Ciprofloxacin N= 56		Control N= 13	
21/56 (37%)		5/13 (38%)	
Pt. Number	COSTART term /Description	Pt. Number	COSTART term/ Description
	pain		
350015/F/12**	Arthralgia/R ankle pain		
9930010/M/8	--/bilateral foot and ankle swelling on joint exam		

* study drug started prior to the baseline exam being conducted
** IPSC inadvertently unblended to study drug

The reviewer noted that there were many arthropathy events which **occurred as a result of "accidental trauma", which for the purposes of this** review is defined as a specific traumatic event which caused the patient injury. Of the patients with arthropathy, 9% of ciprofloxacin patients compared to 15% of control patients developed an arthropathy event as a result of a traumatic injury, as shown in Table 35.

TABLE 35
Arthropathy Events Associated with "Accidental Trauma"

Ciprofloxacin N= 56			Control N= 13		
5/56 (9%)			2/13 (15%)		
Pt. #/Sex/Age in years	COSTART term/Description	Rel Start to End of Tx	Pt. #/Age (yrs) /Country	COSTART term/Description	Rel Start to End of Tx
250003/M/9	Arthralgia/L wrist pain (pt. wrestling with brother)	42	70152/M/7	Sprained hip (pt. playing football)	92
60003/F/9	Arthralgia/L ankle pain (pt. cheerleading and playing on the trampoline)	38	870034/F/11	Abnormal gait (Pt. hurt hip while playing)	36
270046/M/10	Accidental injury/ L wrist sprain (pt. fell off bike)	27			
370010/M/3	Arthralgia/R knee pain; arthralgia/ R knee injury (Pt. drove into a house on his battery-operated moped)	28			
300001/M/12	Accidental injury/L knee sprain;				

Ciprofloxacin N= 56			Control N= 13		
5/56 (9%)			2/13 (15%)		
Pt. #/Sex/Age in years	COSTART term/Description	Rel Start to End of Tx	Pt. #/Age (yrs) /Country	COSTART term/Description	Rel Start to End of Tx
	accidental injury/R wrist sprain (no info)				

In addition to the events related to traumatic injury, the reviewer also noted that events were associated with strenuous physical activity (PA) or physical exercise (PE). Table 36 shows the cases for ciprofloxacin and control. Of the patients with arthropathy, there was approximately an equal distribution of events associated with PA or PE in both groups (i.e., 11% vs. 15%).

TABLE 36
Arthropathy Events Associated with Physical Activity (PA) or Exercise (PE)

Ciprofloxacin N= 56		Control N= 13	
6/56 (11%)		2/13 (15%)	
Pt. Number/Sex/Age in years	COSTART term /Description	Pt. Number	COSTART term/ Description
80006/F/14	Arthralgia/shoulder pain (associated with exercising in the pool)	280018/F/14	Tendon disorder/bilateral Achillean tendonitis (pt. not warming up in sports)
80006/F/14	Arthralgia/shoulder pain (associated with swimming)	830028/F/9	Arthralgia/R knee pain **(pt. doesn't stretch** before running)
170001/M/2 (pt. rolling around on the ground with a ball)	Arthralgia/ L ankle tenderness		
	Arthralgia/ L knee tenderness		
	Arthralgia/ L knee swelling		
350011/M/13	Tendon disorder/ R elbow tendonitis (present at baseline, exacerbated by pitching baseball)		
250033/F/13	Arthralgia/ L wrist pain (associated with gymnastics)		
350021/F/11	Accidental injury/R		

Ciprofloxacin N= 56		Control N= 13	
6/56 (11%)		2/13 (15%)	
Pt. Number/Sex/Age in years	COSTART term /Description	Pt. Number	COSTART term/ Description
	knee injury (associated with dancing and soccer)		

12.15.17 Time to Musculoskeletal Events

Ciprofloxacin

Figure 1 in Appendix 1 shows the Kaplan-Meier estimates of time to any musculoskeletal event for ciprofloxacin patients valid for safety, through the Day +42 time point. Figures 2 and 3 in Appendix 1 show the same curves by age group and treatment type, respectively. Figures 4 through 6 in Appendix 1 provide these estimates through the 1-year follow-up time point.

Note: In all the curves, the last day of treatment is shown as Day 1 on the x-axis with each day afterwards representing the relative time from end of treatment to musculoskeletal adverse event or arthropathy. For this reason, any events that occurred during therapy (and therefore had a negative start day relative to the end of treatment) were considered to have occurred at Day +1 so as not to be excluded from the analysis. In addition, for events that were documented but were missing relative day information, the mean time of musculoskeletal event or arthropathy for **that patient's treatment group was used.**

Figures 1 and 4 reinforce the results from the tables that show that approximately 70% of the musculoskeletal events reported had been reported by Day +42. Many events were reported during therapy (evidenced by the sharp drop in the curve at Day +1), then fairly uniformly through Day +42 post-therapy (evidenced by the fairly constant slope from Day +42).

Figures 2 and 5 show that the age group differences seen in the incidence rates of any musculoskeletal event were defined very early in the treatment regimen. Within 10 days after the end of therapy, the ordering of the age groups (increasing incidence with increasing age group) had been established, and remained this way throughout the 42-day and 1-year follow-up periods. This is evidenced by the fact that the age-specific survival curves do not cross beyond 10 days.

Figures 3 and 6 indicate that the only constant difference in time to musculoskeletal event or arthropathy according to treatment type (oral, IV or sequential) was that the oral group had the lowest event rate. This was due to the fact that although the treatment-specific survival curves for IV and sequential therapy cross, the oral therapy curve remains above them. This was seen over the Day +42 and one year periods.

Control

Figure 7 in Appendix 1 shows the Kaplan-Meier estimates of time to any musculoskeletal event for ciprofloxacin patients valid for safety, through the Day +42 time point. Figures 8 and 9 in Appendix 1 show the same curves by age group and treatment type, respectively. Figures 10 through 12 in Appendix 1 provide these estimates through the 1-year follow-up time point.

Note: In all the curves, the last day of treatment is shown as Day 1 on the x-axis with each day afterwards representing the relative time from end of treatment to musculoskeletal adverse event or arthropathy. For this reason, any events that occurred during therapy (and therefore had a negative start day relative to the end of treatment) were considered to have occurred at Day +1 so as not to be excluded from the analysis. In addition, for events that were documented but were missing relative day information, the mean time of musculoskeletal event or arthropathy for **that patient's treatment group was used.**

Figures 7 and 10 reinforce the results from the tables that show that approximately 70% of the musculoskeletal events reported had been reported by Day +42. Many events were reported during therapy (evidenced by the sharp drop in the curve at Day +1), then fairly uniformly through Day +42 post-therapy (evidenced by the fairly constant slope from Day +42).

Figures 8 and 11 show that as in the ciprofloxacin group, the oldest age group had the highest event rate by Day +42 post-therapy and continuing to Day +365 post-therapy.

Figures 9 and 12 show that the IV control group had the lowest event rate until approximately Day +32 post-therapy, and the highest event rate afterwards.

12.15.18 Parental Questionaire – Adverse Musculoskeletal or CNS Events

Adverse musculoskeletal or CNS events were reported infrequently for ciprofloxacin using the parental questionnaire at 3, 6, 9, and 12 month periods (data not shown). Incidence rates of any musculoskeletal or CNS event reported were 5% or below at each time point and for each subgroup except patients 12-16 years of age at 9 and 12 months (10%).

In the control group, musculoskeletal or CNS events reported using the parental questionnaire were also infrequent and were reported below 5% at each time point and for each subgroup. (data not shown). Only 5 events were reported through the 12-month follow-up period. Three of these events were arthralgia, all from patients in the 6 to 11 age group.

12.15.19 All Adverse Events Through One Year

Table 37 shows adverse events, for all adverse events and those related to study drug, respectively, for all body systems through the one year

follow-up period for ciprofloxacin and control patients. The results for events, regardless of relationship to study drug that occurred in at least 2% of patients in either group are shown in Table 38. The most common events for ciprofloxacin (other than musculoskeletal events) were accidental injury (7% incidence rate), otitis media, pharyngitis, and headache (6% each). The most common events for control (other than musculoskeletal events) were pharyngitis and accidental injury (4% each).

TABLE 37
Incidence Rates of Adverse Events by Body System Through One Year
Ciprofloxacin (N=487) and Control (N=507) Patients

Body System	Ciprofloxacin		Control	
Any Event	252	(52%)	141	(28%)
Body as a Whole	131	(27%)	60	(12%)
Cardiovascular	11	(2%)	1	(<1%)
Digestive	46	(9%)	17	(3%)
Endocrine	2	(<1%)	0	(0%)
Hemic and Lymphatic	14	(%)	5	(<1%)
Metabolic & Nutritional	6	(%)	2	(<1%)
Musculoskeletal	64	(13%)	14	(3%)
Nervous	56	(11%)	11	(2%)
Respiratory	75	(15%)	52	(10%)
Skin & Appendages	27	(6%)	23	(5%)
Special Senses	41	(8%)	29	(6%)
Urogenital	19	(4%)	4	(<1%)

TABLE 38
Incidence Rates of Adverse Events Through One Year (Other than Musculoskeletal and CNS) Occurring in at Least 2% of Patients (Regardless of Relationship to Study Drug) in Either Group
Ciprofloxacin (N=487) and Control (N=507) Patients

Adverse Event	Ciprofloxacin		Control	
Any event	252	(52%)	141	(28%)
Accidental Injury	34	(7%)	21	(4%)
Allergic Reaction	1	(<1%)	9	(2%)
Otitis Media	28	(6%)	15	(3%)
Pharyngitis	27	(6%)	22	(4%)
Headache	27	(6%)	7	(1%)
Rhinitis	22	(5%)	15	(3%)
Fever	22	(5%)	7	(1%)
Leg Pain	18	(4%)	5	(<1%)
Vomiting	18	(4%)	5	(<1%)
Asthenia	18	(4%)	0	(0%)

Rash	17	(3%)	13	(3%)
Abdominal Pain	17	(3%)	7	(1%)
Cough Increased	15	(3%)	3	(<1%)
Diarrhea	14	(3%)	2	(<1%)
Sinusitis	8	(2%)	7	(1%)

Most of the adverse events reported in either group were not considered drug-related. The incidence rate of any drug-related adverse event in the ciprofloxacin group was 18% and 5% in the control group. The only events with drug-related incidence rates of 1% or higher (other than musculoskeletal or CNS events) in the ciprofloxacin group were abdominal pain (8 patients, 2%), diarrhea (9 patients, 2%), vomiting (10 patients, 2%), and headache (5 patients, 1%); and rash (6 patients, 1%) in the control group.

12.15.20 Deaths

There was one death in the study. Patient narrative is provided below.

Patient 490055
Patient is a 5-month old male was treated with ciprofloxacin 100 mg IV bid for the indication of bacteremia and sepsis due to *Morganella morganii* from June 8, 2001 to June 24, 2001 (for a total of 32 doses).

The patient was a critically ill full-term infant who had been hospitalized — He had a history of VACTERL syndrome (vertebral, anal, cardiac, tracheal, esophageal, renal, and limb pattern of congenitial **anomalies), Hirschsprung's disease, (congenital megacolon), primary** pulmonary hypertension, hemivertebra, imperforate anus/colostomy, duodenal atresia/ end to end repair anastomosis, hyposadias, and patent ductus arteriosis since birth. He also had a history of RSV (March 6, 2001 to April 13 2001), respiratory failure requiring intubation (since March 6, 2001), hepatomegaly (since April 5, 2001), sepsis from central venous catheter infections with isolates of *S. homins*, *Enterococcus faecalis*, and *E. coli* (April 8, 2001 to April 23, 2001), anemia/decreased oxygen carrying capacity (since April 2001), small bowel obstruction/ileostomy (April 14, 2001), electrolyte abnormalities (since April 18, 2001), post-operative wound dehiscence/cellulitis (since May 14, 2001), feeding intolerance (since May 27, 2001), and fungemia sepsis (*Malassezia furfur*; since June 7, 2001). The patient was receiving multiple concomitant medications.

The serious adverse event of deterioration in cardiac function began on July, 9 2001 (ciprofloxacin treatment June 8, 2001 to June 24, 2001). The ongoing respiratory failure and electrolyte abnormalities most likely contributed to this event. The patient was hyperkalemic and acidotic with decreased oxygenation and perfusion. Widening of QRS complex, hypotension and bradycardia were noted. The patient responded well to electrolyte correction, diuresis, and increased ventilatory settings. The

investigator considered the event to have no association to the study drug.

The patient was stable in the morning of ——— and by afternoon (4:15 pm) was noted to have low blood pressure, no peripheral pulses, and low oxygen saturation. An ECG was done which showed abnormally narrow QRS complexes. CPR was initiated with chest compressions and epinephrine, sodium bicarbonate, calcium chloride were given. Patient returned to normal sinus rhythm after 20 minutes. An echocardiogram showed a right atrial thrombus/vegetation with extension from the inferior vena cava. The patient was then started on heparin. Cardiac pressors as drips were initiated (epinephrine, dopamine and dobutamine). At 7:15 **pm, the patient's blood pressure dropped. The patient again was dosed** with epinephrine, sodium bicarbonate, calcium chloride. Despite all of the above, patient became pulseless and expired at 7:59 pm.

Information from the death certificate considered cardiac arrest as the immediate cause of death and pulmonary hypertension as a contributory cause of death. As per the death certificate, other significant conditions **that contributed to the patient's death were VACTERL syndrome, Hirschsprung's disease, and sepsis. An autopsy was not performed. The** relative day of death to end of treatment was — days.

