KEY for Table 20 (Study 100169)

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

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

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

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

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

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

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

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

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

KEY for Table 21 (Study 100169)

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

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

TABLE 24
Ciprofloxacin Cases of Arthropathy Occurring by Day +42 as Assessed by the IPSC
[redacted]
ARTHRALGIA as the Event occurring by Day +42
[redacted]

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

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

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

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

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

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

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

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

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

KEY for Table 24 (Study 100169)

Pos = possible, Prob = probable; Def = definite
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Unk = unknown; Hosp = hospitalization; RDT = remedial drug therapy;
Mod = Moderate; Sev = severe
Res = Resolved; Unch = unchanged; Insuf f/u = insufficient follow-up; Imp = improved
-- = information not available

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

TABLE 25
Comparator Cases of Arthropathy Occurring by Day +42 as Assessed by the IPSC
[redacted]
ARTHRALGIA as the Event occurring by Day +42
[redacted]

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

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

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

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

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

KEY for Table 25 (Study 100169)

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

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

TABLE 27
Ciprofloxacin Cases of Arthropathy as Assessed by the IPSC Occurring between Day 42 and 1 Year of Follow-Up
[redacted]
ARTHRALGIA as the Event occurring after Day 42
[redacted]

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

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										existing)	
			BACK PAIN			Other: x-ray of hips (negative), x-ray of "spinal cord" (negative)	MILD	7	1		RES
			BACK PAIN/ Thoracolumbar pain			None	MILD	404	UNK		RES
			BONE PAIN/Thoracic spine pain			None	MILD	92	UNK		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
			MYASTHENIA/ Muscle weakness			None	MILD	199	72		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
701014/F/11	MEX	NO	LEG PAIN	Pos	NONE	None	MILD	335	29	Eval by physiotherapist (no inflammation problems);	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										IPSC: may be related to toting heavy backpack	
			BACK PAIN			None	MILD	335	30		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]	–/ bilateral ankle and foot tenderness on joint exam	Pos	NONE	None	–	150	273	IPSC: history of ankle pain while running – growing pains or bony abnormality	RES
402052/F/11	PERU	YES[8]	ACCIDENTAL INJURY/ worsening articular hypermotility	Pos	NONE	None	MILD	215	39	Eval by rheuma-tologist: episodic pain in knees lasting for < 1 hour, related to articular hypermotility	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
[redacted]	US	NO	–/ bilateral knee redness and warmth on joint exam	Def	Pos	None	–	-10	14	IPSC: transient arthralgia during infection is not unusual	RES
			–/ bilateral ankle warmth			None	–	4	35		RES
			ARTHRALGIA/ Joint pain, non-specific, generalized			None	MILD	229	10	Pt doing increased physical activity prior to joint pain; normal joint exam	RES
[redacted]	US	NO	ARTHRALGIA/ Bilateral wrist tenderness	Def	Pos	RDT: APAP	MILD	5	3	Associated with wrestling event	RES
			ARTHRALGIA/ L wrist discomfort			None	MILD	9	1		RES
			LEG CRAMPS/ change in knee flexion (stiffness)			RDT: APAP	MILD	5	3		RES
			ARTHRALGIA/ Bilateral wrist discomfort			None	MILD	70	14	Hyper-extended wrists during volleyball	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										game	
1031/F/10	US	NO	LEG PAIN/ R foot arch pain and collapse	Def	NONE	Other	MILD	87	6	Accidental trauma (twisted ankle)	RES
2015/F/7	US	YES[10]	ARTHRALGIA/ L hip arthralgia	Def	Pos	Other	SEV	45	5		RES
			ARTHRALGIA/ Bilateral knee pain			Other	SEV	186	52		RES
			MYALGIA/ Fibromyalgia			RDT	MOD	202	Ongoing		RES
			ACCIDENTAL INJURY/joint hypermobility (wrists/elbows/hips/etc.)			None	MILD	66	Ongoing	Diagnosis performed by rheuma-tologist	UNCH
8001/F/5	US	NO	--/ L ankle swelling noted on joint exam	Def	NONE	None	--	125	242	Accidental trauma (pt. tripped and rolled ankle)	RES
[redacted]	US	NO	ARTHRALGIA/ Knee pain	Pos	Pos	None	MILD	0	3		RES
			ARTHRALGIA/ Bilateral wrist pain			None	MILD	215	19		RES
			ARTHRALGIA/			None	MILD	215			RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
			Bilateral elbow pain						19		
13047/F/9 (Stratum II)	US	NO	ARTHRALGIA/ Bilateral knee pain	Prob	NONE	RDT: ibuprofen	MILD	199	UNK	Accidental trauma (pt. fell on stairs); lost to follow-up	INSUF F/U
[redacted]	US	YES[11]	ARTHRALGIA/ Bilateral intermittent ankle pain	Def	Pos	None	MILD	14	32	Pt. active in sports	RES
			ACCIDENTAL INJURY/ L foot trauma			None	MOD	102	3	Accidental trauma (horse stepped on pt. foot during an equestrian event)	RES
			PAIN/ Bilateral intermittent foot pain			None	MILD	14	32	Pt. active in sports	RES
			ACCIDENTAL INJURY/ Lateral-collateral ligament injury			None	MOD	246	217	Accidental trauma (soccer injury)	RES
			ACCIDENTAL INJURY/ R ankle injury			None	MILD	522	1	Accidental trauma (soccer injury)	RES
			ARTHRALGIA/ R knee pain			None	MILD	74	31	Accidental trauma	RES

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
										(soccer injury)	
			LEG PAIN/ Plantar surface heel pain (sports injury)			None	MILD	23	23	Accidental trauma (sports injury)	RES
26018/F/7	US	NO	ARTHRALGIA/ Bilateral knee pain	Pos	Pos	None	MILD	89	93	2 days of ciprofloxacin; IPSC: pain attributed to growing pains; not usually found in knees	RES
44036/F/7	US	YES[14]	ARTHRALGIA/ Bilateral ankle pain	Pos	NONE	None	MILD	370	UNK	2 days of ciprofloxacin; intermittent pain (few times per week and worse after increased activity); IPSC: abnormal spinal cord terminus may be reason for asymmetry on ROM, ankle pain	INSUF F/U

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comment	Arth Outcome
204033/F/8	SA	YES[15]	ARTHRALGIA/ Bilateral painful knees	Def	Pos	Other: Patellar tap (negative)	MILD	331	66	Painful knees at night and after walking long distances	RES
205010/F/4	SA	NO	MOVEMENT DISORDER/ Hip rotation decreased	Pos	NONE	None	MILD	368	UNK	No pain, normal waling pattern; IPSC: not considered significant, baseline values suggest improper positioning	UNCH

KEY for Table 27 (Study 100169)

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

[1]History of R thigh pain
[2]Kyphosis
[6] pain in L hip at quadriceps area and L ankle
[7] History of ankle pain when running
[8] Articular hypermotility
[10] History of pain in leg, back, knee, hip, which was diagnosed as "growing pains"; myelomeningocele
[11]Abnormal gait (decreased hip extension bilaterally); swelling of R and L knees
[14] Abnormal spinal cord terminus @ T12
[15]L shoulder pain

TABLE 28
Comparator Cases of Arthropathy Occuring between Day 42 and 1 Year of Follow-Up as Assessed by the IPSC
[redacted]
ARTHRALGIA as the Event occurring after Day 42
[redacted]

Pt #/ Sex/Age in yrs	Country	Pre-Exist?	COSTART/ Description	Arth Class by IPSC	Relation to Study Drug by IPSC	Action	Severity	Rel Start to End of Tx	Duration (days)	Comments from CRF and IPSC	Arth Outcome
12001/F/14	US	YES[1]	ARTHRALGIA/ Intermittent L knee pain	Def	Pos	RDT: ibuprofen, APAP	MILD	160	Ongoing	Possible retropatellar syndrome	INSUF F/U
13011/F/7 (Stratum II)	US	NO	ARTHRALGIA/ R knee soreness and R ankle warmth	Prob	NONE	None	MILD	363	81	Accidental trauma (pt. fell); Pre-existing condition	RES
2012/F/9	US	NO	MYALGIA/ fibromyalgia	Def	NONE	RDT: APAP, Flexeril	SEV	326	Ongoing	Eval by rheumatologist, dx fibromyalgia	UNCH
33025/M/9	US	NO	ARTHRALGIA/ Bilateral hip pain	Prob	Pos	None	MILD	99	15	Anterior pain with extension; gluteal pain when sitting 30 min	RES
37001/F/4	US	NO	ARTHRALGIA/ L ankle pain	Pos	Pos	Other: x-ray (neg)	MILD	85	12	Noted when running	RES
103015/F/6	CAN	NO	—/ on caregiver questionnaire noted difficulty walking, bending, kneeling, and	Pos	NONE	None	—	192	169	Bilateral knee pain, and ankle/foot pain on joint exam; possibly related to obesity	RES

			stooping; trouble climbing stairs								
306004/F/5	ARG	NO	ARTHRALGIA/ Shoulder pain	Pos	NONE	None	MILD	364	Ongoing		INSUF F/U
			ARTHRALGIA/ Knee pain			None	MILD	364	Ongoing		INSUF F/U
309018/F/9	ARG	YES[10]	--/ elbow pain and weakness in forearm	Pos	NONE	None	--	93	4	Pre-existing	RES
[redacted]	PERU	NO	ARTHRALGIA/ Mechanical gonalgia	Pos	Pos	RDT: topical diclofenac Other: articular protection	MILD	20	25	Dx by rheumatologist	RES
			ARTHRALGIA/ Oligoarthraligia			RDT: topical diclofenac, APAP Other: articular protection measures	MILD	136	15		RES
			ARTHRALGIA/ R ankle arthralgia			None	MILD	257	1	Dx by rheumatologist	RES
			ARTHRALGIA/ Mechanical arthralgia			None	MILD	357	16	Dx by rheumatologist	RES

