/U
		ARTHRALGIA/ Knee pain			None	MILD	UNK	Ongoing		INSUF F/U
		ARTHRALGIA/ Shoulder pain			None	MILD	UNK	Ongoing		INSUF F/U
380006/F/10	NO	ARTHRALGIA/ Jaw pain	Pos	Pos	d/c study drug	MOD	-1	5	Described as feeling like "pins and needles" by pt.	RES
400049/F/11	NO	ARTHRALGIA/ Intermittent L shoulder pain	Pos	Pos	None	MILD	0	6		RES
490054/F/15	YES[8]	--/L shoulder pain/tenderness on joint exam	Pos	Pos	None	--	-10	57		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		--/ R ankle/foot pain on joint exam			None	--	-10	Ongoing		IMP
580001/F/6	UNK	--/ R shoulder tenderness on joint exam	Pos	Pos	None	--	-12	45	IPSC: baseline exam showed tenderness of R shoulder (study drug started one day earlier)	RES
610001/M/8	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	16	2		RES
		ARTHRALGIA/ Knee pain			None	MILD	122	UNK		RES
760005/F/14	YES[9]	ARTHRALGIA/ Hip pain	Pos	Pos	Hosp, RDT: IV morphine	SEV	23	UNK	IPSC: myopathy or neuropathy, could be chemo-related (vincristine)	RES
		BACK PAIN/ Back pain			Hosp, RDT: IV morphine	SEV	23	UNK		RES
870053/M/7	YES[10]	--/ R hip pain on joint exam	Pos	Pos	None	--	29	Ongoing	*OF NOTE: IPSC was inadvertently unblinded to study drug*	INSUF F/U
		--/ pain in R great toe on joint exam			None	--	29	Ongoing		INSUF F/U
920005/F/9	YES[11]	LEG PAIN/ L heel pain	Pos	Pos	RDT: ibuprofen	MOD	31	15		RES
		ARTHRALGIA/ L knee pain			None	MILD	31	2		RES
9930001/F/10	YES[12]	--/ bilateral hip pain on joint exam	Pos	NONE	None	--	-6	39	Pre-exisiting	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
220001/F/2	NO	ARTHRALGIA/ Elbow pain	Prob	Prob	d/c study drug (due to parent's schedule and not event)	MOD	-6	7		RES
250003/M/9	NO	ARTHRALGIA/ L wrist pain	Prob	NONE	RDT: ibuprofen; Other: X-ray (normal)	MILD	42	3	Accidental injury, pt. wrestling with his brother; IPSC: traumatic arthropathy vs. contusion outside joint	RES
250033/F/13	NO	ARTHRALGIA/ R wrist pain	Prob	Prob	d/c study drug	MILD	-4	UNK	No trauma or injury	IMP
		ARTHRALGIA/ L wrist pain				MILD	24	UNK	Dx by rheum: tenosynovitis vs. overuse syndrome due to gymnastics	IMP
270017/F/8	NO	ARTHRALGIA/ Bilateral knee pain	Prob	Pos	RDT: Ibuprofen and APAP	MOD	-14	66		RES
		ARTHRALGIA/ Bilateral ankle pain			RDT	MOD	-14	66		RES
		ARTHRALGIA/ Pains on ankles			RDT	MILD	301	481		RES
		ARTHRALGIA/ Knee pains			RDT	MILD	301	481	Pain at rest and increased with ambulation and most prominent when knees were straight	RES
290007/F/13	YES[13]	ARTHRALGIA/ L shoulder pain	Prob	Pos	Other: referred to rheum	MILD	22	23		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
400033/M/11	YES[15]	ARTHRALGIA/ R knee pain	Prob	Pos	None	MOD	16	22	IPSC: hard to distinguish neuro from joint findings	RES
460001/F/10	YES[16]	ARTHRALGIA/ L wrist pain	Prob	Pos	RDT: ibuprofen	MOD	-4	8	wrist fracture about 2 months prior	RES
		ARTHRALGIA/ R knee pain			RDT: ibuprofen	MOD	-4	8	History of R knee strain	RES
870056/M/5	NO	ARTHRALGIA/ Aching in knees	Prob	Pos	RDT: ibuprofen	MOD	16	16	Intermittent pain, no change in exam or ROM	RES
870060/F/8	NO	SYNOVITIS/ Synovitis of hip	Prob	Prob	None	MILD	9	11		RES
60003/F/9	NO	ARTHRALGIA/ L ankle pain	Def	NONE	RDT: APAP	MILD	38	8	Accidental injury (pt. injured ankle cheerleading and playing on the trampoline)	RES
210004/F/11	YES[17]	ARTHRALGIA/ L elbow pain	Def	NONE	None	MOD	-11	3	Pt. had L elbow and shoulder pain pre-existing; IPSC: pt. has ALL which is associated with intermittent polyarthralgia. OF	RES
		ARTHRALGIA/ L shoulder pain			None	MOD	-10	2		RES
		ARTHRALGIA/ L elbow pain			None	MILD	-5	7		RES
		ARTHRALGIA/ L elbow pain			None	MILD	6	3	*OF NOTE: IPSC inadvertently unblinded to study drug*	RES
210015/M/11	UNK	ARTHRALGIA/ Jaw pain	Def	Pos	RDT: morphine	SEV	47	5	Possible vincristine toxicity; IPSC: can not exclude study drug (although remote)	RES
		JOINT DISORDER/ Stiffness in hands and fingers			None	MILD	0	12	IPSC: Pts with ALL have a lot of intermittent polyarthralgia	RES
		JOINT DISORDER/			None	MILD	7	Ongoing	*OF NOTE: IPSC inadvertently unblinded to*	UNCH