Clinical Reviewer's Comment: ***The reviewer agrees that ciprofloxacin administration was not directly related to the patient's death, although*** *sepsis, the infection for which ciprofloxacin was being given, did* ***contribute to the patient's death.***

12.15.21 Serious Adverse Events

Serious adverse events were reported for 22 patients in the ciprofloxacin group as shown in Table 41. The most commonly reported serious adverse events were fever (5 patients) and sepsis (4 patients). One ciprofloxacin patient died from cardiac arrest — days after the end of treatment. In the control arm, there were 5 patients (2 patients with acute asthma exacerbations and one patient each with abscess, vertigo and pleural effusion) with serious adverse events as shown in Table 42.

Two ciprofloxacin patients had serious adverse events considered at least possibly related to study drug. Patient 270024 had acute gastroenteritis and *Clostridium difficile* colitis considered possibly related to study drug. Patient 500011 had *Clostridium difficile* colitis considered probably related to study drug. All other serious adverse events reported in the ciprofloxacin group were judged by the investigators to be unlikely or not related to study drug. Two ciprofloxacin patients had musculoskeletal serious adverse events. Patient 310019 had severe osteomyelitis, which resolved and was considered unlikely related to study drug. Patient 760005 had severe hip pain, which resolved and was not considered related to study drug.

TABLE 41
Serious Adverse Events
Ciprofloxacin Patients Valid for Safety

PATIENT	TREATMENT GROUP	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	OUTCOME	ACTION TAKEN 1	SEVERITY
90025	CIPROFLOXACIN	DEHYDRATION	47	49	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
200008	CIPROFLOXACIN	CENTRAL VENOUS	24	31	RESOLVED	HOSPITALIZATION	SEVERE
210015	CIPROFLOXACIN	NEUTROPENIA	49	78	RESOLVED	HOSPITALIZATION	SEVERE
210015	CIPROFLOXACIN	BACTEREMIA	49	58	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
210015	CIPROFLOXACIN	NEUTROPENIC FEV	61	67	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
210015	CIPROFLOXACIN	BACTEREMIA	63	69	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
220013	CIPROFLOXACIN	RECURRENT URINA	47	52	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
270024	CIPROFLOXACIN	ACUTE GASTROENT	4	9	RESOLVED	HOSPITALIZATION	SEVERE
270024	CIPROFLOXACIN	CLOSTRIDIUM DIF	23	39	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
270024	CIPROFLOXACIN	SEPSIS	27	41	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
290062	CIPROFLOXACIN	FAILURE ACUTE R	23	29	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
290062	CIPROFLOXACIN	HEMOLYTIC UREMI	63	65	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
300002	CIPROFLOXACIN	PERIANAL ABSCES	13	18	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
300004	CIPROFLOXACIN	OTITIS MEDIA (R	54	57	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
300004	CIPROFLOXACIN	OTITIS MEDIA (R	65	68	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
310017	CIPROFLOXACIN	WORSENING OTITI	6	15	RESOLVED	STUDY DRUG DISCONTINUED PERMANENTLY	SEVERE
310019	CIPROFLOXACIN	OSTEOMYELITIS	23	156	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
350014	CIPROFLOXACIN	FEVER	18	27	RESOLVED	REMEDIAL DRUG THERAPY	MODERATE
360002	CIPROFLOXACIN	FEVER	27	30	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
360002	CIPROFLOXACIN	RULE OUT BACTER	27	30	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
420010	CIPROFLOXACIN	ACUTE LYMPHOCYT	22	24	RESOLVED	HOSPITALIZATION	MILD
420010	CIPROFLOXACIN	ACUTE LYMPHOCYT	38	39	RESOLVED	HOSPITALIZATION	MILD
490055	CIPROFLOXACIN	DETERIORATION I	32	34	WORSENED	OTHER	SEVERE
490055	CIPROFLOXACIN	RIGHT ATRIUM TH	34	34	WORSENED	OTHER	SEVERE
490055	CIPROFLOXACIN	CARDIAC ARREST	34	34	DEATH	OTHER	SEVERE
500008	CIPROFLOXACIN	ABDOMINAL WOUND	4	42	RESOLVED	STUDY DRUG DISCONTINUED PERMANENTLY	SEVERE
500011	CIPROFLOXACIN	CLOSTRIDIUM DIF	17	33	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
500011	CIPROFLOXACIN	THROMBUS IN RIG	21	31	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
500011	CIPROFLOXACIN	URETERAL REFLUX	11	13	RESOLVED	OTHER	SEVERE
500011	CIPROFLOXACIN	NEPHROPATHY	11	13	RESOLVED	OTHER	SEVERE
500024	CIPROFLOXACIN	ABDOMINAL WOUND	4	.	.	STUDY DRUG DISCONTINUED PERMANENTLY	SEVERE
500024	CIPROFLOXACIN	REHOSPITALIZATI	8	19	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
500024	CIPROFLOXACIN	NAUSEA	32	34	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
500024	CIPROFLOXACIN	VOMITING	32	34	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
510009	CIPROFLOXACIN	STENOTROPHOMONA	19	28	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
760005	CIPROFLOXACIN	HIP PAIN	38	48	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
760005	CIPROFLOXACIN	BACK PAIN	38	48	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
760005	CIPROFLOXACIN	NEUTROPENIA	38	52	RESOLVED	HOSPITALIZATION	SEVERE
760005	CIPROFLOXACIN	FEVER	38	44	RESOLVED	HOSPITALIZATION	SEVERE
770002	CIPROFLOXACIN	PYELONEPHRITIS	.	.	RESOLVED	REMEDIAL DRUG THERAPY	MODERATE
770002	CIPROFLOXACIN	LEFT URETEROPEL	.	.	RESOLVED	OTHER	MODERATE
790011	CIPROFLOXACIN	NEUTROPENIA	44	47	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
790011	CIPROFLOXACIN	FEVER	44	47	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
9930010	CIPROFLOXACIN	NEUROGENIC BLAD	12	12	RESOLVED	HOSPITALIZATION	SEVERE

PATIENT	TREATMENT GROUP	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	OUTCOME	ACTION TAKEN 1	SEVERITY
9930010	CIPROFLOXACIN	SMALL BOWEL OBS	31	31	RESOLVED	HOSPITALIZATION	SEVERE
9930010	CIPROFLOXACIN	SMALL BOWEL OBS	40	40	RESOLVED	HOSPITALIZATION	SEVERE

TABLE 42
Serious Adverse Events
Control Patients Valid for Safety

PATIENT	TREATMENT GROUP	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	OUTCOME	ACTION TAKEN 1	SEVERITY
510013	AMOXICILLIN	VERTIGO	39	43	RESOLVED	HOSPITALIZATION	SEVERE
800051	AMOXICILLIN	ACUTE ASTHMA EX	22	24	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
800016	AUGMENTIN	ACUTE ASTHMA EX	16	17	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
800021	UNASYN	PERITONSILLAR A	29	30	RESOLVED	REMEDIAL DRUG THERAPY	SEVERE
470048	AMPICILLIN, CEFOTAXIME, ROCEPHIN	INCREASING PLEU	15	18	RESOLVED	OTHER	SEVERE

12.15.22 Premature Discontinuations

Adverse events caused discontinuation of study drug in 14 ciprofloxacin patients as shown in Table 39. Arthralgia (4 patients), vomiting (2 patients), and rash or urticaria (2 patients) were the most common events causing discontinuation. Adverse events caused discontinuation of study drug in 3 control patients as shown in Table 40. One patient discontinued therapy due to vomiting, one due to rash, and one due to abdominal pain.

TABLE 39
Premature Discontinuations Due to Adverse Events
Ciprofloxacin Patients Valid for Safety

PATIENT	TREATMENT GROUP	COSTART TERM	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	SEVERITY	OUTCOME
80006	CIPROFLOXACIN	ARTHRALGIA	SHOULDER PAIN	13	20	MILD	RESOLVED
90026	CIPROFLOXACIN	DIZZINESS	DIZZINESS	1	7	MODERATE	RESOLVED
90026	CIPROFLOXACIN	DIZZINESS	LIGHTHEADEDNESS	1	7	MILD	RESOLVED
90026	CIPROFLOXACIN	HEADACHE	HEADACHES	1	7	MILD	RESOLVED
90026	CIPROFLOXACIN	TACHYCARDIA	TACHYCARDIA	1	7	MODERATE	RESOLVED
220001	CIPROFLOXACIN	ARTHRALGIA	ELBOW PAIN	11	17	MODERATE	RESOLVED
250027	CIPROFLOXACIN	RASH	ALLERGIC RASH	2	4	MILD	RESOLVED
250033	CIPROFLOXACIN	ARTHRALGIA	WRIST PAIN, RIG	4	.	MILD	IMPROVED
290060	CIPROFLOXACIN	INJECTION SITE	INFUSION SITE R	3	3	MILD	RESOLVED
290060	CIPROFLOXACIN	ALLERGIC REACTI	ALLERGIC REACTI	3	3	MILD	RESOLVED
310012	CIPROFLOXACIN	VOMITING	VOMITING	1	2	MILD	RESOLVED
310017	CIPROFLOXACIN	OTITIS MEDIA	WORSENING OTITI	8	15	SEVERE	RESOLVED
310026	CIPROFLOXACIN	VOMITING	VOMITING	1	1	MILD	RESOLVED
320023	CIPROFLOXACIN	INFECTION BACTE	CHRONIC STREPTO	7	10	MODERATE	RESOLVED
320023	CIPROFLOXACIN	SINUSITIS	CHRONIC SINUSIT	7	10	MODERATE	RESOLVED
320023	CIPROFLOXACIN	SINUSITIS	SINUSITIS	12	25	MILD	RESOLVED
380006	CIPROFLOXACIN	ARTHRALGIA	JAW PAIN	5	9	MODERATE	RESOLVED
500008	CIPROFLOXACIN	INFECTION	ABDOMINAL WOUND	4	42	SEVERE	RESOLVED
500024	CIPROFLOXACIN	ABSCESS	ABDOMINAL WOUND	4	.	SEVERE	.
680001	CIPROFLOXACIN	URTICARIA	HIVES	5	.	.	INSUFFICIENT FOLLOW-UP

TABLE 40
Premature Discontinuations Due to Adverse Events
Control Patients Valid for Safety

PATIENT	TREATMENT GROUP	COSTART TERM	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	SEVERITY	OUTCOME
70194	AMOXICILLIN	VOMITING	VOMITING	1	3	MILD	RESOLVED
760008	AMOXICILLIN	RASH	RASH	7	19	MODERATE	RESOLVED
870039	CEFZIL	ABDOMINAL PAIN	ABDOMINAL PAIN	.	46	MILD	RESOLVED

12.15.23 Clinical Laboratory Evaluation

The study did not require any scheduled laboratory assessments.

12.15.24 Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs
Vital signs were not collected as a routine assessment in this study.

Range of Motion (ROM) Assessments (data not shown)
The mean change in ROM from pre-therapy to post-therapy for ciprofloxacin patients was small (less than 4 degrees), but positive, in all joints; the largest changes were 3.1 degrees extension increase in the right shoulder and 3.0 degrees extension increase in the left shoulder. In the control arm, most mean changes were very small (less than 3 degrees), but positive, in all joints; the largest change post-therapy was 2.6 degrees plantar flexion in the right ankle/foot.

Gait and Joint Assessments (data not shown)
In ciprofloxacin patients, the vast majority had a normal assessment that remained the same from baseline to post-therapy. In the shoulder joint, **only one patient's assessment changed from normal to pain. In the hip,** one patient changed from normal to pain, and one changed from normal to tenderness. In the left knee, 9 patients changed from normal to swelling, pain, or tenderness. In the right knee, 6 patients changed from

normal to redness, swelling, pain, tenderness, or brace. In the left ankle/foot, 7 patients changed from normal to swelling, pain, or tenderness. In the right ankle/foot, 4 patients changed from normal to redness, swelling, pain, or tenderness.

In control patients, the majority had their assessment remain the same from baseline to post-therapy. In the left hip, one patient's assessment changed from normal to pain. Changes from normal to pain or tenderness were similarly rare in the shoulder, knee, ankle and foot.

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

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

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

X-ray Findings (data not shown)
X-rays were performed 28 times on ciprofloxacin patients and 4 times on control patients (one patient could have had more than one x-ray). Of the 28 x-rays in e ciprofloxacin group, 19 were within normal limits and 3 were abnormal, but with clinically insignificant findings (as per the investigator). There were 2 lower arm, 2 hip, 1 throacic spine, and one lumbar spine x-rays that were abnormal and clinical significant. Three of the 4 x-rays in the control group were within normal limits and one that was considered abnormal, but clinically insignificant in the control group.

Developmental Milestones (data not shown)
At baseline, 95% of ciprofloxacin patients were developmentally on target. By the 1-year follow-up timepoint, only 2 patients were not developmentally on target, with 1 patient being deficient in gross motor skills and one being deficient in language. At baseline, 99% of control

patients were developmentally on target. By the 1-year follow-up timepoint, all patients were developmentally on target.

Electroencephalography (EEG) Findings (data not shown)
In the ciprofloxacin patients 30 EEGs were performed (a patient may have had more than one EEG). One ciprofloxacin patient reported an abnormal clinically significant EEG finding. In the control patients 12 EEGs were performed and one abnormal, clinically significant EEG abnormality was noted.

12.16 Safety Conclusions

In this open-label, non-randomized study involving pediatric patients with a variety of infections, ciprofloxacin was compared to active control. Of the 1029 patients enrolled in the study, 994 (96.6%; 487 ciprofloxacin and 507 non-quinolone controls) were considered to have received at least one dose of study drug and were valid for the safety analysis. Of those 994 patients valid for safety, 21 ciprofloxacin patients and 1 control patient had participated in Study 100169 (complicated urinary tract infection and pyelonephritis trial). By June 30, 2003 (date form the interim analysis cut-off), 355 ciprofloxacin and 267 non-quinolone patients had been contacted by telephone for at least 1-year post-treatment follow-up (all 22 patients that participated in Study 100169 had 1-year follow-up). This is an ongoing clinical study. The data presented is from an interim analysis and additional follow-up information is still being pursued.

