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

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

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

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

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

11.24.6 Demographic and Other Baseline Characteristics

Valid for Efficacy Population

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

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

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

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

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

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

TABLE 9
Demographic and Other Baseline Characteristics
Patients Valid for Efficacy

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

Valid for Safety Population

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

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

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

TABLE 10
Demographic and Other Baseline Characteristics
Patients Valid for Safety

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

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

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

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

TABLE 11
Age Distribution of Patients Valid for Efficacy

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

11.24.7 Microbiology Results

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

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

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

11.24.8 Concomitant Medications

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

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

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

11.24.9 Compliance with Study Medication

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

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

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

11.24.10 Analysis of Efficacy

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

* excluding indeterminate and missing results

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*patient with more than one superinfecting organism

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

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

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

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

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

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

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

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

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

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

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

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

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

Bacteriologic Response at the Follow-up Visit

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

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

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

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

* excluding indeterminate and missing results

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

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

11.25 Summary of Efficacy

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

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

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

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

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

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

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

11.26 SAFETY RESULTS

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

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

TABLE 21
Age Distribution of Patients Valid for Safety

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

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

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

TABLE 22A
Treatment Duration
All Patients Valid for Safety

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

TABLE 22B
Dosing Information
All Patients Valid for Safety

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

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

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

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

11.26.1 *Analysis of Adverse Event Rates*

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

TABLE 23
Overview of Adverse Events
Patients Valid for Safety

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

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

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

11.26.2 *Overview of Arthropathy Adverse Events*

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

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

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

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

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

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

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

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

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

group differences across treatment routes were not completely consistent.

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

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

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

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

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

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

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

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

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

Arthropathy rates were slightly lower than the overall rates in Mexico (0% both treatment groups) and Peru (2% ciprofloxacin versus 3% comparator). There was a much bigger difference between treatment group arthropathy rates in the United States (21% ciprofloxacin versus 11% comparator) than in the overall rates. The arthropathy rate was higher than the overall rate in Caucasians (14% ciprofloxacin versus 10% comparator) and lower than the overall rate in Hispanics (8% ciprofloxacin versus 3% comparator) and the "uncodable" race group (5% ciprofloxacin versus 3% comparator). The arthropathy rates were quite similar between males and females and consistent between treatment groups.

Differences between treatment groups in the arthropathy rate by Day +42 were fairly consistent with the overall rate in the different age groups, and the arthropathy rate in both treatment groups increased with age. The highest arthropathy rate was seen in the ≥12 year to <17 year age group, where the rate was 22% for ciprofloxacin patients and 14% for comparator patients. Theoretical reasons for this difference posed by the applicant for explaining the higher rate in the older patients are: greater physical activity, more accurate ability to report pain, and greater weight across weight-bearing joints of adolescents versus younger children.

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

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

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

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

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

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

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

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

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

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

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

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

TABLE 29
Arthropathy Rate in Patients Valid for Safety

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

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

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

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

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

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

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

TABLE 30
Arthropathy Rates by Country of Enrollment

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

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

TABLE 31
Sex Distribution of Patients with Arthropathy

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

TABLE 34
Severity of Arthropathy Events

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

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

TABLE 35
Serious Arthropathy Adverse Events

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

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

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

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

TABLE 36
Patients with Arthropathy Developing During Study Drug Administration

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

*Patient in Stratum II (IV or sequential therapy)

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

TABLE 37
Arthropathy Events Associated with "Accidental Trauma"

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

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

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

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

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

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

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

11.26.5 All Adverse Events Occurring by Day +42

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

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

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

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

11.26.6 Musculoskeletal Adverse Events Occurring by Day +42

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

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

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

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

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

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

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

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

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

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

TABLE 42
ARTHRALGIA Cases Occurring by Day +42

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11.26.8 *Musculoskeletal Adverse Events at One Year of Follow-up*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11.26.9 Range of Motion Examination

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

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

11.26.10 Joint Examination

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

11.26.11 Gait Assessment

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

11.26.12 Findings from Other Diagnostic Tests

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

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

11.26.13 Caregiver Questionnaire

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

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

11.26.14 Neurological Adverse Events

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

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

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

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

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

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

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

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

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

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

11.26.15 *Deaths*

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

Patient narratives are included:

Patient 306056

A 3 year old female received oral study drug from January 9,2002 to January 18, 2002 (20 doses) for the indication of pyelonephritis. Past medical history is significant for urinary incontinence and cellulitis of the right arm. No baseline concomitant medications were reported. During the treatment phase, she had the non-serious adverse event of a Mod-severity broken right collarbone on January 13, 2002. The patient fell from bed. The collarbone was immobilized with plaster. On ' — **he patient's mother cut her throat and the patient died of** hypovolemic shock. The mother, due to a psychotic attack, killed her three children. The event was not considered related to study drug.