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		Intermittent bilateral stiffness of shoulders							*study drug*	
270046/M/10	YES[18]	ACCIDENTAL INJURY/ L wrist sprain	Def	NONE	None	MILD	27	7	Accidental injury (pt. fell off bike and sprained wrist)	RES
300011/M/6	NO	ARTHRALGIA/ L elbow pain	Pos	Pos	None	MILD	0	1		RES
320002/F/11	NO	ARTHRALGIA/ Soreness in knees	Def	Pos	RDT: APAP	MILD	30	1		RES
350015/F/12	YES[19]	ARTHRALGIA/ R ankle pain	Def	NONE	None	MOD	-11	3	Pre-existing injury	RES
		ARTHRALGIA/ R ankle pain			Other: referred to rheum	MILD	27	6	OF NOTE: IPSC inadvertently unblinded to study drug	RES
		PERIPHERAL EDEMA/ R ankle swelling			Other: Referred to rheum	MILD	27	6		RES
370010/M/3	NO	ARTHRALGIA/ R knee pain	Def	NONE	Other:	MOD	28	7	Accidental injury (pt. drove into the side of a house on his battery-operated moped)	RES
		ACCIDENTAL INJURY/ R knee injury			Other:	MOD	28	43		RES
790011/M/16	UNK	ARTHROSIS/ R knee swelling	Def	Prob	RDT: rofecoxib	MOD	7	12	IPSC: ALL patients have a lot of polyarthralgia	RES
		ARTHRALGIA/ R knee pain			RDT: rofecoxib	MOD	7	12	OF NOTE: IPSC inadvertently unblended to study drug	RES
9930010/M/8	YES[20]	--/ bilateral foot/ankle swelling	Def	Pos	None	--	-10	83	IPSC: pts. With syringe-myelomeningocele may have neuropathic joints	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		ARTHRALGIA/ Hip pain				MILD	70	Ongoing		UNCH

KEY for Table 12(Study 100201)

Pos= possible; prob=probable; def = definite
Arg = Argentina; US = United States; Mex = Mexico; SA = South Africa; Ger = Germany; CR = Costa Rica; CAN = Canada;
Unk = unknown; Hosp = hospitalization; RDT = remedial drug therapy;
Mod = Moderate; Sev = servere
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

[1] redness of L ankle/foot on baseline joint exam due to puncture wound, accounting for abnormal gait
[2] history of fractured tibia and fractured L radius (on different occasions) and ongoing hip apin
[3] swelling of R elbow noted at baseline on joint exam
[4] bilateral ankle/foot swelling at baseline joint exam
[5] history of intermittent lower back pain and shin pain
[6] abnormal gait at baseline
[7] abnormal gait at baseline (pt. states he was heavily medicated post-surgery)
[8] abnormal gait at baseline
[9] ataxic gait at baseline (s/p craniospinal radiation therapy for medulloblastoma)
[10] abnormal gait at baseline
[11] pain in L hip at baseline (attributed to cellulites)
[12] bilateral hip pain at baseline
[13] no baseline gait assessment; gait exam on therapy was abnormal (genu valgus bilaterally and knee hyperextension bilaterally)
[15] history of meningomyelocele, release of tethered cord (twice), groin pain
[16] history of L wrist pain/Colles fracture of radium and ulnar
[17] history of L elbow and shoulder pain intermitently
[18] gait assessment at baseline was abnormal (patient was felling ill with nausea and dizziness)
[19] patient sprained R ankle two day before beginning study drug
[20] abnormal gait at baseline, bilateral feet in valgus; history of spina bifida, syringomyelomeningocele

TABLE 13
Comparator Cases of Arthropathy Occurring by Day +42
as Assessed by the IPSC
N= 9 patients
ARTHRALGIA as the Event occurring by Day +42