In the ciprofloxacin group, 55% (269/487) of the patients were female compared to 485 (242/507) in the control group). Although the majority of the ciprofloxacin patients were Caucasian (60%; 292/487), patients of other racial and ethnic origins were represented (7% [33/487] Black, 3% [16/487] Asian, 28% [138/487] Hispanic, **and 2% [8/487] were not codable using the applicant's coding system). The control** group had slightly more Caucasians (65%; 330/507) with 5% [27/507] Black, 2% [8/507] Asian, 25% [138/507] Hispanic, <1% [1/507] American Indian, and 3% [13/507] were not codable.

The mean age of ciprofloxacin patients was 6.2 years (range: 2 months to 16 years) while the mean age of control patients was slightly lower (5.3 years with a range of 2 months to 16 years). Of the patients ≤ 5 years of age, 48% (235/487) were in the ciprofloxacin group and 52% (265/507) were in the control group. More ciprofloxacin patients (12%; 58/487) were 12 years to <17 years of age compared to control patients (4%; 19/507).

The most common (defined as > 2%) baseline infection types for the ciprofloxacin patients were urinary tract (22%; 105/487) and otitis media (29%; 143/487). The most common baseline infections in the control group were otitis media (41%; 207/507) and pharyngitis/tonsillitis (29%; 148/507).

The mean (± standard deviation) total treatment durations were 12.4 ± 7.9 (range 1 to 88 days) and 11.3 ± 6.7 days (range: 3 to 70 days) for the ciprofloxacin and control groups, respectively.

Previous antimicrobial use was 17% (81/487) in the ciprofloxacin group and 1% (3/507) in the control group. Ciprofloxacin and Bactrim® were the most commonly used previous antimicrobials in the ciprofloxacin group.

Notable differences (>2% differences) were observed in medical history (ICD-9 class) between the two treatment groups. The conditions with the greatest discrepancy between the groups are as follows. Ciprofloxacin-treated patients had a higher incidence of genitourinary system (23% [114/487] versus 8% [41/507]) and digestive system disorders (17% [81/487] versus 8% [43/507]) compared to the control group. The control group had a higher incidence of medical histories of conditions in the nervous system and sense organs (53% [270/507] control versus 31% [150/487] ciprofloxacin; mainly attributed to a higher incidence of otitis media), respiratory system (62% [315/507] control versus 37% [181/487] ciprofloxacin; mainly attributed to differences in upper respiratory infections, pharyngitis, and chronic sinusitis), and injury and poisoning (40% [205/507] control versus 17% [85/487] ciprofloxacin; mainly attributed to allergy).

Known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy were to be excluded from the study. However, 7% (32/487) of ciprofloxacin patients and 5% (24/507) control patients were enrolled with a medical history of any abnormal musculoskeletal or connective tissue finding. In addition, at study entry 7% (36/487) of ciprofloxacin patients and 0.8% (4/507) of control patients had an abnormal gait assessment at baseline and 5% (23/487) of ciprofloxacin patients and 2% (9/507) of control patients had an abnormal joint appearance at baseline. These patients were **included in the applicant's valid for safety population. However, these baseline** abnormalities and medical histories may have rendered it difficult to assess any potential drug effect on gait or joint appearance.

Prevalence rates of concomitant medication use (at the time of enrollment) were 76% for ciprofloxacin patients and 68% for control patients (data not shown). Antimicrobial use was much more common among ciprofloxacin patients (41%; 201/487) than control patients (17%; 88/507). Ciprofloxacin patients also had higher use of vitamins (8% [40/487] versus 2% [11/507]), antacids (6% [27/487] versus 2% [11/507]), antifungals for dermatologic use (4% [20/487] versus 1% [7/507]), urologicals (5% [24/487] versus 0% [0/507]), antimycotics for systemic use (3% [13/487] versus <1% [1/507]), analgesics (23% [112/487] versus 14% [72/507]), and anti-asthmatics (14% [70/487] versus 11% [55/507]).

Due to the demographic and baseline characteristic differences described, and because the study was not blinded or randomized, safety results of this study should be interpreted with caution. These differences should be considered when reviewing adverse event rates for the two treatment groups and the population of ciprofloxacin patients should not be directly compared to the population of control patients.

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

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

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

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

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

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

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

The incidence rates of arthropathy increased with increasing age. Among ciprofloxacin patients less than 6 years old, the incidence rate of arthropathy was 5% (12/235); for patients ages 6 to 11 years, the incidence rate was 15% (29/194); for patients ages 12 to 16, the incidence rate was 26% (15/58). Among control patients

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

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

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

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

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

12.17 APPENDIX – Additional Tables from Study 100201

TABLE 1
List of COSTART Terms for the Musculoskeletal System

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

COSTART NUMBER	COSTART TERM
7070015	Tendon Disorder
7070020	Tendon Rupture
7070030	Tenosynovitis
7999998	Diagnostic Procedure
7999999	Surgery

TABLE 2
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
2	EGK	13OCT00	09MAY02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	1	1	1	1	1
				TOTAL	2	2	2	2	2
3	Jannetti	18AUG00	26MAR03	CIPROFLOXACIN	10	9	9	9	8
				COMPARATOR	0	0	0	0	0
				TOTAL	10	9	9	9	8
5	Deeths	07JUL00	11MAY01	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
6	Congeni	25AUG00	17DEC02	CIPROFLOXACIN	5	5	5	5	5
				COMPARATOR	2	2	2	2	2
				TOTAL	7	7	7	7	7
7	Hedrick	08MAY00	22MAY03	CIPROFLOXACIN	14	14	14	14	14
				COMPARATOR	223	223	223	223	221
				TOTAL	237	237	237	237	235
8	Sumerson	07SEP00	15MAY02	CIPROFLOXACIN	3	2	2	2	1
				COMPARATOR	1	1	1	1	1
				TOTAL	4	3	3	3	2
9	Maguire	24APR00	20MAY03	CIPROFLOXACIN	33	33	33	33	32
				COMPARATOR	0	0	0	0	0
				TOTAL	33	33	33	33	32
10	Tarpay	30JUN01	20MAY02	CIPROFLOXACIN	4	4	4	4	4
				COMPARATOR	0	0	0	0	0
				TOTAL	4	4	4	4	4
13	Harmon	17OCT00	19DEC00	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	1	1
15	Chartrand	30SEP00	11FEB02	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3

TABLE 2 (continued)
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
17	Mulcihy	06DEC00	24OCT02	CIPROFLOXACIN	1	1	1	1	0
				COMPARATOR	4	4	4	4	4
				TOTAL	5	5	5	5	4
18	Paredes	14FEB01	18OCT02	CIPROFLOXACIN	9	9	9	9	9
				COMPARATOR	0	0	0	0	0
				TOTAL	9	9	9	9	9
20	SanJoaquin	20NOV01	12JUL02	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
21	Seto	19MAY01	27NOV02	CIPROFLOXACIN	7	7	7	7	6
				COMPARATOR	0	0	0	0	0
				TOTAL	7	7	7	7	6
22	Murphey	24SEP01	09DEC02	CIPROFLOXACIN	9	7	7	7	6
				COMPARATOR	0	0	0	0	0
				TOTAL	9	7	7	7	6
23	Heilman	29MAY01	16JUL01	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	1	1
25	Oca	19MAY00	07FEB03	CIPROFLOXACIN	43	42	42	42	39
				COMPARATOR	59	58	58	58	57
				TOTAL	102	100	100	100	96
27	Lieberman	23MAY00	21FEB03	CIPROFLOXACIN	24	24	24	24	23
				COMPARATOR	1	1	1	1	1
				TOTAL	25	25	25	25	24
28	Bui	21JUN00	30OCT02	CIPROFLOXACIN	5	4	4	4	4
				COMPARATOR	9	8	8	8	5
				TOTAL	14	12	12	12	9
29	Mitchell	31JUL00	28MAY03	CIPROFLOXACIN	20	18	18	18	17
				COMPARATOR	2	2	2	2	2
				TOTAL	22	20	20	20	19

TABLE 2 (continued)
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
30	Sharma	23FEB01	07APR03	CIPROFLOXACIN	8	8	8	8	8
				COMPARATOR	2	2	2	2	2
				TOTAL	10	10	10	10	10
31	Schechtman	12AUG00	13SEP02	CIPROFLOXACIN	37	37	37	37	32
				COMPARATOR	1	1	1	1	1
				TOTAL	38	38	38	38	33
32	Melamed	21AUG00	03FEB03	CIPROFLOXACIN	33	33	33	33	30
				COMPARATOR	4	4	4	4	4
				TOTAL	37	37	37	37	34
35	Arrieta	18OCT99	03APR03	CIPROFLOXACIN	15	12	12	12	11
				COMPARATOR	0	0	0	0	0
				TOTAL	15	12	12	12	11
36	Rathore	08MAR01	25APR01	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	1	1
37	Slavin	19OCT00	18MAR02	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
38	Stavola	13SEP00	03OCT02	CIPROFLOXACIN	7	6	6	6	5
				COMPARATOR	3	3	3	3	3
				TOTAL	10	9	9	9	8
39	Stolovitzky	29SEP00	26NOV01	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3
40	McKinney, Jr.	11SEP01	24APR02	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3
42	Flynn	28AUG01	01NOV02	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	1	1	1	1	1
				TOTAL	3	3	3	3	3

TABLE 2 (continued)
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
43	Hawa	22AUG00	15JUL02	CIPROFLOXACIN	11	8	8	8	7
				COMPARATOR	0	0	0	0	0
				TOTAL	11	8	8	8	7
44	Bradburn	08AUG00	11DEC00	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
45	Wolff	08SEP00	31JUL02	CIPROFLOXACIN	4	4	4	4	4
				COMPARATOR	0	0	0	0	0
				TOTAL	4	4	4	4	4
46	Griffin	28JUL00	27MAR01	CIPROFLOXACIN	4	4	4	4	4
				COMPARATOR	0	0	0	0	0
				TOTAL	4	4	4	4	4
47	Anderson	15JUN01	08NOV02	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	15	14	14	14	13
				TOTAL	18	17	17	17	16
49	Saiman	26OCT00	17OCT02	CIPROFLOXACIN	7	7	7	7	6
				COMPARATOR	1	1	1	1	1
				TOTAL	8	8	8	8	7
50	Patel	24OCT00	12NOV02	CIPROFLOXACIN	14	14	14	14	9
				COMPARATOR	11	11	11	11	9
				TOTAL	25	25	25	25	18
51	Sindel	27SEP00	23OCT02	CIPROFLOXACIN	11	10	10	10	8
				COMPARATOR	1	1	1	1	1
				TOTAL	12	11	11	11	9
52	Casale	09JUL01	16OCT02	CIPROFLOXACIN	9	9	9	9	9
				COMPARATOR	0	0	0	0	0
				TOTAL	9	9	9	9	9
54	Pollara	02MAY02	10JAN03	CIPROFLOXACIN	4	4	4	4	4
				COMPARATOR	1	1	1	1	1
				TOTAL	5	5	5	5	5

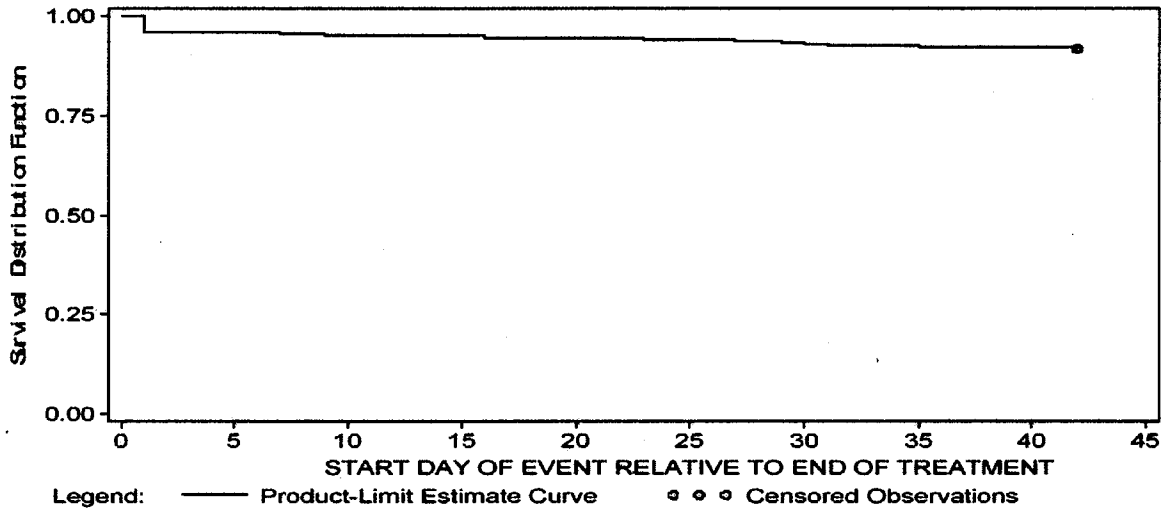
TABLE 2 (continued)
Patient Enrollment by Center

CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
56	Johnson	06APR01	26JUN01	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
57	Weisse	25OCT00	15MAY02	CIPROFLOXACIN	9	8	8	8	6
				COMPARATOR	0	0	0	0	0
				TOTAL	9	8	8	8	6
58	Chaudhary	27APR01	10MAY02	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3
59	Norris	26SEP00	15FEB01	CIPROFLOXACIN	3	3	3	3	2
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	2
61	Krieger	28JUL01	04DEC01	CIPROFLOXACIN	2	2	2	2	2
				COMPARATOR	0	0	0	0	0
				TOTAL	2	2	2	2	2
63	Molina	02NOV00	16DEC02	CIPROFLOXACIN	30	27	27	27	27
				COMPARATOR	0	0	0	0	0
				TOTAL	30	27	27	27	27
64	Phillips	19FEB01	15NOV01	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3
65	Ayoub	01MAY01	21JAN03	CIPROFLOXACIN	4	4	4	4	3
				COMPARATOR	0	0	0	0	0
				TOTAL	4	4	4	4	3
66	Plaire	10AUG01	30OCT02	CIPROFLOXACIN	6	5	5	5	5
				COMPARATOR	1	1	1	1	1
				TOTAL	7	6	6	6	6
67	Nachman	17JUL01	11FEB03	CIPROFLOXACIN	10	10	10	10	10
				COMPARATOR	0	0	0	0	0
				TOTAL	10	10	10	10	10

TABLE 2 (continued)
Patient Enrollment by Center

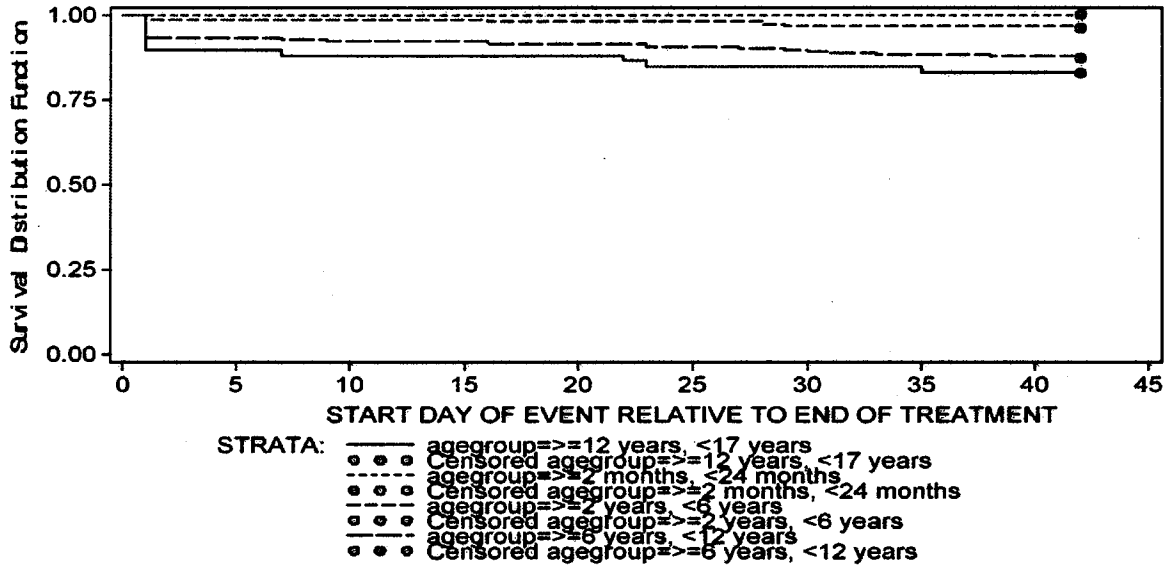
CENTER	INVESTIGATOR	START OF ENROLLMENT	DATE OF LAST VISIT	TREATMENT	NUMBER OF PATIENTS ENTERED	VALID FOR SAFETY	ITT	PER PROTOCOL	COMPLETED STUDY
68	Iezzi	12FEB01	12FEB01	CIPROFLOXACIN	1	1	1	1	0
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	1	0
69	Rolston	27MAR02	14OCT02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	1	1	1	1	1
				TOTAL	2	2	2	2	2
70	Alter	27NOV01	10DEC02	CIPROFLOXACIN	3	3	3	3	3
				COMPARATOR	0	0	0	0	0
				TOTAL	3	3	3	3	3
73	Abdel-Mageed	07AUG01	05APR02	CIPROFLOXACIN	6	6	6	6	4
				COMPARATOR	0	0	0	0	0
				TOTAL	6	6	6	6	4
76	Lavoie	28MAR02	02DEC02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	9	9	9	9	7
				TOTAL	10	10	10	10	8
77	Diamond	19AUG02	19AUG02	CIPROFLOXACIN	1	1	1	1	0
				COMPARATOR	0	0	0	0	0
				TOTAL	1	1	1	1	0
78	Abughali	27FEB02	18JUL02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	6	6	6	6	6
				TOTAL	7	7	7	7	7
79	Rajan	03APR02	20NOV02	CIPROFLOXACIN	4	4	4	4	3
				COMPARATOR	1	1	1	1	1
				TOTAL	5	5	5	5	4
80	Fennelly	11APR02	19MAR03	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	19	17	17	17	17
				TOTAL	20	18	18	18	18
81	Menendez	11APR02	09OCT02	CIPROFLOXACIN	1	1	1	1	1
				COMPARATOR	3	3	3	3	3
				TOTAL	4	4	4	4	4

FIGURE 1
Survival Curve for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
Ciprofloxacin Treated Patients Valid for Safety



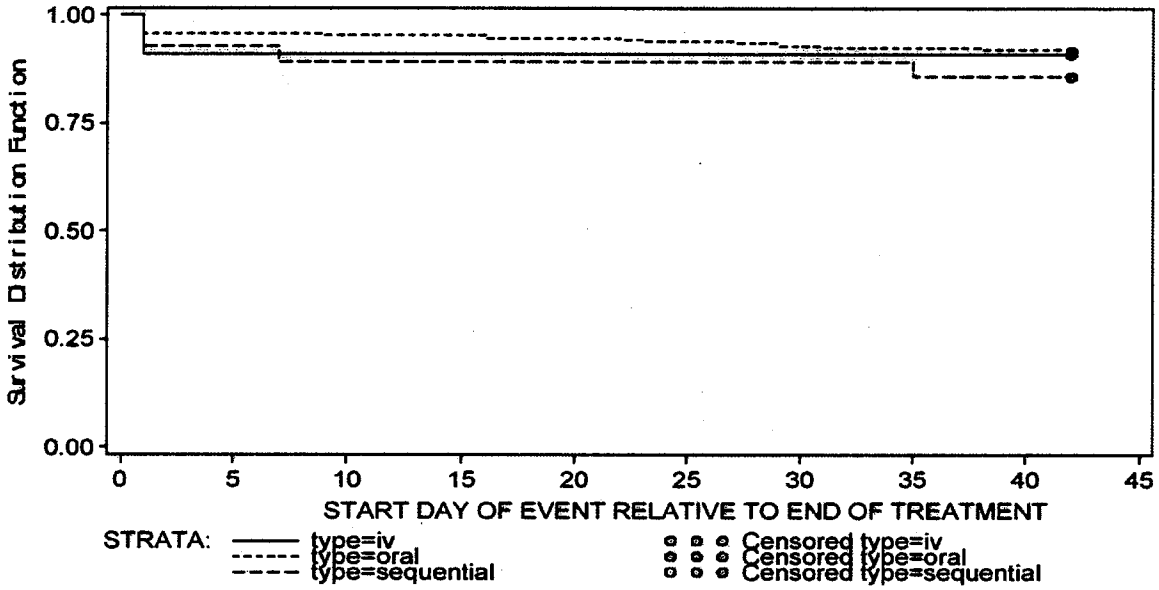
NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DAY

FIGURE 2
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
By Age Group
Ciprofloxacin Treated Patients Valid for Safety



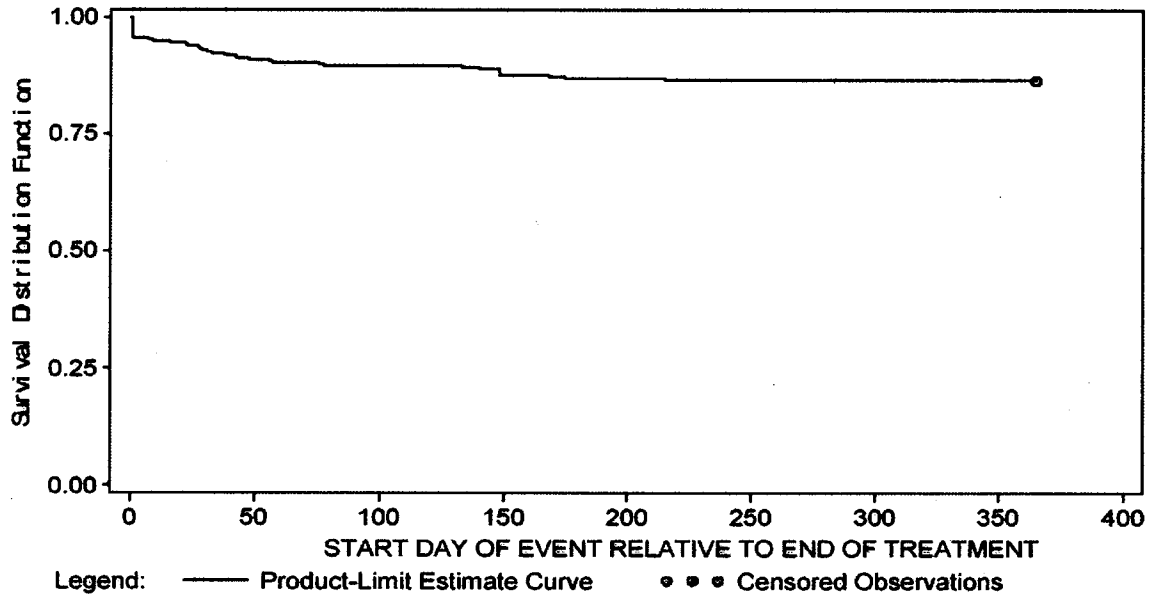
NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DAY 1

FIGURE 3
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
By Treatment Route (Oral, IV, Sequential)
Ciprofloxacin Treated Patients Valid for Safety



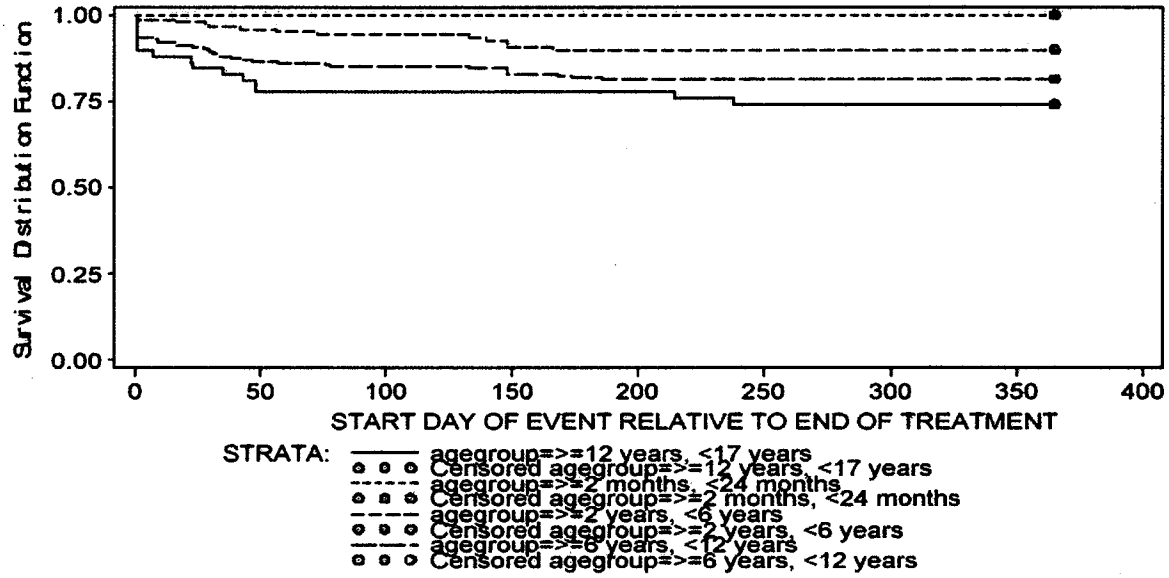
NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DAY 1

FIGUE 4
Survival Curve for Time to Musculoskeletal Event (Including Arthopathy) by One Year
Ciprofloxacin Treated Patients Valid for Safety



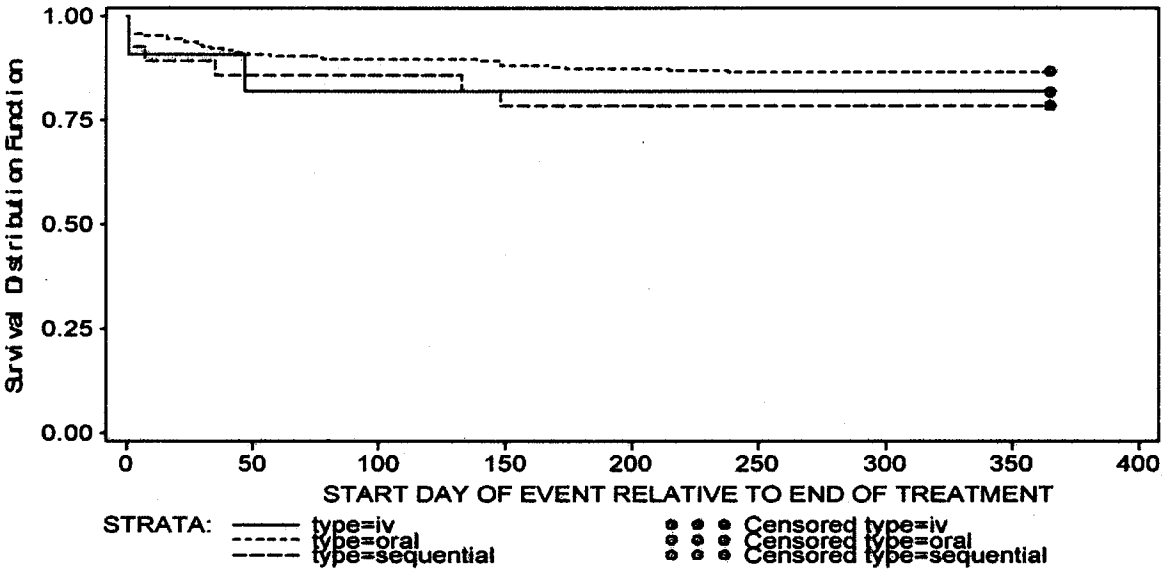
NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DAY