402007/F/6	PERU	YES[11]	MYALGIA/ Myalgia	Pos	Pos	None	MILD	124	69	Growing pains pre-existing; IPSC: possible myalgia vs. arthralgia	RES
402037/F/12	PERU	YES[13]	ACCIDENTAL INJURY/ Worsening of articular hypermotility	Pos	NONE	None	MOD	159	31	Worsening of pre-existing condition	RES
502008/F/9 (Stratum II)	GER	NO	–/ R ankle pain on joint exam	Pos	NONE	None	–	363	Ongoing	Pt. played soccer on the day prior	INSUF F/U
506009/F/2 (Stratum II)	GER	NO	MOVEMENT DISORDER/ Reduced hip movement	Pos	NONE	Other: ultrasound of both hips (WNL)	MILD	271	Ongoing	IPSC: would have expected fluid on US if arthropathy	INSUF F/U

KEY for Table 28 (Study 100169)

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

[1]Spina bifida occulta; baseline stiff knees and L ankle swelling; gait abnormal
[10]L elbow pain
[11]History of growing pains
[13] articular hypermotility

TABLE 53
Serious Adverse Events by Patient and Treatment Group
Patients Valid for Safety

TREATMENT GROUP	PATIENT	COSTART TERM	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	OUTCOME OF EVENT
CIPROFLOXACIN	1003	OVERDOSE	INCORRECT DOSE OF ST	1	1	RESOLVED
CIPROFLOXACIN	1040	URINARY INCONTINENCE	REPAIR OF NEUROGENIC	11	50	RESOLVED
CIPROFLOXACIN	14001	PYELONEPHRITIS	PYELONEPHRITIS	2	7	RESOLVED
CIPROFLOXACIN	15028	UROGENITAL SURGERY	LEFT PYELOPLASTY	38	38	RESOLVED
CIPROFLOXACIN	16001	PYELONEPHRITIS	PYELONEPHRITIS	43	45	RESOLVED
CIPROFLOXACIN	16001	CONVULSION	ACUTE ONSET SEIZURES	311	316	RESOLVED
CIPROFLOXACIN	16001	OVERDOSE	DILANTIN TOXICITY	329	331	RESOLVED
CIPROFLOXACIN	36002	CONSTIPATION	WORSENING CONSTIPATI	28	118	RESOLVED
CIPROFLOXACIN	36002	ABDOMINAL PAIN	CHRONIC ABDOMINAL DI	28	118	RESOLVED
CIPROFLOXACIN	36002	ASPIRATION PNEUMONIA	ASPIRATION PNEUMONIA	29	33	RESOLVED
CIPROFLOXACIN	201005	UROGENITAL SURGERY	URETHROTOMY	13	16	RESOLVED
CIPROFLOXACIN	301100	MYOPATHY	DUCHENNE DISEASE.	19	.	UNCHANGED
CIPROFLOXACIN	301100	CONVULSION	SEIZURE	112	112	RESOLVED
CIPROFLOXACIN	301100	MYOPATHY	DUCHENNE DISEASE	133	135	UNCHANGED
CIPROFLOXACIN	301213	CONVULSION	SEIZURE ASSOCIATED W	212	212	RESOLVED
CIPROFLOXACIN	303010	HYDROURETER	RIGHT URETER STENOSI	14	33	RESOLVED
CIPROFLOXACIN	303033	ACCIDENTAL INJURY	CRANIUM TRAUMA	46	46	RESOLVED
CIPROFLOXACIN	304001	HYDRONEPHROSIS	HYDRONEFROSIS	28	33	RESOLVED
CIPROFLOXACIN	304004	HYDRONEPHROSIS	HYDRONEFROSIS	49	58	RESOLVED
CIPROFLOXACIN	305007	HYPERTENSION	HYPERTENSION	4	46	RESOLVED
CIPROFLOXACIN	306003	PYELONEPHRITIS	PYELONEPHRITIS(NEPH	5	8	RESOLVED
CIPROFLOXACIN	306005	PYELONEPHRITIS	PIELONEPHRITIS WORSE	2	5	RESOLVED
CIPROFLOXACIN	306005	HEPATITIS	HEPATITIS A	8	37	RESOLVED
CIPROFLOXACIN	306054	PYOGENIC ARTHRITIS	ARTHRITIS SEPTIC ON	63	83	RESOLVED
CIPROFLOXACIN	306056	RESPIRATORY DISORDER	THROAT CUT	24	24	DEATH
CIPROFLOXACIN	307006	INFECTION VIRAL	SYNDROME WITH FEVER,	3	8	RESOLVED
CIPROFLOXACIN	309014	PYELONEPHRITIS	PYELONEPHRITIS	1	5	RESOLVED
CIPROFLOXACIN	505010	URTICARIA	URTICARIA	28	30	RESOLVED
CIPROFLOXACIN	601079	VOMITING	VOMITING	37	41	RESOLVED
CIPROFLOXACIN	601079	PYELONEPHRITIS	PYELONEPHRITIS	37	41	RESOLVED
CIPROFLOXACIN	701032	ACCIDENTAL INJURY	LEFT FEMUR FRACTURE	220	470	RESOLVED
CIPROFLOXACIN	704006	PYELONEPHRITIS	PYELONEPHRITIS	13	18	RESOLVED
CIPROFLOXACIN	707021	CARCINOMA	PINEAL GERMINOM	6	264	IMPROVED
CEFTAZIDIME	15060	SEPSIS	UROSEPSIS	12	16	RESOLVED
CEFTAZIDIME	44030	URINARY TRACT INFECTION	UTI	51	54	RESOLVED
CEFTAZIDIME	303001	PYELONEPHRITIS	ACUTE PYELONEPHRITIS	20	22	RESOLVED
CEFTAZIDIME	303001	URINARY TRACT INFECTION	ASYMPTOMATIC BACTERI	57	61	RESOLVED
CEFTAZIDIME	303046	PYELONEPHRITIS	PYELONEPHRITIS WORSE	3	5	RESOLVED
CEFIXIME	13031	ACCIDENTAL INJURY	CLOSED FRACTURE OF L	53	488	RESOLVED
CEFIXIME	13031	ACCIDENTAL INJURY	CLOSED FRACTURE L FI	53	488	RESOLVED
CEFIXIME	16009	URINARY TRACT INFECTION	BREAKTHROUGH URINARY	10	17	RESOLVED
CEFIXIME	16009	PYELONEPHRITIS	PYELONEPHRITIS	38	43	RESOLVED
CEFIXIME	27005	URINARY TRACT DISORDER	BILATERAL URETERAL R	31	36	RESOLVED
CEFIXIME	28009	HYPERTONIA	HYPERTONIA	120	.	UNCHANGED

TABLE 53 (continued)
Serious Adverse Events by Patient and Treatment Group
Patients Valid for Safety

TREATMENT GROUP	PATIENT	COSTART TERM	INVESTIGATOR TERM	RELATIVE DAY OF EVENT START	RELATIVE DAY OF EVENT STOP	OUTCOME OF EVENT
CEFIXIME	28009	URINARY INCONTINENCE	INCREASING URINARY I	120	238	RESOLVED
CEFIXIME	28009	NEUROPATHY	TETHERED SPINAL CORD	218	218	RESOLVED
CEFIXIME	301080	ACCIDENTAL INJURY	RIGHT ORBIT FRACTURE	228	234	RESOLVED
CEFIXIME	301080	SUBDURAL HEMATOMA	SUBDURAL HEMATOMA.	228	234	RESOLVED
CEFIXIME	301089	PURPURA	SCHONLEIN-HENOCH PUR	275	282	RESOLVED
CEFIXIME	301297	UROGENITAL ANOMALY	BLADDER EXTROPHY REP	12	14	RESOLVED
CEFIXIME	301297	ACCIDENTAL INJURY	LEFT TOE PHALANXÀS F	79	191	RESOLVED
CEFIXIME	301297	ACCIDENTAL INJURY	LEFT TIBIAL FRACTURE	79	191	RESOLVED
CEFIXIME	306024	PENIS DISORDER	PHIMOSIS	24	25	RESOLVED
CEFIXIME	306072	CONVULSION	FEBRILE SEIZURE	205	207	RESOLVED
CEFIXIME	307024	URINARY TRACT DISORDER	URETEROCELE WITH VES	8	28	RESOLVED
CEFIXIME	401098	CEREBRAL HEMORRHAGE	INTRACRANIAL HEMATOM	78	100	RESOLVED
CEFIXIME	401098	CONVULSION	SEIZURES DUE TO HEAD	79	79	RESOLVED
CEFIXIME	402031	CELLULITIS	LEFT SUBMANDIBULAR C	45	52	RESOLVED
CEFIXIME	601009	HYDRONEPHROSIS	RIGHT HYDRONEPHROSIS	14	18	RESOLVED
CEFIXIME	601039	MENINGOMYELOCELE	WORSENING OF MYELOME	273	280	RESOLVED
CEFIXIME	706051	URINARY TRACT INFECTION	URINARY INFECTION RE	21	30	RESOLVED
TMP/SMX 160/800 MG BID	105002	URINARY TRACT INFECTION	PSEUDOMONAS UTI	20	31	RESOLVED

12. APPENDIX 2 - REVIEW OF STUDY 100201 (INTERIM REPORT 100225)

A Prospective, Open-label, Non-randomized, Naturalistic, Long-term Safety Surveillance, Observational Study of Either Ciprofloxacin (either as oral suspension, oral tablets or sequential IV → oral therapy or purely IV therapy) or a Non-Quinolone Antibiotic (either as oral suspension, oral tablets or sequential IV → oral therapy or purely IV therapy) in the Treatment of Pediatric Patients with Infectious Diagnoses

Study Number: 100225 (an interim analysis of Study 100201 of all data collected as of June 30, 2003)
Date of the Study Report: September 12, 2003
Study centers: This study was conducted at 67 study sites in the US and one in Canada.