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
70085/M/11	NO	ARTHRALGIA/ R wrist pain	Pos	Pos	None	MILD	27	5	IPSC: history of wrist fracture, but should be healed	RES
70101/M/11	NO	ARTHRALGIA/ R knee pain	Pos	Pos	None	MILD	30	88		RES
70104/F/5	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MOD	31	236	Soft tissue and tibial tuberosity tenderness	RES
500026/M/1	UNK	--/ R hip pain/tenderness on joint exam	Pos	Pos	None	--	-6	42	IPSC: difficult to assess due to age, present at baseline (2 days after study drug started)	RES
500032/M/1.5	UNK	--/ R hip pain/tenderness on joint exam	Pos	Pos	None	--	-7	41	IPSC: present at baseline (1 day after study drug started), paucity of data	RES
870025/M/2	UNK	--/ bilateral knee tenderness	Pos	Pos	None	--	-9	42	IPSC: present at baseline (1 day after study drug started)	RES
870034/F/11	NO	--/ abnormal gait assessment	Pos	NONE	None	--	36	Ongoing	Accidental injury (pt. hurt hip while playing)	INSUF F/U
910007/M/6	UNK	--/ L hip tenderness on joint exam	Pos	Pos	None	--	-7	40	IPSC: present at baseline (4 days after study drug started)	RES
280018/F/14	NO	TENDON DISORDER/	Prob	Prob	RDT: analgesic	MILD	-6	5	IPSC: not warming up in sports, spondyloarthritis	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		Bilateral Achillean tendonitis								

TABLE 21
Ciprofloxacin Cases of Arthropathy as Assessed by the IPSC Occurring between Day 42 and 1 Year of Follow-Up
N=23 patients (7 patients had events occurring before Day 42)
ARTHRALGIA as the Event occurring after Day 42
Patients with any event (not just arthralgia) both pre-Day 42 and after Day 42

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
60001/M/13	NO	NECK PAIN	Pos	Pos	None	MILD	48	9	IPSC: can not exclude arthropathy, mostly likely myalgia and not joint related	RES
		BACK PAIN			None	MILD	48	9		RES
70062/M/14	YES[1]	MYALGIA/ Bilateral knee muscle pain	Pos	Pos	None	SEV	48	34	Association with exercising in the pool; IPSC: poor quality data, can not exclude arthropathy, ↓ ROM in shoulder not likely as per ortho consult	RES
		MYALGIA/ Bilateral shoulder muscle pain			None	SEV	48	34		RES
210005/M/7	UNK	ARTHRALGIA/ Intermittent jaw pain	Pos	NONE	None	SEV	-12	633	X-ray was normal; IPSC: mastoiditis could have been a factor, diagnosis is TMJ	RES
		ARTHRALGIA/ Unable to bend second toe on R foot			None	MOD	158	Ongoing		UNCH
		ARTHRALGIA/ Intermittent bilateral knee pain (back of knees)			RDT	SEV	158	Ongoing	IPSC: Too remote to be drug related	IMP
290002/F/4	NO	--/ R hip pain with abduction on joint exam	Pos	Pos	None	MOD	154	86		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
300001/M/12	UNK	ARTHROSIS/ L knee swelling	Def	Pos	None	MILD	8	2		RES
		ACCIDENTAL INJURY/ L knee sprain			None	MILD	-17	5		RES
		ARTHRALGIA/ R knee pain			RDT: x-ray and MRI (normal)	MILD	166	Ongoing	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	UNCH
		ACCIDENTAL INJURY/ R wrist sprain			RDT: x-ray and MRI (normal)	MILD	166	92		RES
		ARTHRALGIA/ L knee pain			RDT	MILD	52	3	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	RES
310011/F/4	NO	ARTHRALGIA/ Bilateral knee pain	Pos	NONE	None	MILD	73	89		RES
		LEG PAIN/ L upper leg pain			RDT	MILD	367	17		RES
		ARTHRALGIA/ Hip pain			None	MILD	377	7		RES
		BACK PAIN/ Back pain			RDT	MILD	378	1		RES
310016/F/4	UNK	ARTHRALGIA/ R ankle pain	Pos	Pos	RDT: ibuprofen and APAP	MILD	179	Ongoing	No pattern or consistency to pains	INSUF F/U
		ARTHRALGIA/			RDT:	MOD	179	ongoing		INSUF