FIGURE 5
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by One Year By Age Group
Ciprofloxacin Treated Patients Valid for Safety



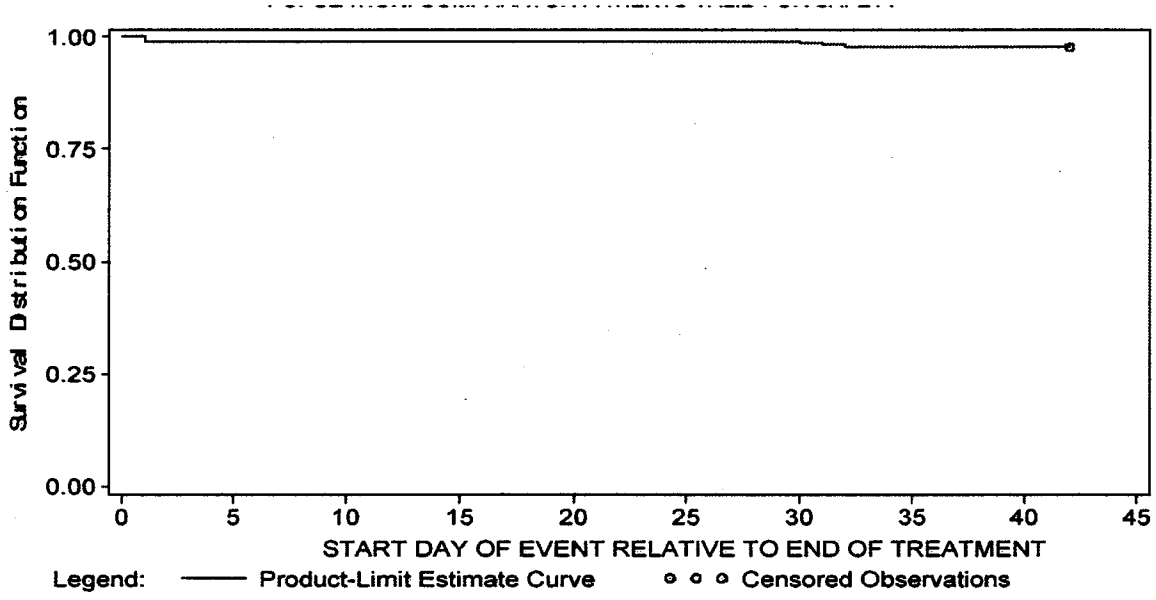
NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DAY

FIGUE 6
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by One Year By Treatment Route (Oral, IV, Sequential)
Ciprofloxacin Treated Patients Valid for Safety



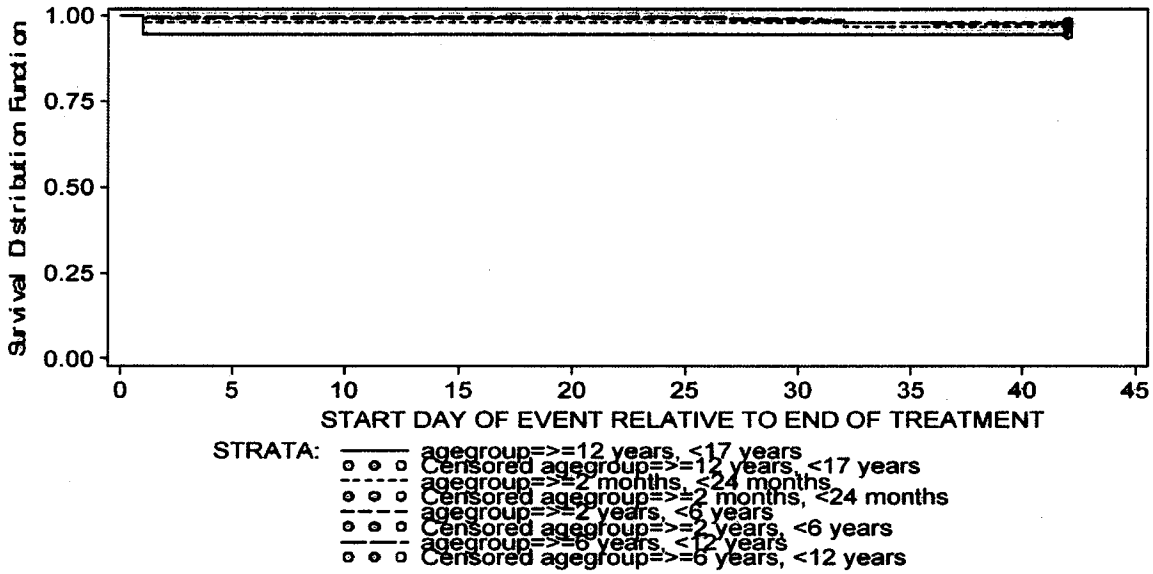
NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DA

FIGURE 7
Survival Curve for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
Control Treated Patients Valid for Safety



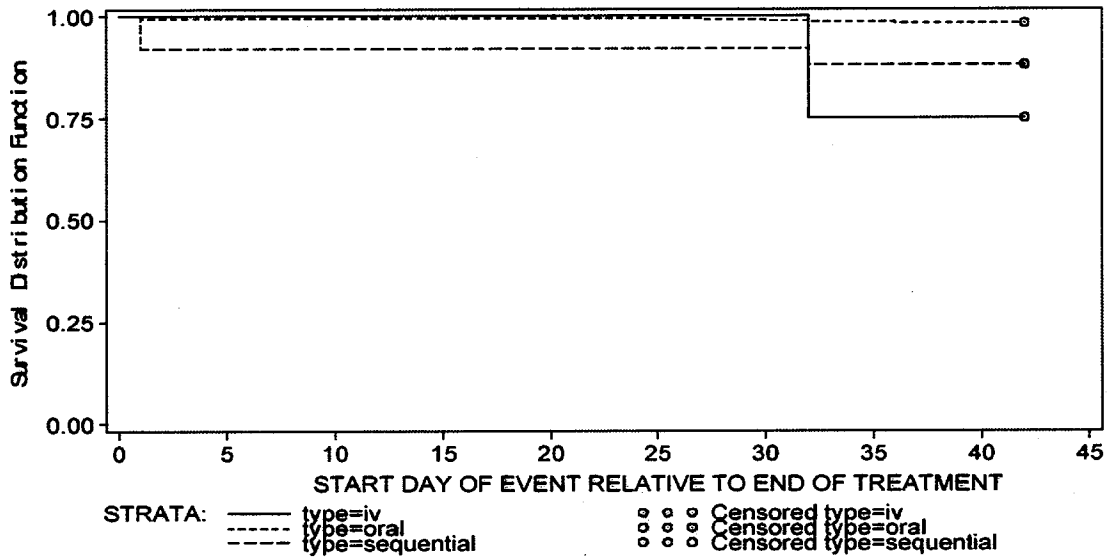
NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DAY

FIGURE 8
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
By Age Group
Control Treated Patients Valid for Safety



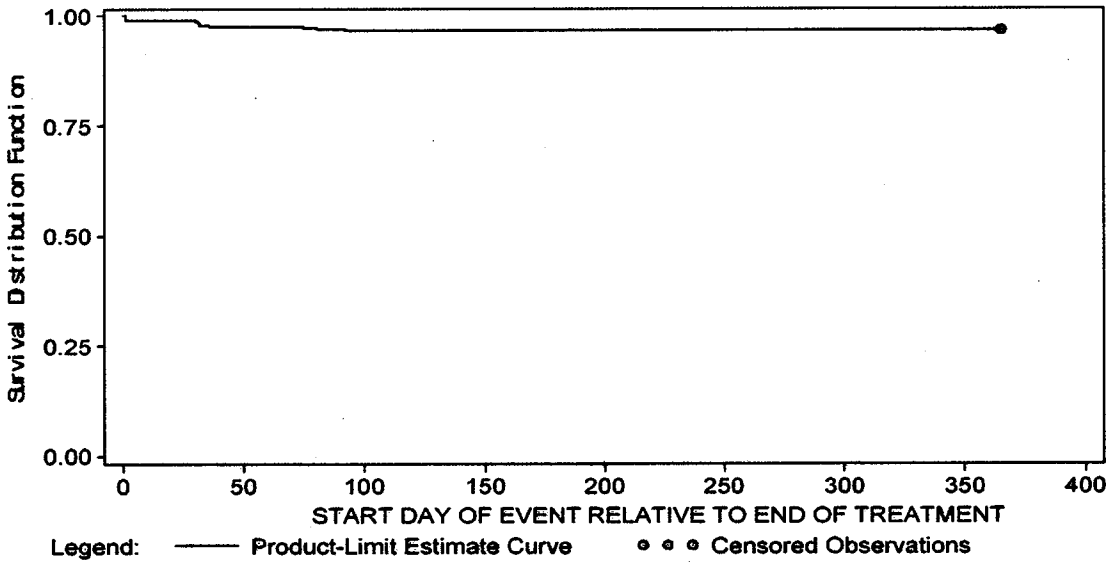
NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DA

FIGURE 9
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by Day +42
By Treatment Route (Oral, IV, Sequential)
Control Treated Patients Valid for Safety



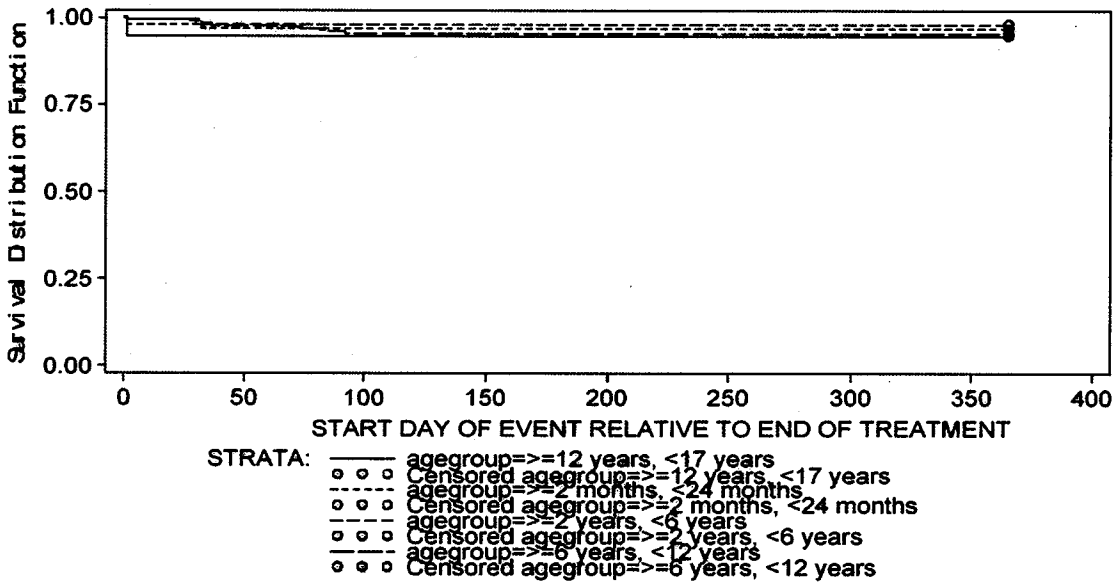
NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DAY 1

FIGURE 10
Survival Curve for Time to Musculoskeletal Event (Including Arthopathy) by One Year
Control Treated Patients Valid for Safety



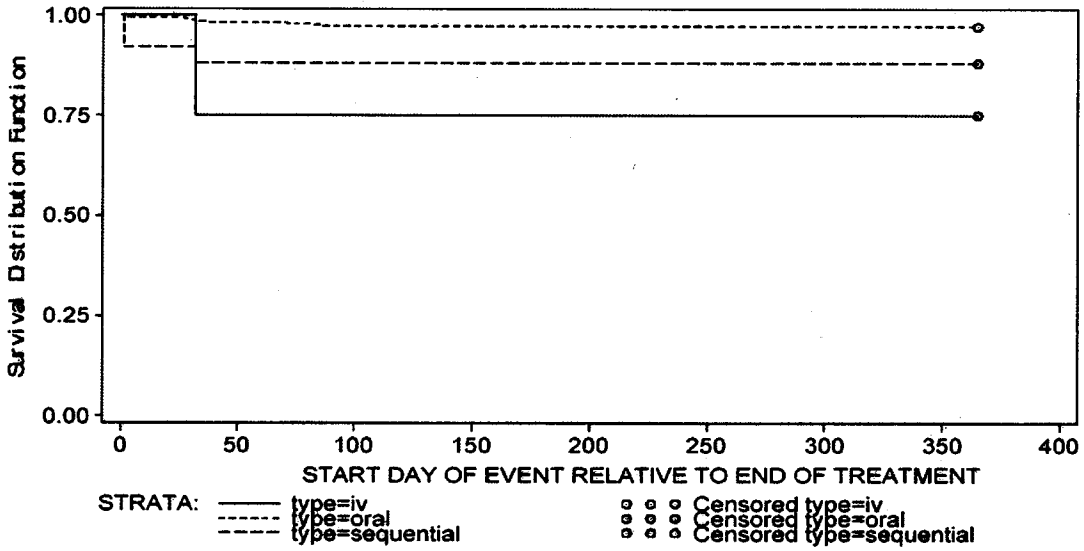
NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DAY 1