Period of study (first patient's first visit to last patient's last visit):
April 25, 2000 to June 30, 2003 (interim analysis cut-off date)

12.1 Ethical Conduct of the Study

This study was conducted in accordance with Good Clinical Practice (GCP) regulations and all applicable US FDA regulations, including the archiving of required documents. These practices included the following areas: IRB procedures; informed consent; protocol adherence; administrative documents (Form FDA-1572, etc); drug supply accountability; data collection; subject records (source documents); adverse event recording and reporting; inspection and audit preparation; and records retention. The investigators were made aware that FDA and Bayer representatives could inspect the documents and patient records at any time.

This study was monitored by a contract research organization (CRO), [redacted] in accordance with GCP guidelines and Standard Operating Procedures (SOP) for Bayer and [redacted]

12.2 Study Objectives

The primary objective of this observational study was to obtain long-term post-exposure, follow-up safety data to determine the potential long-term incidence of arthropathy (i.e., pathology of the joint) and other musculoskeletal sequelae (i.e., articular cartilage, tendon and ligament), if any, of IV, sequential (IV→ PO), and purely oral ciprofloxacin therapy or non-quinolone antibiotic therapy in pediatric patients with various infectious conditions. A co-primary objective was to determine the short- and long-term neurological system tolerability of courses of ciprofloxacin or non-quinolone antibiotic therapy.

12.3 Study Design

This observational study was planned to be a prospective, open-label, non-randomized, multi-center, North American pediatric clinical trial to assess long-term musculoskeletal and neurological system health in infants and younger children (i.e., ≤6 years of age at trial entry) for up to 5 years post-exposure to ciprofloxacin or a non-quinolone antibiotic for pre-pubescent and pubescent children and for 1 year post-exposure to ciprofloxacin or non-quinolone antibiotic for post-pubescent children. There were 4 amendments to the original protocol, which are summarized

in the following section. Originally, the study protocol was not designed for a control group. However, a non-quinolone treatment arm was added to this study at the request of the FDA in Amendment 4.

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

Similarly, after the investigator determined that a particular infant or child with an eligible infection was suitable for a non-quinolone antibiotic therapy, the selection of that agent and its unit dose, total daily dose, duration of therapy, route of administration, and formulation (i.e., whether IV, PO tablets or suspension) was left to the discretion of the pediatric investigator.

12.4 Summary of Amendments

There were 4 amendments made to the original protocol dated July 22, 1999 and a summary of the changes accounted for in each amendment are summarized below.

Amendment 1 (December 15, 1999)

- Clarified the timing interval between ciprofloxacin and infant formula (i.e., feeding two hours before or after dosing)
- Corrected discrepancies among the referred to age groups
- Deleted a reference to a data collection instrument other than a CRF
- Provided clarification on performance of required gait/joint examinations and the category of professional evaluator required to perform the exams (physical therapist or rheumatologist)
- Specified the type of intervention (i.e., imaging) to evaluate cases presenting with signs and/or symptoms suggestive of arthropathy
- Added a cap on enrollment of patients in the adolescent age group (a single center should not have enrolled more than 2 patients aged 12 to 16 years of age)
- Clarified the categorization and reporting of adverse events during the long term follow-up

Amendment 2 (July 20, 2000)

- Replaced Joseph Barone, MD (Bayer) with _____ as the Medical Monitor;
- **Extended the permissible window for a patient's pre-therapy gait/joint** examination from 48 hours prior to initiation of study drug therapy up to 24 hours after receipt of the first dose of study drug. This permitted study enrollment in the overnight hours when children presented through the emergency department and qualified physical therapy personnel might not have been available.
- Allowed for enrollment of children reliant on infant formula provided they were treated with IV medication only;
- Corrected a typographical error in the dose strength of the 5% suspension;

- Clarified the exclusion of all children with a diagnosis of cystic fibrosis whether or not this current infection was an exacerbation of the underlying disease;
- Clarified that patients enrolled into Study 100169 (complicated UTI study) could be enrolled into the observational study provided informed consent was provided to allow for retrospective collection of the data from the initial year

Amendment 3 (January 23, 2001)

- Allowed for enrollment of patients up to 72 hours after initiation of study drug treatment;
- Specified provisions for performance of the gait/joint examination when a certified physical therapist was not available;
- Clarified the expectation for documentation of the ROM examination within the CRF;
- Allowed for enrollment of children with febrile neutropenia receiving ciprofloxacin prophylaxis pending recovery of white blood cell (WBC) count to ≥ 500 cells per mm^3;
- Clarified the exclusion of children with cystic fibrosis from the protocol;
- Provided a gait/joint examination flow diagram

Amendment 4 (October 20, 2001)

- Added a non-quinolone arm to the present study. The objective was to obtain information (i.e., assess the "background noise") on musculoskeletal adverse events that could have occurred in this pediatric population had they received treatment with a non-quinolone antibiotic and to monitor these adverse events for the same duration as the ciprofloxacin-treated patients.
- Shortened the long-term follow-up period from 5 to 10 years to 1 to 5 years. Pre-pubescent and pubescent children were to be followed for 5 years and post-pubescent children were to be followed for 1 year. Patients who experienced a musculoskeletal adverse event during therapy were to be followed for 5 years regardless of their stage of pubescence.
- Revised downward the total number of patients to be enrolled from 3,000 to approximately 900 patients. Approximately half (450) of these 900 patients were to be in the ciprofloxacin arm and approximately half (450) in the non-quinolone antibiotic arm. This sample size would provide 95% probability of seeing at least one event that had the event rate of 1 in 250. This is based on combining these 900 patients with at least 600 patients available from another pediatric ciprofloxacin trial (Study 100169).
- Specified demographic and baseline characteristics were to be summarized by treatment group as well as type of ciprofloxacin treatment (IV versus oral), age group (≥ 2 months to < 24 months; 2 years to < 6 years; ≥ 6 years to < 12 years; ≥ 12 years to < 17 years).

The decision to treat with ciprofloxacin or a non-quinolone antibiotic was made prior to a patient's enrollment in the study and was based on the particular infection, type of patient, medical history and the clinical evaluation by the prescribing physician.

This amendment was not intended to change any treatment decisions to be made by the prescribing physician, but merely to add a comparator group of patients who were treated with anon-quinolone antibiotic over the same 1 to 5 year time period as

the treatment group and to document the musculoskeletal and CNS adverse events in both groups.

12.5 Inclusion Criteria

Patients in the age range of 2 months through 16 years of age (i.e., had not reached their 17th birthday) were eligible for enrollment in the study.
A parent/caregiver must have signed an informed consent form, and the patient must have provided assent, as appropriate, based on local IRB guidelines.
Low-risk febrile patients with neutropenia during cancer chemotherapy could be enrolled provided their neutropenia was expected to resolve (>=500 cells per mm^3) within 10 days after the onset of fever. Neutropenic patients with abdominal pain, nausea and vomiting, or diarrhea (passage of 6 loose stools daily) could be enrolled provided they were treated with IV medication and did not meet any of the exclusion criteria.

12.6 Exclusion Criteria

Patients meeting any of the following criteria were not to be enrolled in this study:

- Low-risk patients with febrile neutropenia during cancer chemotherapy who were unstable hemodynamically, had neurological or mental status changes, intravascular catheter infection, catheter tunnel infection, or a new pulmonary infiltrate.
- Underlying diagnosis of or acute exacerbation of cystic fibrosis (CF);
- Acute or chronic meningitis;
- Brain abscess;
- Acute or subacute bacterial endocarditis (ie, ABE or SBE);
- Ciprofloxacin as antimicrobial prophylaxis (except for cases of low-risk febrile neutropenia during cancer chemotherapy);
- Bone and joint infections (e.g., septic arthritis);
- A medical history of one or more of the following conditions:
- Arthritis, not further categorized
- Juvenile rheumatoid arthritis (JRA)
- Rheumatoid arthritis (RA)
- Systemic lupus erythematosis (SLE)
- Spondylitis, of any etiology
- History of rheumatic fever
- Psoriasis
- Inflammatory bowel disease
- Behcet's syndrome
- Chondromalacia
- Hypermobility
- Osteoarthritis (OA);
- Sustained broken bones including small and large bone fractures within 90 days prior to their course of study drug;
- Known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy. Patients with conditions precluding the performance of a reliable series of musculoskeletal examinations were to be excluded from trial participation.