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		R knee pain			ibuprofen and APAP					F/U
320004/ F/3	NO	ARTHRALGIA/ Joint pain in knees	Pos	NONE	None	MILD	166	16		RES
320032/F/11	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	57	Ongoing		INSUF F/U
350022/F/11	YES[6]	ARTHRALGIA/ Bilateral elbow pain	Pos	Pos	None	MILD	1	UNK	Associated with viral illness	RES
		ARTHRALGIA/ Bilateral wrist pain			None	MILD	1	UNK		RES
		ARTHRALGIA/ R hip pain			None	MILD	82	UNK		INSUF F/U
610001/M/8	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	16	2		RES
		ARTHRALGIA/ Knee pain			None	MILD	122	UNK		RES
630005/F/10	NO	ARTHRALGIA/ Pain in fingers and back	Pos	NONE	None	MILD	186	34		RES
640008/F/5	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	None	MOD	56	16		RES
830089/F/10	NO	--/ bilateral knee pain	Pos	Pos	RDT: APAP	--	78	Ongoing	IPSC: paucity of data	INSUF F/U
270017/F/8	NO	ARTHRALGIA/ Bilateral knee pain	Prob	Pos	RDT: Ibuprofen and APAP	MOD	-14	66		RES
		ARTHRALGIA/ Bilateral ankle pain			RDT	MOD	-14	66		RES
		ARTHRALGIA/ Pains on ankles			RDT	MILD	301	481		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		ARTHRALGIA/ Knee pains			RDT	MILD	301	481	Pain at rest and increased with ambulation and most prominent when knees were straight	RES
270024/M/5	NO	ARTHRALGIA/ Knee pain	Prob	NONE	None	MILD	140	68	Dx by rheum: possible trauma; IPSC: not comfortable with trauma dx, too remote to be drug related *OF NOTE: IPSC was inadvertently unblinded to study drug*	RES
320029/ M/11	NO	ARTHRALGIA/ Joint pain in knees	Prob	Pos	None	MILD	76	Ongoing		UNCH
		ARTHRALGIA/ Joint pain			None	MILD	320	62		RES
		ARTHRALGIA/ Bilateral joint pain in knees			None	MILD	79	Ongoing		UNCH
350014/M/6	YES[14]	--/ bilateral knee swelling	Prob	Pos	None	--	168	ongoing	IPSC: chemo agents may have contributed *OF NOTE: IPSC was inadvertently unblinded to study drug*	INSUF F/U
210015/M/11	UNK	ARTHRALGIA/ Jaw pain	Def	Pos	RDT: morphine	SEV	47	5	Possible vincristine toxicity; IPSC: can not exclude study drug (although remote)	RES
		JOINT DISORDER/ Stiffness in hands			None	MILD	0	12	IPSC: pts with ALL have a lot of intermittent	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		and fingers							polyarthralgia	
		JOINT DISORDER/ Intermittent bilateral stiffness of shoulders			None	MILD	7	Ongoing	*OF NOTE: IPSC inadvertently unblended to study drug*	UNCH
320001/M/13	NO	BONE DISORDER/ Chondromalacia	Def	NONE	None	MOD	215	Ongoing		INSUF F/U
		BONE DISORDER/ Osgood Schlatter			None	MILD	215	ongoing		INSUF F/U
350021/F/11	UNK	ACCIDENTAL INJURY/ R knee injury	Def	Pos	None	MILD	43	62	IPSC: possible relationship to trauma (dancing and soccer)	RES
420010/F/14	UNK	BONE NECROSIS/ Avascular necrosis of the knees	Def	Pos	Other	MOD	238	Ongoing	IPSC: probably due to steroid use	UNCH
9930010/M/8	YES[20]	--/ bilateral foot/ankle swelling	Def	Pos	None	--	-10	83	IPSC: pts. With syringe-myelomeningocele may have neuropathic joints	RES
		ARTHRALGIA/ Hip pain				MILD	70	Ongoing		UNCH

KEY for Table 21 (Study 100201)

Pos= possible; prob=probable; def = definite
Arg = Argentina; US = United States; Mex = Mexico; SA = South Africa; Ger = Germany; CR = Costa Rica; CAN = Canada;
Unk = unknown; Hosp = hospitalization; RDT = remedial drug therapy;
Mod = Moderate; Sev = servere
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

[1] redness of L ankle/foot on baseline joint exam due to puncture wound, accounting for abnormal gait
[6] abnormal gait at baseline
[14] sponsor noted baseline condition, not apparent to reviewer
[20] abnormal gait at baseline, bilateral feet in valgus; history of spina bifida, syringomyelomeningocele

TABLE 22
Comparator Cases of Arthropathy Occuring between Day 42 and 1 Year of Follow-Up as Assessed by the IPSC
N=4 patients
ARTHRALGIA as the Event occurring after Day 42

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
70152/M/7	NO	ACCIDENTAL INJURY/ Sprained hip	Pos	None	RDT: ibuprofen, naproxen Other: x-ray (normal)	MOD	92	7	Accidental injury (pt. playing football)	RES
320036/F/8	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	RDT: APAP	MOD	75	Ongoing		INSUF F/U
70130/M/10	NO	ACCIDENTAL INJURY/ R ankle sprained	Def	NONE	RDT: ibuprofen	MOD	71	9		RES
		ACCIDENTAL INJURY/ L ankle sprained			RDT: Tylenol #3 Other: x-ray: lateral soft tissue swelling, crutches, air cast	MOD	136	Ongoing		UNCH
830028/F/9	NO	ARTHRALGIA/ R knee pain	Def	NONE	RDT: APAP, ibuprofen Other: ACE bandage, x-ray (normal)	SEV	85	27	Pt. doesn't stretch before running, symptoms also include ↓ ROM, erythema, joint stiffness, myalgia, swelling and warm joint; IPSC:may be due to	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
									sports activity	