FIGURE 11
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by One Year
By Age Group
Control Treated Patients Valid for Safety



NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DAY 1

FIGURE 12
Survival Curves for Time to Musculoskeletal Event (Including Arthopathy) by One Year
By Treatment Route (Oral, IV, Sequential)
Control Treated Patients Valid for Safety



NOTE: THE AVERAGE TREATMENT GROUP EVENT TIME WAS USED FOR PATIENTS WITH MISSING TIMES
NOTE: EVENT TIMES DURING THERAPY WERE SET TO END OF THERAPY DAY 1

TABLE 12
Ciprofloxacin Cases of Arthropathy Occurring by Day +42
as Assessed by the IPSC
[redacted]
ARTHRALGIA as the Event occurring by Day +42
[redacted]

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
80006/F/14	YES[2]	ARTHRALGIA/ Shoulder pain	Pos	Pos	d/c study drug	MILD	-2	8	Associated with swimming; IPSC: paucity of data, in close proximity to study drug, doubt swimming is the only factor	RES
90014/F/4	NO	LEG PAIN/ L thigh pain	Pos	Pos	None	MILD	42	1	Noted on ROM exam, possibly growing pains; IPSC: resolved in one day, unusual for arthropathy, growing pains not usually in thighs	RES
		ARTHRALGIA/ L knee pain			None	MILD	42	1		RES
170001/M/2	NO	ARTHRALGIA/ L ankle tenderness	Pos	Pos	None	MILD	-8	9	Pt. had been playing with siblings and rolling around on the ground with a ball; resolved on therapy IPSC: could be trauma or "reactive arthritis" due infection (not study drug).	RES
		ARTHRALGIA/ L knee tenderness			None	MILD	-8	9		RES
		ARTHROSIS/ L knee swelling			None	MILD	-8	9		RES
[redacted]	UNK	ARTHRALGIA/ Intermittent jaw pain	Pos	NONE	None	SEV	-12	633	X-ray was normal; IPSC: mastoiditis could have been a factor, diagnosis is TMJ	RES
		ARTHRALGIA/ Unable to bend second toe on R			None	MOD	158	Ongoing		UNCH

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		foot								
		ARTHRALGIA/ Intermittent bilateral knee pain (back of knees)			RDT	SEV	158	Ongoing		IMP
290023/F/3	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	Other: MRI (results unknown)	MOD	29	Ongoing		INSUF F/U
[redacted]	UNK	ARTHROSIS/ L knee swelling	Def	Pos	None	MILD	8	2		RES
		ACCIDENTAL INJURY/ L knee sprain			None	MILD	-17	5		RES
		ARTHRALGIA/ R knee pain			RDT: x-ray and MRI (normal)	MILD	166	Ongoing	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	UNCH
		ACCIDENTAL INJURY/ R wrist sprain			RDT: x-ray and MRI (normal)	MILD	166	92		RES
		ARTHRALGIA/ L knee pain			RDT	MILD	52	3	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	RES
350011/M/13	YES[3]	PERIPHERAL EDEMA/ L ankle swelling	Pos	NONE	None	MILD	35	339		RES
		TENDON DISORDER/ R elbow tendonitis			Other: MRI (WNL)	MILD	UNK	≈ 2 years	Present at baseline, exacerbated by pitching baseball	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
350012/M/15	YES[4]	–/ bilateral ankle/foot swelling on joint exam	Pos	Pos	None	–	-6	178	IPSC: could be fluid retention from surgery	RES
350013/F/9	UNK	PERIPHERAL EDEMA/ Bilateral ankle swelling	Prob	Prob	None	MILD	-7	115		RES
350020/F/7	YES[5]	–/ L shoulder pain	Pos	NONE			-1	51	IPSC: pre-existing and may have been due to pneumonia and not arthropathy	RES
[redacted]	YES[6]	ARTHRALGIA/ Bilateral elbow pain	Pos	Pos	None	MILD	1	UNK	Associated with viral illness	RES
		ARTHRALGIA/ Bilateral wrist pain			None	MILD	1	UNK		RES
		ARTHRALGIA/ R hip pain			None	MILD	82	UNK		INSUF F/U
350023/M/8	YES[7]	ARTHRALGIA/ Ankle pain	Pos	NONE	None	MILD	UNK	Ongoing		INSUF F/U
		ARTHRALGIA/ Knee pain			None	MILD	UNK	Ongoing		INSUF F/U
		ARTHRALGIA/ Shoulder pain			None	MILD	UNK	Ongoing		INSUF F/U
380006/F/10	NO	ARTHRALGIA/ Jaw pain	Pos	Pos	d/c study drug	MOD	-1	5	Described as feeling like "pins and needles" by pt.	RES
400049/F/11	NO	ARTHRALGIA/ Intermittent L shoulder pain	Pos	Pos	None	MILD	0	6		RES
490054/F/15	YES[8]	–/L shoulder pain/tenderness on joint exam	Pos	Pos	None	–	-10	57		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		–/ R ankle/foot pain on joint exam			None	–	-10	Ongoing		IMP
580001/F/6	UNK	–/ R shoulder tenderness on joint exam	Pos	Pos	None	–	-12	45	IPSC: baseline exam showed tenderness of R shoulder (study drug started one day earlier)	RES
[redacted]	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	16	2		RES
		ARTHRALGIA/ Knee pain			None	MILD	122	UNK		RES
760005/F/14	YES[9]	ARTHRALGIA/ Hip pain	Pos	Pos	Hosp, RDT: IV morphine	SEV	23	UNK	IPSC: myopathy or neuropathy, could be chemo-related (vincristine)	RES
		BACK PAIN/ Back pain			Hosp, RDT: IV morphine	SEV	23	UNK		RES
870053/M/7	YES[10]	–/ R hip pain on joint exam	Pos	Pos	None	–	29	Ongoing	*OF NOTE: IPSC was inadvertently unblinded to study drug*	INSUF F/U
		–/ pain in R great toe on joint exam			None	–	29	Ongoing		INSUF F/U
920005/F/9	YES[11]	LEG PAIN/ L heel pain	Pos	Pos	RDT: ibuprofen	MOD	31	15		RES
		ARTHRALGIA/ L knee pain			None	MILD	31	2		RES
9930001/F/10	YES[12]	–/ bilateral hip pain on joint exam	Pos	NONE	None	–	-6	39	Pre-exisiting	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
220001/F/2	NO	ARTHRALGIA/ Elbow pain	Prob	Prob	d/c study drug (due to parent's schedule and not event)	MOD	-6	7		RES
250003/M/9	NO	ARTHRALGIA/ L wrist pain	Prob	NONE	RDT: ibuprofen; Other: X-ray (normal)	MILD	42	3	Accidental injury, pt. wrestling with his brother; IPSC: traumatic arthropathy vs. contusion outside joint	RES
250033/F/13	NO	ARTHRALGIA/ R wrist pain	Prob	Prob	d/c study drug	MILD	-4	UNK	No trauma or injury	IMP
		ARTHRALGIA/ L wrist pain				MILD	24	UNK	Dx by rheum: tenosynovitis vs. overuse syndrome due to gymnastics	IMP
[redacted]	NO	ARTHRALGIA/ Bilateral knee pain	Prob	Pos	RDT: Ibuprofen and APAP	MOD	-14	66		RES
		ARTHRALGIA/ Bilateral ankle pain			RDT	MOD	-14	66		RES
		ARTHRALGIA/ Pains on ankles			RDT	MILD	301	481		RES
		ARTHRALGIA/ Knee pains			RDT	MILD	301	481	Pain at rest and increased with ambulation and most prominent when knees were straight	RES
290007/F/13	YES[13]	ARTHRALGIA/ L shoulder pain	Prob	Pos	Other: referred to rheum	MILD	22	23		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
400033/M/11	YES[15]	ARTHRALGIA/ R knee pain	Prob	Pos	None	MOD	16	22	IPSC: hard to distinguish neuro from joint findings	RES
460001/F/10	YES[16]	ARTHRALGIA/ L wrist pain	Prob	Pos	RDT: ibuprofen	MOD	-4	8	wrist fracture about 2 months prior	RES
		ARTHRALGIA/ R knee pain			RDT: ibuprofen	MOD	-4	8	History of R knee strain	RES
870056/M/5	NO	ARTHRALGIA/ Aching in knees	Prob	Pos	RDT: ibuprofen	MOD	16	16	Intermittent pain, no change in exam or ROM	RES
870060/F/8	NO	SYNOVITIS/ Synovitis of hip	Prob	Prob	None	MILD	9	11		RES
60003/F/9	NO	ARTHRALGIA/ L ankle pain	Def	NONE	RDT: APAP	MILD	38	8	Accidental injury (pt. injured ankle cheerleading and playing on the trampoline)	RES
210004/F/11	YES[17]	ARTHRALGIA/ L elbow pain	Def	NONE	None	MOD	-11	3	Pt. had L elbow and shoulder pain pre-existing; IPSC: pt. has ALL which is associated with intermittent polyarthralgia. OF	RES
		ARTHRALGIA/ L shoulder pain			None	MOD	-10	2		RES
		ARTHRALGIA/ L elbow pain			None	MILD	-5	7		RES
		ARTHRALGIA/ L elbow pain			None	MILD	6	3	*OF NOTE: IPSC inadvertently unblinded to study drug*	RES
[redacted]	UNK	ARTHRALGIA/ Jaw pain	Def	Pos	RDT: morphine	SEV	47	5	Possible vincristine toxicity; IPSC: can not exclude study drug (although remote)	RES
		JOINT DISORDER/ Stiffness in hands and fingers			None	MILD	0	12	IPSC: Pts with ALL have a lot of intermittent polyarthralgia	RES
		JOINT DISORDER/			None	MILD	7	Ongoing	*OF NOTE: IPSC inadvertently unblinded to*	UNCH

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		Intermittent bilateral stiffness of shoulders							*study drug*	
270046/M/10	YES[18]	ACCIDENTAL INJURY/ L wrist sprain	Def	NONE	None	MILD	27	7	Accidental injury (pt. fell off bike and sprained wrist)	RES
300011/M/6	NO	ARTHRALGIA/ L elbow pain	Pos	Pos	None	MILD	0	1		RES
320002/F/11	NO	ARTHRALGIA/ Soreness in knees	Def	Pos	RDT: APAP	MILD	30	1		RES
350015/F/12	YES[19]	ARTHRALGIA/ R ankle pain	Def	NONE	None	MOD	-11	3	Pre-existing injury	RES
		ARTHRALGIA/ R ankle pain			Other: referred to rheum	MILD	27	6	OF NOTE: IPSC inadvertently unblinded to study drug	RES
		PERIPHERAL EDEMA/ R ankle swelling			Other: Referred to rheum	MILD	27	6		RES
370010/M/3	NO	ARTHRALGIA/ R knee pain	Def	NONE	Other:	MOD	28	7	Accidental injury (pt. drove into the side of a house on his battery-operated moped)	RES
		ACCIDENTAL INJURY/ R knee injury			Other:	MOD	28	43		RES
790011/M/16	UNK	ARTHROSIS/ R knee swelling	Def	Prob	RDT: rofecoxib	MOD	7	12	IPSC: ALL patients have a lot of polyarthralgia	RES
		ARTHRALGIA/ R knee pain			RDT: rofecoxib	MOD	7	12	OF NOTE: IPSC inadvertently unblended to study drug	RES
[redacted]	YES[20]	--/ bilateral foot/ankle swelling	Def	Pos	None	--	-10	83	IPSC: pts. With syringe-myelomeningocele may have neuropathic joints	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		ARTHRALGIA/ Hip pain				MILD	70	Ongoing		UNCH

KEY for Table 12(Study 100201)

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

[1] redness of L ankle/foot on baseline joint exam due to puncture wound, accounting for abnormal gait
[2] history of fractured tibia and fractured L radius (on different occasions) and ongoing hip apin
[3] swelling of R elbow noted at baseline on joint exam
[4] bilateral ankle/foot swelling at baseline joint exam
[5] history of intermittent lower back pain and shin pain
[6] abnormal gait at baseline
[7] abnormal gait at baseline (pt. states he was heavily medicated post-surgery)
[8] abnormal gait at baseline
[9] ataxic gait at baseline (s/p craniospinal radiation therapy for medulloblastoma)
[10] abnormal gait at baseline
[11] pain in L hip at baseline (attributed to cellulites)
[12] bilateral hip pain at baseline
[13] no baseline gait assessment; gait exam on therapy was abnormal (genu valgus bilaterally and knee hyperextension bilaterally)
[15] history of meningomyelocele, release of tethered cord (twice), groin pain
[16] history of L wrist pain/Colles fracture of radium and ulnar
[17] history of L elbow and shoulder pain intermitently
[18] gait assessment at baseline was abnormal (patient was felling ill with nausea and dizziness)
[19] patient sprained R ankle two day before beginning study drug
[20] abnormal gait at baseline, bilateral feet in valgus; history of spina bifida, syringomyelomeningocele

TABLE 13
Comparator Cases of Arthropathy Occurring by Day +42
as Assessed by the IPSC
[redacted]
ARTHRALGIA as the Event occurring by Day +42