- Patients with any pretreatment baseline musculoskeletal abnormalities on examination;
- Infants and children with spina bifida with: total or near total paralysis of the lower extremities (i.e., motor strength of 0/1+ in the major muscle groups of both lower extremities), and/or who could ambulate only with the recruitment of the upper extremity muscle groups, and/or have associated significant congenital or acquired neuro-orthopedic structural pathology of the lower extremities (i.e., bilateral neuropathic joints, hip dysplasias or dislocations, or arthrogryposis) were to be excluded from trial participation. Enrollment of children with an underlying diagnosis of spina bifida was not to exceed 20% of the target enrollment. [The applicant was to notify centers at the time enrollment of spina bifida patients was to be stopped.]
- Known risk of experiencing seizures, a history of any convulsive disorders or head injury/trauma, current use of anti-seizure medication or within 2 months post-stroke;
- Concomitant systemic antibacterial agents known to have arthropathic effects. Patients could not receive additional quinolone therapy during the observational period during which they received ciprofloxacin for the trial.
- Participation in any industry-sponsored clinical drug development study within one month prior to this study. An exception was infants, children and adolescents enrolled into the ciprofloxacin pediatric complicated UTI study (Study 100169). These patients did not receive treatment with a second course of ciprofloxacin or a new course of a non-quinolone antibiotic; rather they could be enrolled into the observational trial at any time during the initial year of the study since the musculoskeletal information collected for the 100169 study was identical to that required by Protocol 100201. Informed consent was to be provided to allow for retrospective collection of data from the initial year.
- Known significant liver impairment (ALT or AST and/or baseline bilirubin >3 times the upper limit of the normal range);
- Known significant renal insufficiency (calculated creatinine clearance of <30 mL/min/1.73 m^2);
- Pregnant or lactating, or sexually active with unreliable contraception. Sexually active females were to use reliable contraception or abstinence during exposure to study drug. Reliable contraception could include barrier methods (e.g., condoms, diaphragms, intra-uterine devices, implants). Patients taking oral contraceptives were to use barrier contraception with spermicidal foam or abstinence during study drug exposure.
- Reliant on infant formula for nutrition such that dosing of study medication two hours before or after a feeding would not be possible. Patients reliant on formula feedings were eligible for enrollment provided they received IV antibiotics for the entire course of treatment.
- For those patients in the non-quinolone antibiotic arm, there could not be a previous history of quinolone use, or a known allergy to the non-quinolone antibiotic (or related class of non-quinolone antibiotic) being prescribed or treatment with Ceclor® (cefaclor).
- No single center could enroll more than 2 patients aged 12 through 16 years.

12.7 Removal of Patients from Therapy or Assessment

If the patient did not show improvement within 2 to 5 days (therapeutic failure), or if a serious allergic reaction occurred or a superinfection developed, ciprofloxacin or non-quinolone antibiotic therapy was to be discontinued and other appropriate therapy initiated.

All patients who discontinued therapy prematurely, including those who received only one dose of study drug, continued to undergo prospective musculoskeletal and neurological system safety assessments (i.e., periodic examination of the weight-bearing joints and shoulder girdle, gait, and other neurological assessments and caregiver questionnaires).

12.8 Treatments Administered

Investigators were to consider the child's age and renal functional status in the selection of a ciprofloxacin dosing regimen. When administered as an oral formulation, the recommended dose of ciprofloxacin was 5 to 20 mg/kg every 12 hours (q12h), depending upon the severity of infection. When administered as an IV formulation, the recommended dose of ciprofloxacin was 6 mg/kg q12h or 12mg/kg q8h, depending on the severity of infection. The maximum permissible doses in this study were 750 mg twice daily orally (i.e., total daily dose 1500 mg) or 400 mg 3 times daily intravenously (i.e., total daily dose 1200 mg) and were not to be exceeded. Investigators were referred to the approved product labeling (i.e., package insert for US sites or product monograph for Canadian sites) for the dosages and frequency of administration of ciprofloxacin within a 24-hour period.

When treatment was with a non-quinolone antibiotic, investigators were to adhere to the prescribing and dosing information found in the approved package label (i.e., package insert for US sites or product monograph for Canadian sites) or the Physicians. Desk Reference (US sites) or Compendium of Pharmaceuticals and Specialties (Canadian sites). In all cases, the maximum daily dose for the prescribed non-quinolone antibiotic was not to be exceeded.

In general, ciprofloxacin therapy was to be administered for a minimum duration of 7 days and a maximum duration of 21 days, and similarly, the non-quinolone-treated patients were to have comparable treatment durations.

Supplies of the study drug ciprofloxacin (ciprofloxacin IV, ciprofloxacin oral tablets and ciprofloxacin oral suspension) or non-quinolone antibiotics were not provided by the sponsor; study supplies were provided by the clinical sites. Medication was dispensed in commercial packaging.

12.9 Prior and Concomitant Therapy

Efforts were to be made to minimize the total number of concomitant drugs (of any kind) administered to the patient during the duration of ciprofloxacin or non-quinolone antibiotic medication administration. All concomitant medications were recorded on the CRF.

Antibacterial agents were not to be administered concomitantly with study medication. Investigators were to avoid the use of fluoroquinolone antibiotics (including ciprofloxacin) or a non-quinolone antibiotic in all study patients following termination or completion of their prescribed drug regimen through completion of the long term follow-up, insofar as clinically feasible, and provided that a fluoroquinolone or non-quinolone antibiotic were not absolutely clinically indicated at any time during the follow-up period.

Prohibited drugs are listed in the package labeling for ciprofloxacin, which recommends cautious use of concomitant administration of sulfonylurea glyburide, fenbufen, and probenecid. If concomitant administration of theophylline and ciprofloxacin could not be avoided, serum levels of theophylline were to be monitored and dosage adjustments made as appropriate. If oral anticoagulants were administered concomitantly with ciprofloxacin, prothrombin time (PT) or other suitable coagulation tests were to be closely monitored. In rare instances, some quinolones, including ciprofloxacin, have been reported to interact with phenytoin leading to altered levels of serum phenytoin concentrations. Concurrent administration of antacids (containing magnesium, aluminum or calcium), sucralfate, iron supplements, and zinc-containing vitamins with ciprofloxacin were to be avoided. Likewise, the administration of infant formula with ciprofloxacin oral suspension was to be avoided. Should concurrent administration be necessary, ciprofloxacin oral suspension was to be given 2 hours before or after a formula feeding. Quinolones, including ciprofloxacin, have also been shown to interfere with the metabolism of caffeine.

The investigators were referred to approved package inserts (US sites) or product monographs (Canadian sites) or full prescribing information as found in The Physicians. Desk Reference (US sites) or Compendium of Pharmaceuticals and Specialties (Canadian sites) for non-quinolone antibiotics and their distinctive drug interactions and warnings.

12.10 Treatment Compliance

In the case of hospitalized patients, medication administration record (MAR) sheets were to be reviewed to determine whether patients were compliant with the prescribed dosing regimen. For those outpatients treated with ciprofloxacin tablets or oral suspension or for those in the non-quinolone antibiotic group, caregivers were instructed to report both the number of days and doses of oral ciprofloxacin or non-quinolone antibiotic which their infant or child received. This information was collected at the required one-month follow-up visit (Day +28 to +42).

All patients who received at least one dose of the prescribed study regimen (regardless of the initially intended duration and frequency of dosing) were considered valid for safety and were to be followed as per protocol.

12.11 Efficacy and Safety Variables

The incidence of arthropathy as a musculoskeletal system adverse event was specifically evaluated. In addition, neurological system adverse event incidence rates were documented. The definition of arthropathy was generally considered as any condition affecting a joint or periarticular tissue where there is historical and/or

physical evidence for structural damage and/or functional limitation that may have been temporary or permanent. This definition was seen as broad and inclusive of such phenomena as bursitis, enthesitis and tendonitis.

The Independent Pediatric Safety Committee (IPSC) determined the arthropathy classification (i.e., definite, probable, possible, none), relationship of arthropathy to study drug therapy (i.e., definite, probable, possible, none, not assessable), and if there were any pre-existing conditions that may/may not have been exacerbated during study. Their assessments of arthropathy classification, relationship of arthropathy to study drug therapy, and possible pre-existing conditions were used for the statistical analyses described in this study.

Parent-reported musculoskeletal and neurological system adverse event incidence rates as documented on the questionnaires initially and later through telephone interviews at 3 months, 6 months, 9 months, and 12 months for the first year post-exposure and were performed quarterly as well for up to one year for post-pubescent children or five years for pre-pubescent and pubescent children. Patients who experienced a musculoskeletal adverse event during therapy were to be followed for 5 years regardless of their stage of pubescence.

12.11.1 Efficacy and Safety Measurements

To fulfill the primary objective of the study and to determine the clinical safety of ciprofloxacin or non-quinolone antibiotic in pediatric patients, two structured assessments for general, neurological and musculoskeletal safety, i.e., evaluations of the joints (especially all weight-bearing joints) and gait, were required. These were to be conducted within 72 hours of initiation of ciprofloxacin or non-quinolone antibiotic administration, which **was considered a patient's baseline, and at the 1-month follow-up (Day** +28 to +42).