TABLE 25
Ciprofloxacin Patients with Arthropathy by One Year
As Assessed by the IPSC
N= 56

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
60001/M/13	NO	NECK PAIN	Pos	Pos	None	MILD	48	9	IPSC: can not exclude arthropathy, mostly likely myalgia and not joint related	RES
		BACK PAIN			None	MILD	48	9		RES
70062/M/14	YES[1]	MYALGIA/ Bilateral knee muscle pain	Pos	Pos	None	SEV	48	34	Association with exercising in the pool; IPSC: poor quality data, can not exclude arthropathy, ↓ ROM in shoulder not likely as per ortho consult	RES
		MYALGIA/ Bilateral shoulder muscle pain			None	SEV	48	34		RES
80006/F/14	YES[2]	ARTHRALGIA/ Shoulder pain	Pos	Pos	d/c study drug	MILD	-2	8	Associated with swimming; IPSC: paucity of data, in close proximity to study drug, doubt swimming is the only factor	RES
90014/F/4	NO	LEG PAIN/ L thigh pain	Pos	Pos	None	MILD	42	1	Noted on ROM exam, possibly growing pains; IPSC: resolved in one day, unusual for arthropathy, growing pains not usually in thighs	RES
		ARTHRALGIA/ L knee pain			None	MILD	42	1		
170001/M/2	NO	ARTHRALGIA/ L ankle tenderness	Pos	Pos	None	MILD	-8	9	Pt. had been playing with siblings and rolling around on the ground with a ball; resolved on therapy IPSC: could be trauma or “reactive arthritis” due	RES
		ARTHRALGIA/ L knee tenderness			None	MILD	-8	9		RES
		ARTHROSIS/ L knee swelling			None	MILD	-8	9		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
									infection (not study drug).	
210005/M/7	UNK	ARTHRALGIA/ Intermittent jaw pain	Pos	NONE	None	SEV	-12	633	X-ray was normal; IPSC: mastoiditis could have been a factor, diagnosis is TMJ	RES
		ARTHRALGIA/ Unable to bend second toe on R foot			None	MOD	158	Ongoing		UNCH
		ARTHRALGIA/ Intermittent bilateral knee pain (back of knees)			RDT	SEV	158	Ongoing		IMP
290002/F/4	NO	--/ R hip pain with abduction on joint exam	Pos	Pos	None	MOD	154	86		RES
290023/F/3	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	Other: MRI (results unknown)	MOD	29	Ongoing		INSUF F/U
300001/M/12	UNK	ARTHROSIS/ L knee swelling	Def	Pos	None	MILD	8	2		RES
		ACCIDENTAL INJURY/ L knee sprain			None	MILD	-17	5		RES
		ARTHRALGIA/ R knee pain			RDT: x-ray and MRI (normal)	MILD	166	Ongoing	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	UNCH