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
70085/M/11	NO	ARTHRALGIA/ R wrist pain	Pos	Pos	None	MILD	27	5	IPSC: history of wrist fracture, but should be healed	RES
70101/M/11	NO	ARTHRALGIA/ R knee pain	Pos	Pos	None	MILD	30	88		RES
70104/F/5	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MOD	31	236	Soft tissue and tibial tuberosity tenderness	RES
500026/M/1	UNK	--/ R hip pain/tenderness on joint exam	Pos	Pos	None	--	-6	42	IPSC: difficult to assess due to age, present at baseline (2 days after study drug started)	RES
500032/M/1.5	UNK	--/ R hip pain/tenderness on joint exam	Pos	Pos	None	--	-7	41	IPSC: present at baseline (1 day after study drug started), paucity of data	RES
870025/M/2	UNK	--/ bilateral knee tenderness	Pos	Pos	None	--	-9	42	IPSC: present at baseline (1 day after study drug started)	RES
870034/F/11	NO	--/ abnormal gait assessment	Pos	NONE	None	--	36	Ongoing	Accidental injury (pt. hurt hip while playing)	INSUF F/U
910007/M/6	UNK	--/ L hip tenderness on joint exam	Pos	Pos	None	--	-7	40	IPSC: present at baseline (4 days after study drug started)	RES
280018/F/14	NO	TENDON DISORDER/	Prob	Prob	RDT: analgesic	MILD	-6	5	IPSC: not warming up in sports, spondyloarthritis	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		Bilateral Achillean tendonitis								

TABLE 21
Ciprofloxacin Cases of Arthropathy as Assessed by the IPSC Occurring between Day 42 and 1 Year of Follow-Up
[redacted]
ARTHRALGIA as the Event occurring after Day 42
[redacted]

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
60001/M/13	NO	NECK PAIN	Pos	Pos	None	MILD	48	9	IPSC: can not exclude arthropathy, mostly likely myalgia and not joint related	RES
		BACK PAIN			None	MILD	48	9		RES
70062/M/14	YES[1]	MYALGIA/ Bilateral knee muscle pain	Pos	Pos	None	SEV	48	34	Association with exercising in the pool; IPSC: poor quality data, can not exclude arthropathy, ↓ ROM in shoulder not likely as per ortho consult	RES
		MYALGIA/ Bilateral shoulder muscle pain			None	SEV	48	34		RES
[redacted]	UNK	ARTHRALGIA/ Intermittent jaw pain	Pos	NONE	None	SEV	-12	633	X-ray was normal; IPSC: mastoiditis could have been a factor, diagnosis is TMJ	RES
		ARTHRALGIA/ Unable to bend second toe on R foot			None	MOD	158	Ongoing		UNCH
		ARTHRALGIA/ Intermittent bilateral knee pain (back of knees)			RDT	SEV	158	Ongoing	IPSC: Too remote to be drug related	IMP
290002/F/4	NO	–/ R hip pain with abduction on joint exam	Pos	Pos	None	MOD	154	86		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
[redacted]	UNK	ARTHROSIS/ L knee swelling	Def	Pos	None	MILD	8	2		RES
		ACCIDENTAL INJURY/ L knee sprain			None	MILD	-17	5		RES
		ARTHRALGIA/ R knee pain			RDT: x-ray and MRI (normal)	MILD	166	Ongoing	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	UNCH
		ACCIDENTAL INJURY/ R wrist sprain			RDT: x-ray and MRI (normal)	MILD	166	92		RES
		ARTHRALGIA/ L knee pain			RDT	MILD	52	3	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	RES
310011/F/4	NO	ARTHRALGIA/ Bilateral knee pain	Pos	NONE	None	MILD	73	89		RES
		LEG PAIN/ L upper leg pain			RDT	MILD	367	17		RES
		ARTHRALGIA/ Hip pain			None	MILD	377	7		RES
		BACK PAIN/ Back pain			RDT	MILD	378	1		RES
310016/F/4	UNK	ARTHRALGIA/ R ankle pain	Pos	Pos	RDT: ibuprofen and APAP	MILD	179	Ongoing	No pattern or consistency to pains	INSUF F/U
		ARTHRALGIA/			RDT:	MOD	179	ongoing		INSUF

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		R knee pain			ibuprofen and APAP					F/U
320004/ F/3	NO	ARTHRALGIA/ Joint pain in knees	Pos	NONE	None	MILD	166	16		RES
320032/F/11	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	57	Ongoing		INSUF F/U
[redacted]	YES[6]	ARTHRALGIA/ Bilateral elbow pain	Pos	Pos	None	MILD	1	UNK	Associated with viral illness	RES
		ARTHRALGIA/ Bilateral wrist pain			None	MILD	1	UNK		RES
		ARTHRALGIA/ R hip pain			None	MILD	82	UNK		INSUF F/U
[redacted]	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	16	2		RES
		ARTHRALGIA/ Knee pain			None	MILD	122	UNK		RES
630005/F/10	NO	ARTHRALGIA/ Pain in fingers and back	Pos	NONE	None	MILD	186	34		RES
640008/F/5	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	None	MOD	56	16		RES
830089/F/10	NO	-/ bilateral knee pain	Pos	Pos	RDT: APAP	–	78	Ongoing	IPSC: paucity of data	INSUF F/U
[redacted]	NO	ARTHRALGIA/ Bilateral knee pain	Prob	Pos	RDT: Ibuprofen and APAP	MOD	-14	66		RES
		ARTHRALGIA/ Bilateral ankle pain			RDT	MOD	-14	66		RES
		ARTHRALGIA/ Pains on ankles			RDT	MILD	301	481		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		ARTHRALGIA/ Knee pains			RDT	MILD	301	481	Pain at rest and increased with ambulation and most prominent when knees were straight	RES
270024/M/5	NO	ARTHRALGIA/ Knee pain	Prob	NONE	None	MILD	140	68	Dx by rheum: possible trauma; IPSC: not comfortable with trauma dx, too remote to be drug related *OF NOTE: IPSC was inadvertently unblinded to study drug*	RES
320029/ M/11	NO	ARTHRALGIA/ Joint pain in knees	Prob	Pos	None	MILD	76	Ongoing		UNCH
		ARTHRALGIA/ Joint pain			None	MILD	320	62		RES
		ARTHRALGIA/ Bilateral joint pain in knees			None	MILD	79	Ongoing		UNCH
350014/M/6	YES[14]	–/ bilateral knee swelling	Prob	Pos	None	–	168	ongoing	IPSC: chemo agents may have contributed *OF NOTE: IPSC was inadvertently unblinded to study drug*	INSUF F/U
[redacted]	UNK	ARTHRALGIA/ Jaw pain	Def	Pos	RDT: morphine	SEV	47	5	Possible vincristine toxicity; IPSC: can not exclude study drug (although remote)	RES
		JOINT DISORDER/ Stiffness in hands			None	MILD	0	12	IPSC: pts with ALL have a lot of intermittent	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		and fingers							polyarthralgia	
		JOINT DISORDER/ Intermittent bilateral stiffness of shoulders			None	MILD	7	Ongoing	*OF NOTE: IPSC inadvertently unblended to study drug*	UNCH
320001/M/13	NO	BONE DISORDER/ Chondromalacia	Def	NONE	None	MOD	215	Ongoing		INSUF F/U
		BONE DISORDER/ Osgood Schlatter			None	MILD	215	ongoing		INSUF F/U
350021/F/11	UNK	ACCIDENTAL INJURY/ R knee injury	Def	Pos	None	MILD	43	62	IPSC: possible relationship to trauma (dancing and soccer)	RES
420010/F/14	UNK	BONE NECROSIS/ Avascular necrosis of the knees	Def	Pos	Other	MOD	238	Ongoing	IPSC: probably due to steroid use	UNCH
[redacted]	YES[20]	–/ bilateral foot/ankle swelling	Def	Pos	None	–	-10	83	IPSC: pts. With syringe-myelomeningocele may have neuropathic joints	RES
		ARTHRALGIA/ Hip pain				MILD	70	Ongoing		UNCH

KEY for Table 21 (Study 100201)

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

[1] redness of L ankle/foot on baseline joint exam due to puncture wound, accounting for abnormal gait
[6] abnormal gait at baseline
[14] sponsor noted baseline condition, not apparent to reviewer
[20] abnormal gait at baseline, bilateral feet in valgus; history of spina bifida, syringomyelomeningocele

TABLE 22
Comparator Cases of Arthropathy Occuring between Day 42 and 1 Year of Follow-Up as Assessed by the IPSC
[redacted]
ARTHRALGIA as the Event occurring after Day 42

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
70152/M/7	NO	ACCIDENTAL INJURY/ Sprained hip	Pos	None	RDT: ibuprofen, naproxen Other: x-ray (normal)	MOD	92	7	Accidental injury (pt. playing football)	RES
320036/F/8	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	RDT: APAP	MOD	75	Ongoing		INSUF F/U
70130/M/10	NO	ACCIDENTAL INJURY/ R ankle sprained	Def	NONE	RDT: ibuprofen	MOD	71	9		RES
		ACCIDENTAL INJURY/ L ankle sprained			RDT: Tylenol #3 Other: x-ray: lateral soft tissue swelling, crutches, air cast	MOD	136	Ongoing		UNCH
830028/F/9	NO	ARTHRALGIA/ R knee pain	Def	NONE	RDT: APAP, ibuprofen Other: ACE bandage, x-ray (normal)	SEV	85	27	Pt. doesn't stretch before running, symptoms also include ↓ ROM, erythema, joint stiffness, myalgia, swelling and warm joint; IPSC:may be due to	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
									sports activity	

TABLE 25
Ciprofloxacin Patients with Arthropathy by One Year
As Assessed by the IPSC
N= 56

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
60001/M/13	NO	NECK PAIN	Pos	Pos	None	MILD	48	9	IPSC: can not exclude arthropathy, mostly likely myalgia and not joint related	RES
		BACK PAIN			None	MILD	48	9		RES
70062/M/14	YES[1]	MYALGIA/ Bilateral knee muscle pain	Pos	Pos	None	SEV	48	34	Association with exercising in the pool; IPSC: poor quality data, can not exclude arthropathy, ↓ ROM in shoulder not likely as per ortho consult	RES
		MYALGIA/ Bilateral shoulder muscle pain			None	SEV	48	34		RES
80006/F/14	YES[2]	ARTHRALGIA/ Shoulder pain	Pos	Pos	d/c study drug	MILD	-2	8	Associated with swimming; IPSC: paucity of data, in close proximity to study drug, doubt swimming is the only factor	RES
90014/F/4	NO	LEG PAIN/ L thigh pain	Pos	Pos	None	MILD	42	1	Noted on ROM exam, possibly growing pains; IPSC: resolved in one day, unusual for arthropathy, growing pains not usually in thighs	RES
		ARTHRALGIA/ L knee pain			None	MILD	42	1		
170001/M/2	NO	ARTHRALGIA/ L ankle tenderness	Pos	Pos	None	MILD	-8	9	Pt. had been playing with siblings and rolling around on the ground with a ball; resolved on therapy IPSC: could be trauma or "reactive arthritis" due	RES
		ARTHRALGIA/ L knee tenderness			None	MILD	-8	9		RES
		ARTHROSIS/ L knee swelling			None	MILD	-8	9		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
									infection (not study drug).	
210005/M/7	UNK	ARTHRALGIA/ Intermittent jaw pain	Pos	NONE	None	SEV	-12	633	X-ray was normal; IPSC: mastoiditis could have been a factor, diagnosis is TMJ	RES
		ARTHRALGIA/ Unable to bend second toe on R foot			None	MOD	158	Ongoing		UNCH
		ARTHRALGIA/ Intermittent bilateral knee pain (back of knees)			RDT	SEV	158	Ongoing		IMP
290002/F/4	NO	-/ R hip pain with abduction on joint exam	Pos	Pos	None	MOD	154	86		RES
290023/F/3	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	Other: MRI (results unknown)	MOD	29	Ongoing		INSUF F/U
300001/M/12	UNK	ARTHROSIS/ L knee swelling	Def	Pos	None	MILD	8	2		RES
		ACCIDENTAL INJURY/ L knee sprain			None	MILD	-17	5		RES
		ARTHRALGIA/ R knee pain			RDT: x-ray and MRI (normal)	MILD	166	Ongoing	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	UNCH