Baseline Visit
Patients had a routine physical examination including neurological assessment performed at the time of study enrollment. If patients started ciprofloxacin therapy or non-quinolone antibiotic within 72 hours prior to study enrollment, it was expected that a thorough history of musculoskeletal and neurological events, including events occurring during the time of ciprofloxacin or non-quinolone antibiotic administration which preceded study enrollment, were recorded in both source documents and on the study CRF. Patients also had a gait/joint examination to assess the range of motion (ROM) of the weight-bearing joints (in particular, the hip, knee and ankle) as well as the shoulder girdle. Parents/caregivers were also asked to complete a short questionnaire concerning their child.s health status and to provide brief details of family history. For the non-quinolone antibiotic group, there was to be confirmation of no prior exposure to quinolone therapy.

Follow Up Visit (Day +28 to +42)
Patients were seen again approximately 4 to 6 weeks (Day +28 to +42) following the course of ciprofloxacin or non-quinolone antibiotic therapy in the office to assess whether there had been any changes in gait, ROM, or

neurological exam. On completion of this visit, the role of the enrolling clinical site was completed, unless a problem was detected during telephone interviews in which case the child was referred back to the clinical site.

Telephone Contact
Patients/caregivers then were interviewed by telephone at 3, 6, 9, and 12 months (of the first year) and quarterly each year thereafter for the purpose of long-term follow-up of musculoskeletal and neurological system status checks.

During the treatment phase, the 1-month follow-up, and the long-term surveillance period, parents/caregivers were provided with a phone number to call in the event their child developed musculoskeletal or neurological symptoms. A triage specialist, who was to assess such events and recommend appropriate follow-up, including specialist referrals, was assigned to answer these calls. The primary focus of this trial was assessment of the musculoskeletal and neurological safety of ciprofloxacin or non-quinolone antibiotics in pediatric patients.

12.11.2 Follow-Up for Musculoskeletal Adverse Events

All serious adverse events reported spontaneously or by the investigator, were reported through the 1-month follow-up visit (Day +28 to +42, inclusive). The reporting of all non-serious and serious adverse events beyond the structured 1-month follow-up visit during the long-term surveillance (i.e., registry) phase of the child's participation was primarily the responsibility of the parent or caregiver.

The musculoskeletal safety assessments were carried out primarily through objective evaluations of joint appearance, structure and function (i.e., ROM testing) and of gait conducted by either rheumatologists or trained physical therapists experienced in musculoskeletal examinations. If the physical therapist and rheumatologist were unavailable at the time of enrollment, the examination could have been conducted by a physician trained in gait/joint examination conduct. This training was to include the review of a videotape provided by the applicant which demonstrated proper passive ROM measurements for each of the joints of interest.

Formal physical examination of all joints was performed; however, special care and attention were given to the weight-bearing joints (i.e., knees, hips, and ankles) and to the shoulder girdle. Joints were examined for pain/tenderness, evidence of inflammation (i.e., redness, warmth, swelling or ballotable fluid), loss of function (to the extent this could be assessed in younger children and infants) and any restrictions to expected active/passive ROM. Both active and passive ROM were always to be assessed. Passive ROM was recorded in the CRF. For shoulders, knees, hips and ankles, the motions tested and their normal ranges recorded were as follows:

- Shoulder: extension, flexion, abduction, internal and external rotation
- Hip: extension, flexion, adduction, abduction, internal and external rotation
- Knees: extension and flexion
- Ankles/feet: plantar flexion, dorsiflexion

Any post-baseline abnormal finding noted on the clinical joint or gait assessment was followed up by a pediatric rheumatology consultation as appropriate. Pending a determination of objective clinical findings by the pediatric rheumatologist, further diagnostic procedures, including performance of an MRI on clinically affected joint(s) (as well as of contralateral non-affected joints, potentially), could be recommended and **offered to the patient's parent or guardian based upon the pediatric rheumatologist's recommendations.**

During the study, subjective complaints spontaneously volunteered by both patients and by their parents or caregivers, especially those attributable to the musculoskeletal and neurological systems, were carefully recorded and followed up with additional objective clinical assessments as warranted. In addition, telephone interviews completed **by the patient's parent or caregiver were performed at 3, 6, 9, and 12** months during the first year post-exposure and, thereafter, performed quarterly as well for up to 1 year for post-pubescent children (older children) or 5 years for prepubescent and pubescent children. Patients who experienced a musculoskeletal adverse event during therapy were to be followed for 5 years regardless of their stage of pubescence. Primary **responsibility for documenting and reporting the child's health throughout the post-exposure follow-up rested with the child's parent or caregiver, to** ensure continuity of assessment over a long time span of observation.

The study flow chart is presented in Figure 1.

FIGURE 1
Study Flow Chart

	Pre-treatment	Post-treatment		
	(Within 48 hours of dosing)	Day +28 to +42 after end of treatment (first follow-up visit)	First Year Post-Exposure Follow-up (ie, Day +355 to +375) Quarterly Modular Assessments	Long-term Follow-up (Years 2 to 5)[a] Quarterly Modular Assessments
Informed consent	I			
Check of inclusion/exclusion criteria	I			
Patient demography	I			
Medical History	I			
Physical examination	I	I	< ---------- I[b] ---------- >	
Gait/joint exam	I	I[c]	< ---------- I[b] ---------- >	
Pediatric or Adolescent Neurological System Exam	I	I	< ---------- I[b] ---------- >	
Pregnancy Test: urine/serum[d]	I	I	< ---------- I[b] ---------- >	
Parental Assessment (Data Module) Completion			C	C
Telephone Contacts			< ---------- C ---------- >	
Adverse event monitoring[e]		I/C[f]	< ---------- (I,C)[g] ---------- >	
Serious AE monitoring[e]		I/C[h]	< ---------- (I, C)[g] ---------- >	
Documentation of concomitant therapy and procedures[e]			< ---------- (I, C)[g] ---------- >	

The symbol "I" represents assessments primarily carried out by the investigator.
The symbol "C" represents assessments carried out by the patient's parent or caregiver.

a Prepubescent and pubescent children were to be followed for 5 years and post-pubescent children were to be followed for 1 year. (Amendment 4, dated October 30, 2001)

b To be performed by the investigator, as warranted and practicable.

c See gait/joint diagram in Figure 9-2. In case of complaints/abnormal findings, appropriate intervention was to be initiated.

d Older female children and female adolescent patients of childbearing potential could be enrolled based upon a negative urine pregnancy test performed in the clinic. In this group, a serum pregnancy test was also performed at the pre-treatment baseline and was repeated at the follow-up visit (Day +28 to +42).

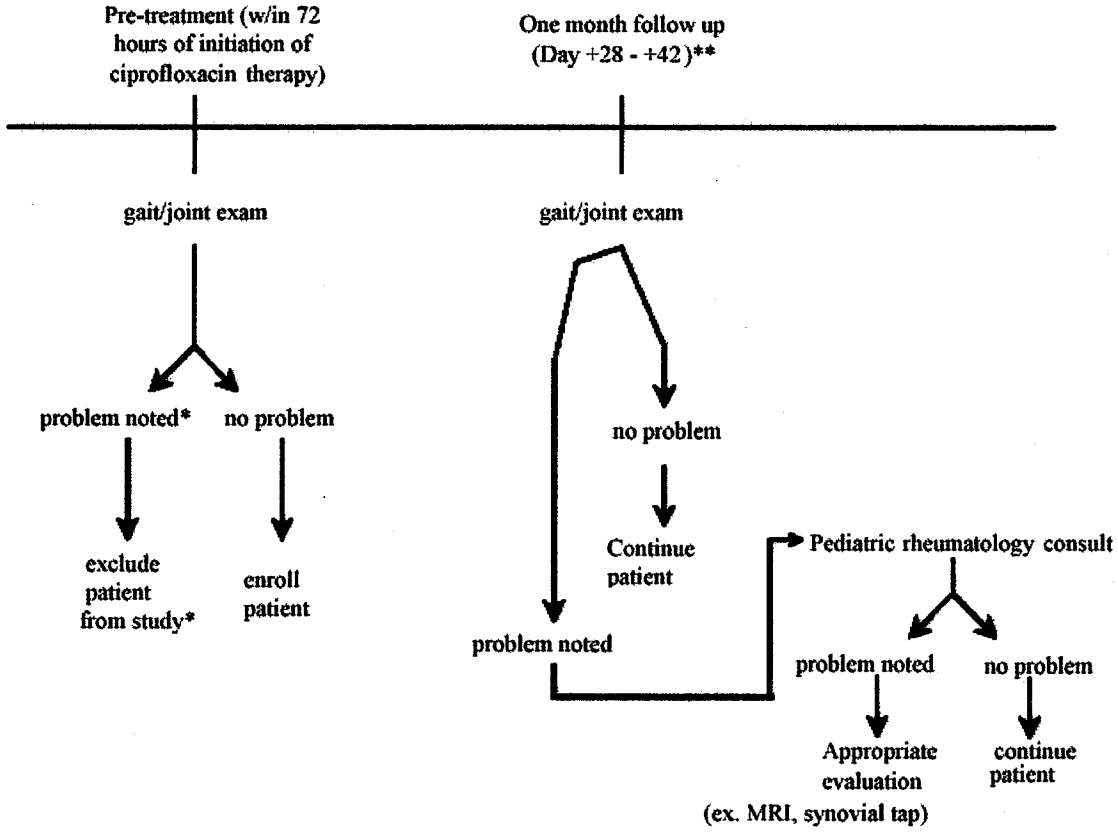
e Beyond the Day +28 to +42 investigative site visit, assessments of both serious (SAEs) and non-serious adverse events referable to either the musculoskeletal or CNS body system, and of all SAEs only (not routine adverse events) referable to other body systems, were performed primarily by the **infant's or child's parent or guardian, and were** supplemented by data and documentation from local investigative sites and other non-study affiliated physicians, as warranted and practical.

f Adverse events were collected through study Day +42

g **A conjoint responsibility of the patient's pa**rent or caregiver, and the investigator (if notified).

h Serious adverse events were reported up until and including the late follow-up visit (Day +28 to +42 after the end of study drug administration).