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		ACCIDENTAL INJURY/ R wrist sprain			RDT: x-ray and MRI (normal)	MILD	166	92		RES
		ARTHRALGIA/ L knee pain			RDT	MILD	52	3	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	RES
310011/F/4	NO	ARTHRALGIA/ Bilateral knee pain	Pos	NONE	None	MILD	73	89		RES
		LEG PAIN/ L upper leg pain			RDT	MILD	367	17		RES
		ARTHRALGIA/ Hip pain			None	MILD	377	7		RES
		BACK PAIN/ Back pain			RDT	MILD	378	1		RES
310016/F/4	UNK	ARTHRALGIA/ R ankle pain	Pos	Pos	RDT: ibuprofen and APAP	MILD	179	Ongoing	No pattern or consistency to pains	INSUF F/U
		ARTHRALGIA/ R knee pain			RDT: ibuprofen and APAP	MOD	179	ongoing		INSUF F/U
320004/ F/3	NO	ARTHRALGIA/ Joint pain in knees	Pos	NONE	None	MILD	166	16		RES
320032/F/11	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	57	Ongoing		INSUF F/U
350011/M/13	YES[3]	PERIPHERAL EDEMA/	Pos	NONE	None	MILD	35	339		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		L ankle swelling								
		TENDON DISORDER/ R elbow tendonitis			Other: MRI (WNL)	MILD	UNK	≈ 2 years	Present at baseline, exacerbated by pitching baseball	RES
350012/M/15	YES[4]	--/ bilateral ankle/foot swelling on joint exam	Pos	Pos	None	--	-6	178	IPSC: could be fluid retention from surgery	RES
350013/F/9	UNK	PERIPHERAL EDEMA/ Bilateral ankle swelling	Prob	Prob	None	MILD	-7	115		RES
350020/F/7	YES[5]	--/ L shoulder pain	Pos	NONE			-1	51	IPSC: pre-existing and may have been due to pneumonia and not arthropathy	RES
350022/F/11	YES[6]	ARTHRALGIA/ Bilateral elbow pain	Pos	Pos	None	MILD	1	UNK	Associated with viral illness	RES
		ARTHRALGIA/ Bilateral wrist pain			None	MILD	1	UNK		RES
		ARTHRALGIA/ R hip pain			None	MILD	82	UNK		INSUF F/U
350023/M/8	YES[7]	ARTHRALGIA/ Ankle pain	Pos	NONE	None	MILD	UNK	Ongoing		INSUF F/U
		ARTHRALGIA/ Knee pain			None	MILD	UNK	Ongoing		INSUF F/U
		ARTHRALGIA/ Shoulder pain			None	MILD	UNK	Ongoing		INSUF F/U
380006/F/10	NO	ARTHRALGIA/ Jaw pain	Pos	Pos	d/c study drug	MOD	-1	5	Described as feeling like “pins and needles” by pt.	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
400049/F/11	NO	ARTHRALGIA/ Intermittent L shoulder pain	Pos	Pos	None	MILD	0	6		RES
490054/F/15	YES[8]	--/L shoulder pain/tenderness on joint exam	Pos	Pos	None	--	-10	57		RES
		--/ R ankle/foot pain on joint exam			None	--	-10	Ongoing		IMP
580001/F/6	UNK	--/ R shoulder tenderness on joint exam	Pos	Pos	None	--	-12	45	IPSC: baseline exam showed tenderness of R shoulder (study drug started one day earlier)	RES
610001/M/8	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	16	2		RES
		ARTHRALGIA/ Knee pain			None	MILD	122	UNK		RES
630005/F/10	NO	ARTHRALGIA/ Pain in fingers and back	Pos	NONE	None	MILD	186	34		RES
640008/F/5	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	None	MOD	56	16		RES
760005/F/14	YES[9]	ARTHRALGIA/ Hip pain	Pos	Pos	Hosp, RDT: IV morphine	SEV	23	UNK	IPSC: myopathy or neuropathy, could be chemo-related (vincristine)	RES
		BACK PAIN/ Back pain			Hosp, RDT: IV morphine	SEV	23	UNK		RES
830089/F/10	NO	--/	Pos	Pos	RDT:	--	78	Ongoing	IPSC: paucity of data	INSUF

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		bilateral knee pain			APAP					F/U
870053/M/7	YES[10]	--/ R hip pain on joint exam	Pos	Pos	None	--	29	Ongoing	*OF NOTE: IPSC was inadvertently unblinded to study drug*	INSUF F/U
		--/ pain in R great toe on joint exam			None	--	29	Ongoing		INSUF F/U
920005/F/9	YES[11]	LEG PAIN/ L heel pain	Pos	Pos	RDT: ibuprofen	MOD	31	15		RES
		ARTHRALGIA/ L knee pain			None	MILD	31	2		RES
9930001/F/10	YES[12]	--/ bilateral hip pain on joint exam	Pos	NONE	None	--	-6	39	Pre-existing	RES
220001/F/2	NO	ARTHRALGIA/ Elbow pain	Prob	Prob	d/c study drug (due to parent's schedule and not event)	MOD	-6	7		RES
250003/M/9	NO	ARTHRALGIA/ L wrist pain	Prob	NONE	RDT: ibuprofen; Other: X-ray (normal)	MILD	42	3	Accidental injury, pt. wrestling with his brother; IPSC: traumatic arthropathy vs. contusion outside joint	RES
250033/F/13	NO	ARTHRALGIA/ R wrist pain	Prob	Prob	d/c study drug	MILD	-4	UNK	No trauma or injury	IMP
		ARTHRALGIA/ L wrist pain					24	UNK	Dx by rheum: tenosynovitis vs. overuse syndrome due to gymnastics	IMP

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
270017/F/8	NO	ARTHRALGIA/ Bilateral knee pain	Prob	Pos	RDT: Ibuprofen and APAP	MOD	-14	66		RES
		ARTHRALGIA/ Bilateral ankle pain			RDT	MOD	-14	66		RES
		ARTHRALGIA/ Pains on ankles			RDT	MILD	301	481		RES
		ARTHRALGIA/ Knee pains			RDT	MILD	301	481	Pain at rest and increased with ambulation and most prominent when knees were straight	RES
270024/M/5	NO	ARTHRALGIA/ Knee pain	Prob	NONE	None	MILD	140	68	Dx by rheum: possible trauma; IPSC: not comfortable with trauma dx, too remote to be drug related *OF NOTE: IPSC was inadvertently unblinded to study drug*	RES
290007/F/13	YES[13]	ARTHRALGIA/ L shoulder pain	Prob	Pos	Other: referred to rheum	MILD	22	23		RES
320029/ M/11	NO	ARTHRALGIA/ Joint pain in knees	Prob	Pos	None	MILD	76	Ongoing		UNCH
		ARTHRALGIA/ Joint pain			None	MILD	320	62		RES
		ARTHRALGIA/ Bilateral joint pain in knees			None	MILD	79	Ongoing		UNCH

