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APPLICATION NUMBER:

19-537 / S-049

20-780 / S-013

19-847 / S-027

19-857 / S-031

MEDICAL REVIEW(S)

**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:

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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 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 to 1 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		
<i>Escherichia coli</i>	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 _____ (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.

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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.

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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 arthrototoxicity 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 arthrototoxicity at an oral dose level of 90 mg/kg/day. Pathological evidence of arthrototoxicity was observed at an oral dose level of 30 mg/kg/day. DSPIDP concluded that juvenile dog arthrototoxicity needed additional evaluation as the sponsor conducted clinical trials in pediatric patients for potential pediatric indications.

The Written Request Letter for ciprofloxacin contained a study request to examine arthrototoxicity in juvenile dogs (males and females) and specifically to address the issues of post-dose recovery and the potential for latent arthrototoxicity 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 arthrototoxicity 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 arthrototoxicity 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 arthrototoxicity 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 arthrototoxicity. 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 arthrototoxicity 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 arthrototoxicity 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 $\mu\text{g}\cdot\text{hr}/\text{ml}$) was similar to the range of ciprofloxacin AUC values generated from pediatric patients at the proposed therapeutic dose level (approximately 20 to 40 $\mu\text{g}\cdot\text{hr}/\text{ml}$). The average AUC values

resulted in an animal to human dose equivalent ratio of approximately 1.3 (32 $\mu\text{g}\cdot\text{hr}/\text{ml}$ / 24 $\mu\text{g}\cdot\text{hr}/\text{ml}$). The ratio for the 90 mg/kg/day dose level was approximately 3.5 (85 $\mu\text{g}\cdot\text{hr}/\text{ml}$ / 24 $\mu\text{g}\cdot\text{hr}/\text{ml}$) while the 10 mg/kg/day ratio was approximately 0.6 (14 $\mu\text{g}\cdot\text{hr}/\text{ml}$ / 24 $\mu\text{g}\cdot\text{hr}/\text{ml}$).

The safety issue that appears to be more of a concern for pediatric patients than adult patients is subclinical or clinical arthrototoxicity. Ciprofloxacin plasma AUC levels in juvenile dogs at a dose level that resulted in arthrototoxicity 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.

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4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

Sources of Clinical Data

Material Submitted Electronic Data, including SAS transport files
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Material Reviewed Electronic Data, including SAS transport files
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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 suspension Ceftazidime (IV), Cefixime (oral) or Trimethoprim/ Sulfamethoxazole (in Canada only)	IV, 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 on _____ 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 on _____ 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 May 7, 2001 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

_____ monitored both Study 100169 and 100201 in accordance with GCP guidelines and Standard Operating Procedures (SOP) for Bayer and _____. 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. Of the three investigators, 2 did not enroll any patients at their site. 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 (\pm 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.

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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		
<i>Escherichia coli</i>	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.

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7. INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

Study 100169

One ciprofloxacin patient (306-056) died on Day 6. 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 14 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 ≥ 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) in 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 ≤ 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 ≥ 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 through 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 $\mu\text{g}\cdot\text{h}/\text{mL}$ and C_{max} of 4.56 $\mu\text{g}/\text{mL}$. Following dosing of 500 mg every 12 hours orally to steady state, the resulting AUC_{0-12} is 13.7 $\mu\text{g}\cdot\text{h}/\text{mL}$ and C_{max} is 2.97 $\mu\text{g}/\text{mL}$. The steady-state AUC over 24 hours (i.e., $AUC_{0-8} \times 3$) 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 $\mu\text{g}\cdot\text{h}/\text{mL}$ and 4.07 $\mu\text{g}/\text{mL}$, 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 $\mu\text{g}\cdot\text{h}/\text{mL}$ in 1- to 5-year-old patients who received 15 mg/kg every 12 hours, 10.3 $\mu\text{g}\cdot\text{h}/\text{mL}$ in <1-year-old patients who received 10 mg/kg every 8 hours; and 9.3 $\mu\text{g}\cdot\text{h}/\text{mL}$ 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 $\mu\text{g}/\text{mL}$, 2.8 $\mu\text{g}/\text{mL}$, and 3.6 $\mu\text{g}/\text{mL}$, respectively. The pharmacokinetics of IV ciprofloxacin have not been investigated in non-cystic fibrosis pediatric patients. However, an AUC_{0-8} of 12.8 $\mu\text{g}\cdot\text{h}/\text{mL}$ and a C_{max} of 5.3 $\mu\text{g}/\text{mL}$ 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 through 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*, patients 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
- *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 _____

_____ 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.

Appears This Way
On Original

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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 breaches 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 Argentina, 3 in Peru, 6 in Germany, 1 in Costa Rica, and 6 in Mexico.

_____ monitored this study in accordance with GCP guidelines and Standard Operating Procedures (SOP) for Bayer and _____. 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.

Amendment 1 (dated July 23, 1999)

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 _____
- Deleted an inconsistency in the collection of data from the local microbiology departments;
- 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 the exclusion of patients with a history of renal stones.

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/1.73m² to greater than 60 mL/min/1.73m²) 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 ≥ 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 ($> 38^{\circ}\text{C}$ $\{100.4^{\circ}\text{F}\}$ obtained orally, $> 38.6^{\circ}\text{C}$ $\{101.4^{\circ}\text{F}\}$ obtained rectally, $> 37.4^{\circ}\text{C}$ $\{99.4^{\circ}\text{F}\}$ axillary temperature, or $> 38.5^{\circ}\text{C}$ $\{101.2^{\circ}\text{F}\}$ 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 ($> 38^{\circ}\text{C}$ $\{100.4^{\circ}\text{F}\}$ obtained orally, $> 38.6^{\circ}\text{C}$ $\{101.4^{\circ}\text{F}\}$ obtained rectally, $> 37.4^{\circ}\text{C}$ $\{99.4^{\circ}\text{F}\}$ axillary temperature, or $> 38.5^{\circ}\text{C}$ $\{101.2^{\circ}\text{F}\}$ 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 ($> 38^{\circ}\text{C}$ $\{100.4^{\circ}\text{F}\}$ obtained orally, $> 38.6^{\circ}\text{C}$ $\{101.4^{\circ}\text{F}\}$ obtained rectally, $> 37.4^{\circ}\text{C}$ $\{99.4^{\circ}\text{F}\}$ axillary temperature or $> 38.5^{\circ}\text{C}$ $\{101.2^{\circ}\text{F}\}$ 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/1.73m²);
- 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/mm³, 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 arthrogyposis).

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 containing 254.4 mg ciprofloxacin lactate (equivalent to 200 mg ciprofloxacin) per 20 mL solution. 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

[] The final dilution volume administered ranged between _____ 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., ≥ 12 months but < 24 months; ≥ 2 years, but < 6 years; ≥ 6 years, but < 12 years; and ≥ 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 $\geq 80\%$ 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 urethral 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 ≥ 10 WBC/mm³ 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.

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TABLE 5
Study Flowchart

	Pre-treatment	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)
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	X	X				
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;

- ≥ 12 months but < 24 months;
- ≥ 2 years, but < 6 years;
- ≥ 6 years, but < 12 years; and
- ≥ 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.

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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