FIGURE 2
Gait/Join Examination Flow Diagram



* If the patient has already received ciprofloxacin prior to the gait/joint examination, and a problem is noted on exam follow-up as per the 1-month follow-up should be conducted.
** If an adverse event related to the musculoskeletal system occurs throughout the long-term follow-up period (1-5 years, per Amendment 4), intervention should occur.

12.12 Statistical and Analytical Plans

The primary objective of the trial was to determine the musculoskeletal and neurological system safety profile of ciprofloxacin in a long-term safety surveillance study. The primary population was to be patients considered valid for safety. The primary outcomes of interest were the incidence of musculoskeletal and CNS adverse events occurring by Day +28 to +42.

Since this was planned as a noncomparative trial, no formal statistical tests were planned.

Demographic and baseline characteristics were summarized for all patients valid for safety using means and standard deviations (for continuous variables) and frequency counts (for categorical variables). Medical conditions were tabulated using ICD-9 codes and concomitant medications using ATC codes.

A summary of incidence rates of serious adverse events (including both serious and non-serious CNS and musculoskeletal events) documented by Day +28 to +42 was presented. Events were to be tabulated by type (according to the COSTART glossary) and frequency, for all events and for those considered by the investigator to have a possible or probable relationship to drug treatment. The tables for musculoskeletal and CNS events were to be further summarized by age groups.

Kaplan-Meier survival curve estimates for the probability of not having any new musculoskeletal events were to be calculated through Day +42. Similar curves were planned for the probability of not having any new CNS event. These curves were also planned to be presented by age groups and by type of treatment (IV versus PO). Life-table estimates were to be used for events occurring after Day +28 to +42, since the exact dates for events occurring after this timepoint were not expected to be available.

12.13 Determination of Sample Size

The protocol specified that 3,000 ciprofloxacin patients would be enrolled into the study (changed as per Amendment 4 to 900 patients; 450 ciprofloxacin and 450 non-quinolone). This sample size was selected by the applicant because it provides a 95% probability of seeing at least one rare event (as defined by an event rate of 1 in 1,000, changed to 1 in 250 as per Amendment 4) using the binomial distribution. This is based on combining the 900 patients from this study with at least 600 patients available from the pediatric complicated UTI trial (Study 100169).

12.14 Independent Pediatric Safety Committee (IPSC)

The purpose of the IPSC was to review musculoskeletal and neurological adverse events. The mission of the IPSC was to determine the arthropathy classification (i.e., definite, probable, possible, none), relationship of arthropathy to study drug therapy (i.e., definite, probable, possible, none, not assessable), and if there were any pre-existing conditions that may/may not have been exacerbated during the study. The IPSC was formed in September 1999 with 2 members, a pediatric infectious disease specialist and a pediatric rheumatologist. By October 2001, it consisted of 4 members, including a pediatric neurologist and a pediatric orthopedic surgeon. They participated in 7 meetings, scheduled by the applicant, from June 2003 through September 2003.

The definition of arthropathy was generally considered as any condition affecting a joint or periarticular tissue where there is historical and/or physical evidence for structural damage and/or functional limitation that may have been temporary or permanent. This definition was seen as broad and inclusive of such phenomena as bursitis, enthesitis and tendonitis.

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

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

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

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

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

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

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

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

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

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

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

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

- Patients with any musculoskeletal adverse events, as identified by the COSTART coding system (COSTART codes between 7000000 and 7999999).
- Patients with changes in gait/joint exams, identified as those patients with decreases in range of motion which were in the lowest 1% of all changes seen in the population.

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

*Clinical Reviewer's Comment: **At the end of the study, 128 patients were identified** using the arthropathy algorithm. One patient did not appear on the algorithm at the end of the study. The patient had arthralgia as an initial event, which was later clarified as an event of neck pain. The patient is included for completeness. In total 141 cases were reviewed by the IPSC. See safety results section of the review.*

12.15 SAFETY RESULTS

12.15.1 Disposition of Patients

Sixty-eight centers (67 from the United States, 1 from Canada) enrolled 1029 patients into the study. Of the 1,029 patients, 510 were in the ciprofloxacin group, and 519 were in the control group. Table 2 in Appendix 1 summarizes patient enrollment by center.

Since the control group was added 2 years after the study started, and since the enrollment process was not randomized, the patient distribution within centers was highly variable. Most of the centers enrolled all or nearly all of their patients into the same treatment group, and very few centers had similar numbers of patients in the two groups. Of the 68 centers, 35 enrolled only ciprofloxacin patients, 30 enrolled patients into both groups, and 3 enrolled only control patients. Most centers enrolled between 1 and 40 patients (only 4 centers enrolled more than 40). Center 7 enrolled 223 control patients, accounting for 43% of the control group population, while only enrolling 14 (3%) ciprofloxacin patients.

As shown in Table 3, 63 ciprofloxacin and 26 control patients did not complete the study drug as planned. The ciprofloxacin patients prematurely discontinued treatment more often than the control patients did (12% versus 5%). The reason for discontinuation with the largest difference between groups was adverse event (3% for ciprofloxacin patients, <1% for control patients), but in all categories there were more ciprofloxacin patients than control patients.

TABLE 3
Number of Patients and Reasons for Premature Discontinuation from Study Treatment

	Ciprofloxacin (N=510)	Control (N=519)
Any reason	63 (12%)	26 (5%)
Adverse event	13 (3%)	3 (<1%)
Patient non-compliance	11 (2%)	6 (1%)
Consent withdrawn	11 (2%)	6 (1%)
Insufficient therapeutic effect	5 (<1%)	2 (<1%)
Patient lost to follow-up	18 (4%)	8 (2%)
Investigator decision	4 (<1%)	1 (<1%)
Death	1 (<1%)	0 (0%)

Efficacy evaluations were not included in this trial, so there is no valid for efficacy population.

12.15.2 Protocol deviations

Overall, 54 patients did not have pages in the CRF completed for study drug schedule. Of those 54, information obtained by the applicant for 19 patients suggested they indeed had received study drug. However, for these 19 patients, information regarding treatment duration, formulation, and dosage was not available. Therefore, for 35 patients (23 ciprofloxacin and 12 control), it could not be confirmed (by the study drug schedule page, end of study page, or additional information page of the CRF), that the patients received any dose of study drug. These patients were excluded from the safety analysis, leaving 487/510 (95%) in the ciprofloxacin group and 507/519 (98%) valid for safety.

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

Clinical Reviewer's Comment: ***The differences in baseline abnormalities*** *and medical histories may make it difficult to assess any potential drug effect on gait or joint appearance and will be taken into consideration when reviewing musculoskeletal adverse event rates and arthropathy rates for the two treatment groups.*

One ciprofloxacin patient (380008) had a baseline history of paraplegia so interpretations of gait assessment were limited.

In total, 21 patients had a history of seizures and should have been excluded as per protocol. In theory, these patients could have been placed at potential risk for a convulsion during the treatment phase. Patient 70203 (control group) had a seizure on Day +38. Patient 9930010 (ciprofloxacin group) with a history of Arnold-Chiari, insertion of a ventriculo-peritoneal shunt, and recurrent seizures (not on baseline anticonvulsant) had a seizure on Day +1.

No other substantial protocol deviations were observed.

By June 30, 2003, 404 ciprofloxacin patients and 315 control patients would have been eligible for 1-year post-treatment follow-up. Of these, it could be verified through phone call records kept by the CRO [redacted] that 355 (88%) ciprofloxacin patients and 267 (85%) control (non-quinolone) patients had been contacted at least through the 1-year follow-up timepoint and beyond.

12.15.3 Control Group – Treatments Administered

In the control group, amoxicillin monotherapy was the most commonly used regimen; 273 of the 507 (54%) control patients received this therapy. Other commonly used monotherapies in the control group included Augmentin® (7%; 34/507), Zithromax® (6%; 30/507), Keflex® (6%;28/507) and Omnicef® (6%; 29/507).

12.15.4 Demographic and Other Baseline Characteristics

Descriptive statistics for some of the key demographic and baseline variables for the population of patients valid for safety are provided in Table 4.

Clinical Reviewer's Comment: Table 4 was expanded by the reviewer to include more variables than the applicant's original table.