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		ACCIDENTAL INJURY/ R wrist sprain			RDT: x-ray and MRI (normal)	MILD	166	92		RES
		ARTHRALGIA/ L knee pain			RDT	MILD	52	3	Pt. receiving montly immune globulin; IPSC: immunoglobulins associated with arthropathies	RES
310011/F/4	NO	ARTHRALGIA/ Bilateral knee pain	Pos	NONE	None	MILD	73	89		RES
		LEG PAIN/ L upper leg pain			RDT	MILD	367	17		RES
		ARTHRALGIA/ Hip pain			None	MILD	377	7		RES
		BACK PAIN/ Back pain			RDT	MILD	378	1		RES
310016/F/4	UNK	ARTHRALGIA/ R ankle pain	Pos	Pos	RDT: ibuprofen and APAP	MILD	179	Ongoing	No pattern or consistency to pains	INSUF F/U
		ARTHRALGIA/ R knee pain			RDT: ibuprofen and APAP	MOD	179	ongoing		INSUF F/U
320004/ F/3	NO	ARTHRALGIA/ Joint pain in knees	Pos	NONE	None	MILD	166	16		RES
320032/F/11	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	57	Ongoing		INSUF F/U
350011/M/13	YES[3]	PERIPHERAL EDEMA/	Pos	NONE	None	MILD	35	339		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		L ankle swelling								
		TENDON DISORDER/ R elbow tendonitis			Other: MRI (WNL)	MILD	UNK	≈ 2 years	Present at baseline, exacerbated by pitching baseball	RES
350012/M/15	YES[4]	–/ bilateral ankle/foot swelling on joint exam	Pos	Pos	None	--	-6	178	IPSC: could be fluid retention from surgery	RES
350013/F/9	UNK	PERIPHERAL EDEMA/ Bilateral ankle swelling	Prob	Prob	None	MILD	-7	115		RES
350020/F/7	YES[5]	–/ L shoulder pain	Pos	NONE			-1	51	IPSC: pre-existing and may have been due to pneumonia and not arthropathy	RES
350022/F/11	YES[6]	ARTHRALGIA/ Bilateral elbow pain	Pos	Pos	None	MILD	1	UNK	Associated with viral illness	RES
		ARTHRALGIA/ Bilateral wrist pain			None	MILD	1	UNK		RES
		ARTHRALGIA/ R hip pain			None	MILD	82	UNK		INSUF F/U
350023/M/8	YES[7]	ARTHRALGIA/ Ankle pain	Pos	NONE	None	MILD	UNK	Ongoing		INSUF F/U
		ARTHRALGIA/ Knee pain			None	MILD	UNK	Ongoing		INSUF F/U
		ARTHRALGIA/ Shoulder pain			None	MILD	UNK	Ongoing		INSUF F/U
380006/F/10	NO	ARTHRALGIA/ Jaw pain	Pos	Pos	d/c study drug	MOD	-1	5	Described as feeling like "pins and needles" by pt.	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
400049/F/11	NO	ARTHRALGIA/ Intermittent L shoulder pain	Pos	Pos	None	MILD	0	6		RES
490054/F/15	YES[8]	–/L shoulder pain/tenderness on joint exam	Pos	Pos	None	–	-10	57		RES
		–/ R ankle/foot pain on joint exam			None	–	-10	Ongoing		IMP
580001/F/6	UNK	–/ R shoulder tenderness on joint exam	Pos	Pos	None	–	-12	45	IPSC: baseline exam showed tenderness of R shoulder (study drug started one day earlier)	RES
610001/M/8	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	16	2		RES
		ARTHRALGIA/ Knee pain			None	MILD	122	UNK		RES
630005/F/10	NO	ARTHRALGIA/ Pain in fingers and back	Pos	NONE	None	MILD	186	34		RES
640008/F/5	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	None	MOD	56	16		RES
760005/F/14	YES[9]	ARTHRALGIA/ Hip pain	Pos	Pos	Hosp, RDT: IV morphine	SEV	23	UNK	IPSC: myopathy or neuropathy, could be chemo-related (vincristine)	RES
		BACK PAIN/ Back pain			Hosp, RDT: IV morphine	SEV	23	UNK		RES
830089/F/10	NO	–/	Pos	Pos	RDT:	–	78	Ongoing	IPSC: paucity of data	INSUF

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
		bilateral knee pain			APAP					F/U
870053/M/7	YES[10]	–/ R hip pain on joint exam	Pos	Pos	None	–	29	Ongoing	*OF NOTE: IPSC was inadvertently unblinded to study drug*	INSUF F/U
		–/ pain in R great toe on joint exam			None	–	29	Ongoing		INSUF F/U
920005/F/9	YES[11]	LEG PAIN/ L heel pain	Pos	Pos	RDT: ibuprofen	MOD	31	15		RES
		ARTHRALGIA/ L knee pain			None	MILD	31	2		RES
9930001/F/10	YES[12]	–/ bilateral hip pain on joint exam	Pos	NONE	None	–	-6	39	Pre-existing	RES
220001/F/2	NO	ARTHRALGIA/ Elbow pain	Prob	Prob	d/c study drug (due to parent's schedule and not event)	MOD	-6	7		RES
250003/M/9	NO	ARTHRALGIA/ L wrist pain	Prob	NONE	RDT: ibuprofen; Other: X-ray (normal)	MILD	42	3	Accidental injury, pt. wrestling with his brother; IPSC: traumatic arthropathy vs. contusion outside joint	RES
250033/F/13	NO	ARTHRALGIA/ R wrist pain	Prob	Prob	d/c study drug	MILD	-4	UNK	No trauma or injury	IMP
		ARTHRALGIA/ L wrist pain				MILD	24	UNK	Dx by rheum: tenosynovitis vs. overuse syndrome due to gymnastics	IMP

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
270017/F/8	NO	ARTHRALGIA/ Bilateral knee pain	Prob	Pos	RDT: Ibuprofen and APAP	MOD	-14	66		RES
		ARTHRALGIA/ Bilateral ankle pain			RDT	MOD	-14	66		RES
		ARTHRALGIA/ Pains on ankles			RDT	MILD	301	481		RES
		ARTHRALGIA/ Knee pains			RDT	MILD	301	481	Pain at rest and increased with ambulation and most prominent when knees were straight	RES
270024/M/5	NO	ARTHRALGIA/ Knee pain	Prob	NONE	None	MILD	140	68	Dx by rheum: possible trauma; IPSC: not comfortable with trauma dx, too remote to be drug related *OF NOTE: IPSC was inadvertently unblinded to study drug*	RES
290007/F/13	YES[13]	ARTHRALGIA/ L shoulder pain	Prob	Pos	Other: referred to rheum	MILD	22	23		RES
320029/ M/11	NO	ARTHRALGIA/ Joint pain in knees	Prob	Pos	None	MILD	76	Ongoing		UNCH
		ARTHRALGIA/ Joint pain			None	MILD	320	62		RES
		ARTHRALGIA/ Bilateral joint pain in knees			None	MILD	79	Ongoing		UNCH

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
350014/M/6	YES[14]	–/ bilateral knee swelling	Prob	Pos	None	–	168	ongoing	IPSC: chemo agents may have contributed *OF NOTE: IPSC was inadvertently unblinded to study drug*	INSUF F/U
400033/M/11	YES[15]	ARTHRALGIA/ R knee pain	Prob	Pos	None	MOD	16	22	IPSC: hard to distinguish neuro from joint findings	RES
460001/F/10	YES[16]	ARTHRALGIA/ L wrist pain	Prob	Pos	RDT: ibuprofen	MOD	-4	8	wrist fracture about 2 months prior	RES
		ARTHRALGIA/ R knee pain			RDT: ibuprofen	MOD	-4	8	History of R knee strain	RES
870056/M/5	NO	ARTHRALGIA/ Aching in knees	Prob	Pos	RDT: ibuprofen	MOD	16	16	Intermittent pain, no change in exam or ROM	RES
870060/F/8	NO	SYNOVITIS/ Synovitis of hip	Prob	Prob	None	MILD	9	11		RES
60003/F/9	NO	ARTHRALGIA/ L ankle pain	Def	NONE	RDT: APAP	MILD	38	8	Accidental injury (pt. injured ankle cheerleading and playing on the trampoline)	RES
210004/F/11	YES[17]	ARTHRALGIA/ L elbow pain	Def	NONE	None	MOD	-11	3	Pt. had L elbow and shoulder pain pre-existing; IPSC: pt. has ALL which is associated with intermittent polyarthralgia. OF *OF NOTE: IPSC inadvertently unblinded to study drug*	RES
		ARTHRALGIA/ L shoulder pain			None	MOD	-10	2		RES
		ARTHRALGIA/ L elbow pain			None	MILD	-5	7		RES
		ARTHRALGIA/ L elbow pain			None	MILD	6	3		RES
210015/M/11	UNK	ARTHRALGIA/ Jaw pain	Def	Pos	RDT: morphine	SEV	47	5	Possible vincristine toxicity; IPSC: can not exclude study	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
									drug (although remote)	
		JOINT DISORDER/ Stiffness in hands and fingers			None	MILD	0	12	IPSC: pts with ALL have a lot of intermittent polyarthralgia	RES
		JOINT DISORDER/ Intermittent bilateral stiffness of shoulders			None	MILD	7	Ongoing	*OF NOTE: IPSC inadvertently unblinded to study drug*	UNCH
270046/M/10	YES[18]	ACCIDENTAL INJURY/ L wrist sprain	Def	NONE	None	MILD	27	7	Accidental injury (pt. fell off bike and sprained wrist)	RES
300011/M/6	NO	ARTHRALGIA/ L elbow pain	Pos	Pos	None	MILD	0	1		RES
320001/M/13	NO	BONE DISORDER/ Chondromalacia	Def	NONE	None	MOD	215	Ongoing		INSUF F/U
		BONE DISORDER/ Osgood Schlatter			None	MILD	215	ongoing		INSUF F/U
320002/F/11	NO	ARTHRALGIA/ Soreness in knees	Def	Pos	RDT: APAP	MILD	30	1		RES
350015/F/12	YES[19]	ARTHRALGIA/ R ankle pain	Def	NONE	None	MOD	-11	3	Pre-existing injury	RES
		ARTHRALGIA/ R ankle pain			Other: referred to rheum	MILD	27	6	*OF NOTE: IPSC inadvertently unblinded to study drug*	RES
		PERIPHERAL EDEMA/ R ankle swelling			Other: Referred to rheum	MILD	27	6		RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
350021/F/11	UNK	ACCIDENTAL INJURY/ R knee injury	Def	Pos	None	MILD	43	62	IPSC: possible relationship to trauma (dancing and soccer)	RES
370010/M/3	NO	ARTHRALGIA/ R knee pain	Def	NONE	Other:	MOD	28	7	Accidental injury (pt. drove into the side of a house on his battery-operated moped)	RES
		ACCIDENTAL INJURY/ R knee injury			Other:	MOD	28	43		RES
420010/F/14	UNK	BONE NECROSIS/ Avascular necrosis of the knees	Def	Pos	Other	MOD	238	Ongoing	IPSC: probably due to steroid use	UNCH
790011/M/16	UNK	ARTHROSIS/ R knee swelling	Def	Prob	RDT: rofecoxib	MOD	7	12	IPSC: ALL patients have a lot of polyarthralgia	RES
		ARTHRALGIA/ R knee pain			RDT: rofecoxib	MOD	7	12	*OF NOTE: IPSC inadvertently unblinded to study drug*	RES
9930010/M/8	YES[20]	--/ bilateral foot/ankle swelling	Def	Pos	None	--	-10	83	IPSC: pts. With syringe-myelomeningocele may have neuropathic joints	RES
		ARTHRALGIA/ Hip pain				MILD	70	Ongoing		UNCH

KEY for Table 25 (Study 100201)

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

[1] redness of L ankle/foot on baseline joint exam due to puncture wound, accounting for abnormal gait
[2] history of fractured tibia and fractured L radius (on different occasions) and ongoing hip apin
[3] swelling of R elbow noted at baseline on joint exam
[4] bilateral ankle/foot swelling at baseline joint exam
[5] history of intermittent lower back pain and shin pain
[6] abnormal gait at baseline
[7] abnormal gait at baseline (pt. states he was heavily medicated post-surgery)
[8] abnormal gait at baseline
[9] ataxic gait at baseline (s/p craniospinal radiation therapy for medulloblastoma)
[10] abnormal gait at baseline
[11] pain in L hip at baseline (attributed to cellulites)
[12] bilateral hip pain at baseline
[13] no baseline gait assessment; gait exam on therapy was abnormal (genu valgus bilaterally and knee hyperextension bilaterally)
[14] sponsor noted baseline condition, not apparent to reviewer
[15] history of meningomyelocele, release of tethered cord (twice), groin pain
[16] history of L wrist pain/Colles fracture of radium and ulnar
[17] history of L elbow and shoulder pain intermitently
[18] gait assessment at baseline was abnormal (patient was felling ill with nausea and dizziness)
[19] patient sprained R ankle two day before beginning study drug
[20] abnormal gait at baseline, bilateral feet in valgus; history of spina bifida, syringomyelomeningocele

TABLE 26
Comparator Patients with Arthropathy by One Year
As Assessed by the IPSC
N= 13

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
70085/M/11	NO	ARTHRALGIA/ R wrist pain	Pos	Pos	None	MILD	27	5	IPSC: history of wrist fracture, but should be healed	RES
70101/M/11	NO	ARTHRALGIA/ R knee pain	Pos	Pos	None	MILD	30	88		RES
70104/F/5	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MOD	31	236	Soft tissue and tibial tuberosity tenderness	RES
70152/M/7	NO	ACCIDENTAL INJURY/ Sprained hip	Pos	None	RDT: ibuprofen, naproxen Other: x-ray (normal)	MOD	92	7	Accidental injury (pt. playing football)	RES
320036/F/8	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	RDT: APAP	MOD	75	Ongoing		INSUF F/U
500026/M/1	UNK	--/ R hip pain/tenderness on joint exam	Pos	Pos	None	--	-6	42	IPSC: difficult to assess due to age, present at baseline (2 days after study drug started)	RES
500032/M/1.5	UNK	--/ R hip pain/tenderness on joint exam	Pos	Pos	None	--	-7	41	IPSC: present at baseline (1 day after study drug started), paucity of data	RES
870025/M/2	UNK	--/ bilateral knee tenderness	Pos	Pos	None	--	-9	42	IPSC: present at baseline (1 day after study drug started)	RES

Pt #/ Sex/Age in yrs	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
870034/F/11	NO	-/ abnormal gait assessment	Pos	NONE	None	–	36	Ongoing	Accidental injury (pt. hurt hip while playing)	INSUF F/U
910007/M/6	UNK	-/ L hip tenderness on joint exam	Pos	Pos	None	–	-7	40	IPSC: present at baseline (4 days after study drug started)	RES
280018/F/14	NO	TENDON DISORDER/ Bilateral Achillean tendonitis	Prob	Prob	RDT: analgesic	MILD	-6	5	IPSC: not warming up in sports, spondyloarthritis	RES
70130/M/10	NO	ACCIDENTAL INJURY/ R ankle sprained	Def	NONE	RDT: ibuprofen	MOD	71	9		RES
		ACCIDENTAL INJURY/ L ankle sprained			RDT: Tylenol #3 Other: x-ray: lateral soft tissue swelling, crutches, air cast	MOD	136	Ongoing		UNCH
830028/F/9	NO	ARTHRALGIA/ R knee pain	Def	NONE	RDT: APAP, ibuprofen Other: ACE bandage, x-ray (normal)	SEV	85	27	Pt. doesn't stretch before running, symptoms also include ↓ ROM, erythema, joint stiffness, myalgia, swelling and warm joint; IPSC:may be due to sports activity	RES

KEY for Table 26 (Study 100201)

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

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/s/

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