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
350014/M/6	YES[14]	--/ bilateral knee swelling	Prob	Pos	None	--	168	ongoing	IPSC: chemo agents may have contributed *OF NOTE: IPSC was inadvertently unblinded to study drug*	INSUF F/U
400033/M/11	YES[15]	ARTHRALGIA/ R knee pain	Prob	Pos	None	MOD	16	22	IPSC: hard to distinguish neuro from joint findings	RES
460001/F/10	YES[16]	ARTHRALGIA/ L wrist pain	Prob	Pos	RDT: ibuprofen	MOD	-4	8	wrist fracture about 2 months prior	RES
		ARTHRALGIA/ R knee pain			RDT: ibuprofen	MOD	-4	8	History of R knee strain	RES
870056/M/5	NO	ARTHRALGIA/ Aching in knees	Prob	Pos	RDT: ibuprofen	MOD	16	16	Intermittent pain, no change in exam or ROM	RES
870060/F/8	NO	SYNOVITIS/ Synovitis of hip	Prob	Prob	None	MILD	9	11		RES
60003/F/9	NO	ARTHRALGIA/ L ankle pain	Def	NONE	RDT: APAP	MILD	38	8	Accidental injury (pt. injured ankle cheerleading and playing on the trampoline)	RES
210004/F/11	YES[17]	ARTHRALGIA/ L elbow pain	Def	NONE	None	MOD	-11	3	Pt. had L elbow and shoulder pain pre-existing; IPSC: pt. has ALL which is associated with intermittent polyarthralgia. OF *OF NOTE: IPSC inadvertently unblinded to study drug*	RES
		ARTHRALGIA/ L shoulder pain			None	MOD	-10	2		RES
		ARTHRALGIA/ L elbow pain			None	MILD	-5	7		RES
		ARTHRALGIA/ L elbow pain			None	MILD	6	3		RES
210015/M/11	UNK	ARTHRALGIA/ Jaw pain	Def	Pos	RDT: morphine	SEV	47	5	Possible vincristine toxicity; IPSC: can not exclude study	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
									drug (although remote)	
		JOINT DISORDER/ Stiffness in hands and fingers			None	MILD	0	12	IPSC: pts with ALL have a lot of intermittent polyarthralgia	RES
		JOINT DISORDER/ Intermittent bilateral stiffness of shoulders			None	MILD	7	Ongoing	*OF NOTE: IPSC inadvertently unblinded to study drug*	UNCH
270046/M/10	YES[18]	ACCIDENTAL INJURY/ L wrist sprain	Def	NONE	None	MILD	27	7	Accidental injury (pt. fell off bike and sprained wrist)	RES
300011/M/6	NO	ARTHRALGIA/ L elbow pain	Pos	Pos	None	MILD	0	1		RES
320001/M/13	NO	BONE DISORDER/ Chondromalacia	Def	NONE	None	MOD	215	Ongoing		INSUF F/U
		BONE DISORDER/ Osgood Schlatter			None	MILD	215	ongoing		INSUF F/U
320002/F/11	NO	ARTHRALGIA/ Soreness in knees	Def	Pos	RDT: APAP	MILD	30	1		RES
350015/F/12	YES[19]	ARTHRALGIA/ R ankle pain	Def	NONE	None	MOD	-11	3	Pre-existing injury	RES
		ARTHRALGIA/ R ankle pain			Other: referred to rheum	MILD	27	6	*OF NOTE: IPSC inadvertently unblinded to study drug*	RES
		PERIPHERAL EDEMA/ R ankle swelling			Other: Referred to rheum	MILD	27	6		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
350021/F/11	UNK	ACCIDENTAL INJURY/ R knee injury	Def	Pos	None	MILD	43	62	IPSC: possible relationship to trauma (dancing and soccer)	RES
370010/M/3	NO	ARTHRALGIA/ R knee pain	Def	NONE	Other:	MOD	28	7	Accidental injury (pt. drove into the side of a house on his battery-operated moped)	RES
		ACCIDENTAL INJURY/ R knee injury			Other:	MOD	28	43		RES
420010/F/14	UNK	BONE NECROSIS/ Avascular necrosis of the knees	Def	Pos	Other	MOD	238	Ongoing	IPSC: probably due to steroid use	UNCH
790011/M/16	UNK	ARTHROSIS/ R knee swelling	Def	Prob	RDT: rofecoxib	MOD	7	12	IPSC: ALL patients have a lot of polyarthralgia	RES
		ARTHRALGIA/ R knee pain			RDT: rofecoxib	MOD	7	12	*OF NOTE: IPSC inadvertently unblinded to study drug*	RES
9930010/M/8	YES[20]	--/ bilateral foot/ankle swelling	Def	Pos	None	--	-10	83	IPSC: pts. With syringe-myelomeningocele may have neuropathic joints	RES
		ARTHRALGIA/ Hip pain				MILD	70	Ongoing		UNCH