TABLE 4
Selected Demographic and Infection Characteristics for Patients Valid for Safety

	Ciprofloxacin N=487	Control N=507
Sex		
% Female	269 (55%)	242 (48%)
Race		
% Caucasian	292 (60%)	330 (65%)
% Black	33 (7%)	27 (5%)
% Hispanic	138 (28%)	128 (25%)
% Asian	16 (3%)	8 (2%)
% Not Coded	8 (2%)	13 (3%)
% American Indian	0	1 (<1%)
Mean ± SD Age at Enrollment in years (range)	6.2 ± 4.3 (0 to 16 years)	5.3 ± 3.5 (0 to 16 years)
Mean ± SD Age in years for Patients ≥ 2 years (range)	7.3 ± 3.7 (2 to 16 years)	6.5 ± 2.9 (2 to 16 years)
Mean ± SD Age in months for Patients < 24 months (range)	13.6 ± 6.3 (2 to 23 months)	12.7 ± 5.7 (2 to 23 months)
Infection Type		
% UTI	105 (22%)	12 (2%)
% Pyelonephritis	24 (5%)	8 (2%)
% Otitis Media	143 (29%)	207 (41%)
% Pharyngitis/Tonsillitis	39 (8%)	148 (29%)
% Sinusitis	39 (8%)	47 (9%)
% Pneumonia	12 (2%)	17 (3%)
% Cellulitis	16 (3%)	11 (2%)
% External Otitis	10 (2%)	1 (<1%)
% Other Infections	99 (21%)	56 (12%)
Patient Prematurely Born		
% Yes	62 (13%)	57 (11%)
% No	386 (79%)	447 (88%)
% Unknown	39 (8%)	3 (<1%)
Country of Enrollment		
Canada	11 (2%)	4 (<1%)
United States	476 (98%)	503 (99%)

There were also more females (55%) in the ciprofloxacin group compared to the control group (48%). The race distribution and percentage of patients born prematurely were very similar in the two groups. The distribution of infections, which led to enrollment in the trial, was very different in the two groups. In the ciprofloxacin group, 27% of patients were enrolled due to a UTI or pyelonephritis, while only 4% of control patients were enrolled due to these infections. In the control group, 70%

of patients were enrolled due to otitis media orpharyngitis/tonsillitis, while only 37% of ciprofloxacin patients were enrolled due to these infections.

The age groups and distributions of patients in each age group that were studied are shown in Table 5. Of the patients ≤ 5 years of age, 48% (235/487) were in the ciprofloxacin group and 52% (265/507) were in the control group. More ciprofloxacin patients (12%; 58/487) were 12 years to <17 years of age compared to control patients (4%; 19/507).

TABLE 5
Age Distribution
Patients Valid for Safety

	Ciprofloxacin N = 487	Control N = 507
2 months, <24 months	85 (17.5%)	100 (19.7%)
2 years, < 6 years	150 (30.8%)	165 (32.5%)
6 years, < 12 years	194 (39.8%)	223 (44.0%)
12 years, <17 years	58 (11.9%)	19 (3.7%)

There was a large difference between groups in the use of previous antimicrobials. Among ciprofloxacin-treated patients, 17% (81/487) had used a previous antimicrobial, while among control patients, less than 1% (3/507) had used a previous antimicrobial. Ciprofloxacin and Bactrim® were the most commonly used previous antimicrobials in the ciprofloxacin group.

Clinical Reviewer's Comment: Ofloxacin was used previously in 9/487 (2%) of *ciprofloxacin patients and none of the control patients.*

The overall rate of any medical history for patients treated with ciprofloxacin was 84% and 83% in the control group. There were many individual conditions for which the percentages differed greatly between groups. Table 6 shows all classes of conditions for which the difference between groups was at least 2%.

The medical history results were consistent with the infections causing patients to be entered into the trial. Many more ciprofloxacin patients had histories in the genitourinary system, and many more control patients had histories in the respiratory infections. The ciprofloxacin group also had many more patients with histories of various types of operations.

TABLE 6
Medical Histories for Conditions with ≥ 2% Difference Between the Treatment Groups

	Ciprofloxacin (N=487)	Control (N=507)
Any History	406 (84%)	422 (83%)
Neoplasms	23 (5%)	5 (<1%)
Endocrine, Nutritional, Metabolic, and Immunity	36 (7%)	12 (2%)
Blood and Blood-Forming Organs	44 (9%)	29 (6%)
Nervous System and Sense Organs	150 (31%)	270 (53%)
Respiratory System	181 (37%)	315 (62%)
Digestive System	81 (17%)	43 (8%)
Genitourinary System	114 (23%)	41 (8%)
Musculoskeletal and Connective Tissue	32 (7%)	24 (5%)
Congenital Abnormalities	58 (12%)	22 (4%)
Symptoms, Signs, Ill-Defined Conditions	128 (26%)	93 (18%)
Injury and Poisoning	85 (17%)	205 (40%)
Operations on the Nervous System	11 (2%)	0 (0%)
Operations on the Ear	74 (15%)	30 (6%)
Operations on the Nose, Mouth, and Pharynx	43 (9%)	21 (4%)
Operations on the Cardiovascular System	17 (3%)	1 (<1%)
Operations on the Digestive System	33 (7%)	11 (2%)
Operations on the Urinary System	31 (6%)	0 (0%)
Operations on the Integumentary System	23 (5%)	7 (1%)

12.15.5 Concomitant Medication Use

Prevalence rates of concomitant medication use (at the time of enrollment) were 76% (369/487) for ciprofloxacin patients and 68% (347/507) for control patients (data not shown). Antimicrobial use was much more common among ciprofloxacin patients (41%; 201/487) than control patients (17%; 88/507). Ciprofloxacin patients also had higher use of vitamins (8% [40/487] versus 2% [11/507]), antacids (6% [27/487] versus 2% [11/507]), antifungals for dermatologic use (4% [20/487] versus 1% [7/507]), urologicals (5% [24/487] versus 0% [0/507]), antimycotics for systemic use (3% [13/487] versus <1% [1/507]), analgesics (23% [112/487] versus 14% [72/507]), and anti-asthmatics (14% [70/487] versus 11% [55/507]).

The incidence rate of treatment-emergent concomitant medication use (i.e., medications started for the first time after enrollment) was 58% (284/487) in the ciprofloxacin group and 60% (303/507) in the control

group (data not shown). There was a difference between groups in the number of patients using general anti-infectives for systemic use (31% [152/487] for ciprofloxacin-treated patients, 17% [84/507] for control patients). The ciprofloxacin group also had higher incidence rates of treatment-emergent use of alimentary tract and metabolism medications (9% [45/487] versus 4% [19/507]), nervous system medications (19% [93/487] versus 14% [71/507]), and sensory organ medications (10% [40/487] versus 7% [34/507]). The control group had a higher incidence rate of treatment-emergent use of respiratory system medications (23% [111/487] versus 34% 170/507]).

When limited to antimicrobials being used at the same time as study drug therapy, there were more ciprofloxacin patients using concomitant antimicrobials than control patients (16% [77/487] versus 3% [13/507]).

12.15.6 Compliance with Study Drug

Tables 7 and 8 display the treatment duration and dosing information, respectively. The mean duration of treatment was one day longer for the ciprofloxacin patients than for the control patients (12.4 days versus 11.3 days). Ciprofloxacin-treated patients had higher mean durations of both oral therapy (12.3 days versus 11.1 days) and IV therapy (5.8 days versus 5.1 days). The maximum duration of ciprofloxacin treatment was 88 days, while the maximum duration of control therapy was 70 days.

Clinical Reviewer's Comment: ***Tables 7 and 8 were created by the*** *reviewer.*

TABLE 7
Mean (± SD) Duration of Study Drug Administration
Patients Valid for Safety

	Ciprofloxacin N=487	Control N=507
Total treatment duration (days)	12.4 ± 7.9 [1 to 88] N=468	11.3 ± 6.7 [3 to 70] N=503
Duration of oral therapy (days)	12.3 ± 7.5 [1 to 88] N=455	11.1 ± 5.8 [3 to 56] N=499
Duration of IV therapy (days)	5.8 ± 4.9 [2 to 21] N=41	5.1 ± 2.8 [1 to 14] N=30

TABLE 8
Mean (± SD) Number of Doses of Study Drug Administered
Patients Valid for Safety

	Ciprofloxacin N=487	Control N=507
Total number of doses	23.4 ± 15.0 [1 to 20] N=464	23.9 ± 16.5 [2 to 139] N=504
Number of oral capsules	23.2 ± 14.1 [1 to 20] N=450	23.4 ± 14.6 [2 to 119] N=500
Number of IV doses	11.0 ± 11.3 [2 to 42] N=41	10.5 ± 7.5 [1 to 37] N=30

Clinical Reviewer's Comment: The safety results of this study should be *interpreted with caution for the reasons outlined below. The applicant acknowledges the limitations in interpreting the data based up the same reasons identified by the reviewer.*

The study was not blinded or randomized and enrollment into the comparator arm was not temporal to the ciprofloxacin arm (i.e., the comparator arm was added to the study 2 years after it had been initiated).

Differences in the reasons for treatment. The distribution of infections, which led to enrollment in the trial, was very different in the two groups. In the ciprofloxacin group, 27% of patients were enrolled due to a UTI or pyelonephritis, while only 4% of control patients were enrolled due to these infections. In the control group, 70% of patients were enrolled due to otitis media orpharyngitis/tonsillitis, while only 37% of ciprofloxacin patients were enrolled due to these infections.

Differences in Age. The most notable difference was in the patient age group of 12 years to < 17 years (12%; (58/487) of ciprofloxacin patients compared to 4% (12/507) control patients.

Differences in previous antimicrobial use. There was a large difference between groups in the use of previous antimicrobials. Among ciprofloxacin-treated patients, 17% (81/487) had used a previous antimicrobial, while among control patients, only 1% (3/507) had used a previous antimicrobial. Ciprofloxacin and Bactrim® were the most commonly used previous antimicrobials in the ciprofloxacin group.