Patient 204016

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

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

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

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

On March 30, 2001, joint exam revealed warmth, pain, and tenderness on the left shoulder. Exam on April 2, 2001 revealed tenderness and bruising of left shoulder. The patient fell from a chair. Exams on Apr 17, 2001; May 15, 2001; July 6, 2001; and March 26, 2002 were normal. On [redacted] the patient died from complications of retroviral disease.

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

11.26.16 *Serious Adverse Events*

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

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

11.26.17 *Discontinuations Due to Adverse Event*

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

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

TABLE 54
Discontinuations Due to Adverse Events
Patients Valid for Safety

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

NR = not reported

11.26.18 Laboratory Parameters

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

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

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

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

11.26.19 Vital Signs

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

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

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

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

11.27 Safety Summary

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

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

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

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

To further evaluate any possible musculoskeletal events, the IPSC reviewed all cases with an adverse event that coded to the musculoskeletal system, all patients with an abnormal joint appearance (baseline and treatment-emergent), and all patients with an abnormal gait (baseline and treatment-emergent). Additionally, all cases of adverse events of leg pain, hand pain, arm pain, movement disorder, abnormal gait, peripheral edema, and selected accidental injury (related to joints or extremities) were reviewed. All cases were evaluated in a blinded fashion by the IPSC. Cases were evaluated as no evidence of arthropathy or at least possible evidence of arthropathy (arthropathy defined as any condition affecting a joint or periarticular tissue where there is historical and/or physical evidence for structural damage and/or functional limitation that may have been temporary or permanent; this definition was seen as broad and inclusive of such phenomena as bursitis, enthesitis and tendonitis).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The incidence of laboratory test abnormalities was comparable between the 2 treatment groups. No trends that appear to be uniquely associated with ciprofloxacin treatment were identified. The most common clinically significant changes (as defined by the applicant) were ≤ 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).

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

11.28 Study Conclusions

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

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

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

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

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

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

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

11.29 APPENDIX – Additional Tables from Study 100169

Appears This Way
On Original

TABLE 1 List of COSTART Terms for the Musculoskeletal System

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

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

TABLE 2
Enrollment by Study Center

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

TABLE 2 (continued)
Enrollment by Study Center

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

TABLE 2 (continued)
Enrollment by Study Center

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

TABLE 2 (continued)
Enrollment by Study Center

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

TABLE 2 (continued)
Enrollment by Study Center

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

TABLE 2 (continued)
Enrollment by Study Center

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

TABLE 2 (continued)
Enrollment by Study Center

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

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

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

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

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

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

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

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			bilateral ankle and foot tenderness on joint exam							of ankle pain while running – growing pains or bony abnormality	
401115/F/9	PERU	NO	ARTHRALGIA/ Elbow arthralgia	Pos	Pos	None	MILD	31	13	2 days of ciprofloxacin; mild sporadic arthralgia	RES
			ARTHRALGIA/ Knee arthralgia			None	MILD	31	13		RES
402049/F/8	PERU	NO	ARTHRALGIA/ Coxalgia	Pos	Pos	None	MILD	4	2	Myalgia vs. athralgia; pt. playing basketball and doing martial arts on day prior	RES
402052/F/11	PERU	YES[6]	ACCIDENTAL INJURY/ worsening articular hypermotility	Pos	NONE	None	MILD	215	39	Eval by rheumatologist: episodic pain in knees lasting for < 1 hour, related to articular hypermotility	RES
1001/F/5	US	NO	–/ bilateral knee redness and warmth on joint	Def	Pos	None	–	-10	14	IPSC: transient arthralgia during	RES

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

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

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

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

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

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

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

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