KEY for Table 25 (Study 100201)

Pos= possible; prob=probable; def = definite
Arg = Argentina; US = United States; Mex = Mexico; SA = South Africa; Ger = Germany; CR = Costa Rica; CAN = Canada;
Unk = unknown; Hosp = hospitalization; RDT = remedial drug therapy;
Mod = Moderate; Sev = servere
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

[1] redness of L ankle/foot on baseline joint exam due to puncture wound, accounting for abnormal gait
[2] history of fractured tibia and fractured L radius (on different occasions) and ongoing hip apin
[3] swelling of R elbow noted at baseline on joint exam
[4] bilateral ankle/foot swelling at baseline joint exam
[5] history of intermittent lower back pain and shin pain
[6] abnormal gait at baseline
[7] abnormal gait at baseline (pt. states he was heavily medicated post-surgery)
[8] abnormal gait at baseline
[9] ataxic gait at baseline (s/p craniospinal radiation therapy for medulloblastoma)
[10] abnormal gait at baseline
[11] pain in L hip at baseline (attributed to cellulites)
[12] bilateral hip pain at baseline
[13] no baseline gait assessment; gait exam on therapy was abnormal (genu valgus bilaterally and knee hyperextension bilaterally)
[14] sponsor noted baseline condition, not apparent to reviewer
[15] history of meningomyelocele, release of tethered cord (twice), groin pain
[16] history of L wrist pain/Colles fracture of radium and ulnar
[17] history of L elbow and shoulder pain intermitently
[18] gait assessment at baseline was abnormal (patient was felling ill with nausea and dizziness)
[19] patient sprained R ankle two day before beginning study drug
[20] abnormal gait at baseline, bilateral feet in valgus; history of spina bifida, syringomyelomeningocele

TABLE 26
Comparator Patients with Arthropathy by One Year
As Assessed by the IPSC
N= 13

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
70085/M/11	NO	ARTHRALGIA/ R wrist pain	Pos	Pos	None	MILD	27	5	IPSC: history of wrist fracture, but should be healed	RES
70101/M/11	NO	ARTHRALGIA/ R knee pain	Pos	Pos	None	MILD	30	88		RES
70104/F/5	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MOD	31	236	Soft tissue and tibial tuberosity tenderness	RES
70152/M/7	NO	ACCIDENTAL INJURY/ Sprained hip	Pos	None	RDT: ibuprofen, naproxen Other: x-ray (normal)	MOD	92	7	Accidental injury (pt. playing football)	RES
320036/F/8	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	RDT: APAP	MOD	75	Ongoing		INSUF F/U
500026/M/1	UNK	--/ R hip pain/tenderness on joint exam	Pos	Pos	None	--	-6	42	IPSC: difficult to assess due to age, present at baseline (2 days after study drug started)	RES
500032/M/1.5	UNK	--/ R hip pain/tenderness on joint exam	Pos	Pos	None	--	-7	41	IPSC: present at baseline (1 day after study drug started), paucity of data	RES
870025/M/2	UNK	--/ bilateral knee tenderness	Pos	Pos	None	--	-9	42	IPSC: present at baseline (1 day after study drug started)	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
870034/F/11	NO	--/ abnormal gait assessment	Pos	NONE	None	--	36	Ongoing	Accidental injury (pt. hurt hip while playing)	INSUF F/U
910007/M/6	UNK	--/ L hip tenderness on joint exam	Pos	Pos	None	--	-7	40	IPSC: present at baseline (4 days after study drug started)	RES
280018/F/14	NO	TENDON DISORDER/ Bilateral Achillean tendonitis	Prob	Prob	RDT: analgesic	MILD	-6	5	IPSC: not warming up in sports, spondyloarthritis	RES
70130/M/10	NO	ACCIDENTAL INJURY/ R ankle sprained	Def	NONE	RDT: ibuprofen	MOD	71	9		RES
		ACCIDENTAL INJURY/ L ankle sprained			RDT: Tylenol #3 Other: x-ray: lateral soft tissue swelling, crutches, air cast	MOD	136	Ongoing		UNCH
830028/F/9	NO	ARTHRALGIA/ R knee pain	Def	NONE	RDT: APAP, ibuprofen Other: ACE bandage, x-ray (normal)	SEV	85	27	Pt. doesn't stretch before running, symptoms also include ↓ ROM, erythema, joint stiffness, myalgia, swelling and warm joint; IPSC:may be due to sports activity	RES

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Mod = Moderate; Sev = servere
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

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