Differences in medical history and concomitant medical conditions. Notable differences (>2% differences) were observed in medical history (ICD-9 class) between the two treatment groups. The conditions with the greatest discrepancy between the groups are as follows. Ciprofloxacin-

treated patients had a higher incidence of genitourinary system (23% [114/487] versus 8% [41/507]) and digestive system disorders (17% [81/487] versus 8% [43/507]) compared to the control group. The control group had a higher incidence of medical histories of conditions in the nervous system and sense organs (53% [270/507] control versus 31% [150/487] ciprofloxacin; mainly attributed to a higher incidence of otitis media), respiratory system (62% [315/507] control versus 37% [181/487] ciprofloxacin; mainly attributed to differences in upper respiratory infections, pharyngitis, and chronic sinusitis), and injury and poisoning (40%[205/507] control versus 17% [85/487] ciprofloxacin; mainly attributed to allergy).

Differences in baseline abnormalities or medical histories of musculoskeletal adverse events. Known underlying rheumatological disease, joint problems secondary to trauma or pre-existing conditions known to be associated with arthropathy were to be excluded from the study. However, 7% (32/487) of ciprofloxacin patients and 5% (24/507) control patients were enrolled with a medical history of any abnormal musculoskeletal or connective tissue finding. In addition, at study entry 7% (36/487) of ciprofloxacin patients and 0.8% (4/507) of control patients had an abnormal gait assessment at baseline and 5% (23/487) of ciprofloxacin patients and 2% (9/507) of control patients had an abnormal joint appearance at baseline.

Differences in concomitant medications. Prevalence rates of concomitant medication use (at the time of enrollment) were 76% (9369/487) for ciprofloxacin patients and 68% (347/507) for control patients (data not shown). Antimicrobial use was much more common among ciprofloxacin patients (41%) than control patients (17%). Ciprofloxacin patients also had higher use of vitamins (8% [40/487] versus 2% [11/507]), antacids (6% [27/487] versus 2% [11/507]), antifungals for dermatologic use (4% [20/487] versus 1% [7/507]), urologicals (5% [24/487] versus 0% [0/507]), antimycotics for systemic use (3% [13/487] versus <1% [1/507]), analgesics (23% [112/487] versus 14% [72/507]), and anti-asthmatics (14% [70/487] versus 11% [55/507]).

The differences between treatment groups outlined above should be considered when reviewing adverse event rates for the two treatment groups and the population of ciprofloxacin patients should not be directly compared to the population of control patients.

12.15.7 Overview of Adverse Events Through Day +42

Table 9 displays a brief summary of the rates of death, any adverse event, any drug-related adverse event, any serious adverse event, and premature discontinuations due to adverse events, for ciprofloxacin and control patients valid for safety through the 42-day follow-up time point.

TABLE 9
Summary of Adverse Events by Day +42
Ciprofloxacin (N=487) and Control (N=507) Patients

	Ciprofloxacin	Control
Deaths	1 (<1%)*	0 (0%)
Adverse Events	210 (43%)	134 (26%)
Drug-Related Adverse Events	70 (14%)	20 (4%)
Serious Adverse Events	22 (5%)	5 (1%)
Premature Discontinuations due to Adverse Events	13 (3%)	3 (<1%)

* One ciprofloxacin-treated patient died (Patient 49-0055) due to right atrial thrombosis with deterioration in cardiac function during the Day +42 follow-up period.

The 13 patients who were premature discontinuations in the ciprofloxacin group had:

- **Arthralgia – shoulder pain (mild); jaw pain (moderate); and R wrist** pain [one patient each]
- **Dizziness – (one moderate one mild) [2 patients]**
- Headache (mild)
- Tachycardia (moderate)
- Rash (mild)
- Injection site reaction (mild)
- Allergic reaction (mild)
- Vomiting (mild) [2 patients]
- Otitis media, worsening (severe)
- Bacteremia (moderate)
- Sinusitis (one moderate one mild) [2 patients]
- Infected abdominal wounds (one moderate, one severe) [2 patients]
- Urticaria, hives (severe)

All ciprofloxacin patients had resolution of their events.

The 3 patients who were premature discontinuations in the comparator group had: vomiting (mild) and rash (moderate) in one patient each who received amoxicillin; and abdominal pain (mild) in a patient who received cefzil. All events resolved.

12.15.8 *Serious Adverse Events Through Day +42*

Patients who experienced serious adverse events through 42 days after the end of therapy are summarized in Table 10. Overall, 5% of ciprofloxacin patients experienced serious adverse events. The most frequent serious adverse events were fever and sepsis (4 patients each). Two patients experienced serious musculoskeletal events; one patient reported osteomyelitis, and one reported arthralgia.

Overall, 5/507 (<1%) of control patients experienced serious adverse events by Day 42. The five events, which all occurred in different patients were: vertigo, acute asthma (2 patients), peritonisllar abcess, and increasing pleural effusion (pt. 470048). All events were severe in intensity and all resolved. The patients with vertigo and pleural effusion were hospitalized. The patients with asthma and the peritonsillar abcess received remedial drug therapy.

TABLE 10
Incidence Rates of Serious Adverse Events by Body System by Day +42 After Treatment
Ciprofloxacin Treated Patients Valid for Safety (N=487)

Event	Number Experiencing Event in Ciprofloxacin Group (%)
Any Body System – Any Event	**22 (5%)**
Body as a Whole	
Any Event	11 (2%)
Fever	4 (<1%)
Sepsis	4 (<1%)
Abscess	2 (<1%)
Back Pain	1 (<1%)
Congenital Anomaly	1 (<1%)
Infection	1 (<1%)
Cardiovascular	
Any Event	2 (<1%)
Heart Arrest	1 (<1%)
Heart Failure	1 (<1%)
Thrombophlebitis	1 (<1%)
Thrombosis	1 (<1%)
Digestive	
Any Event	4 (<1%)
Pseudomembranous enterocolitis	2 (<1%)
Intestinal obstruction	1 (<1%)
Gastroenteritis	1 (<1%)
Nausea	1 (<1%)
Vomiting	1 (<1%)
Hemic and Lymphatic	
Any Event	4 (<1%)
Leukopenia	3 (<1%)
Acute Leukemia	1 (<1%)
Metabolic and Nutritional	
Any Event	1 (<1%)
Dehydration	1 (<1%)
Musculoskeletal	
Any Event	2 (<1%)
Osteomyelitis	1 (<1%)
Arthralgia	1 (<1%)

Event	Number Experiencing Event in Ciprofloxacin Group (%)
Respiratory	
Any Event	1 (<1%)
Bronchitis	1 (<1%)
Special Senses	
Any Event	2 (<1%)
Otitis Media	2 (<1%)
Urogenital	
Any Event	5 (1%)
Acute Kidney Failure	1 (<1%)
Kidney Function Abnormal	1 (<1%)
Pyleonephritis	1 (<1%)
Uremia	1 (<1%)
Urinary Incontinence	1 (<1%)
Urinary Tract Disorder	1 (<1%)
Urinary Tract Infection	1 (<1%)

Serious adverse events for ciprofloxacin believed to be drug related occurred in two patients, both in the digestive body system. There were 2 patients with pseudomembranous enterocolitis (270024 and 500011); one of these patients also had gastroenteritis (270024).

12.15.9 Musculoskeletal and CNS Adverse Events Through Day +42

The incidence rates of musculoskeletal or CNS events occurring in ≥1% of ciprofloxacin patients, including arthropathy, through the 42-day follow-up period for ciprofloxacin and control patients valid for safety are shown in Table 11. The overall rate of any musculoskeletal or CNS event for ciprofloxacin was 13%, with a corresponding 95% confidence interval of (10.5%, 16.7%) and 4% with a corresponding 95% confidence interval of (2.1%, 5.6%) for control. The incidence rate of arthropathy (assessed by the IPSC) for ciprofloxacin was 8%, with a 95% confidence interval of (5.4%, 10.3%) and 2%, with a 95% confidence interval of (0.8%, 3.3%) for control.

TABLE 11
Musculoskeletal or CNS Events by Day +42 Occurring in ≥1% of Ciprofloxacin Patients Ciprofloxacin (N=487) and Control (N=507) Patients

	Ciprofloxacin 95% Confidence Interval		Control 95% Confidence Interval	
Any Musculoskeletal or CNS Event	65 (13%)	(10.5%, 16.7%)	18 (4%)	(2.1%, 5.6%)
Any Musculoskeletal Event	42 (9%)	(6.3%, 11.5%)	9 (2%)	(0.8%, 3.3%)
Arthropathy (assessed by IPSC)	37 (8%)	(5.4%, 10.3%)	9 (2%)	(0.8%, 3.3%)
Arthralgia	26 (5%)	(3.5%, 7.7%)	3 (<1%)	(0.1%, 1.7%)
Any CNS Event	28 (6%)	(3.9%, 8.2%)	9 (2%)	(0.8%, 3.3%)
Insomnia	17 (3%)	(2.1%, 5.5%)	3 (<1%)	(0.1%, 1.7%)

Clinical Reviewer's Comment: ***Tables 12 and 13 Appendix 1 were*** *created by the reviewer and list the ciprofloxacin and comparator patients, respectively, with arthropathy occurring by Day +42, as assessed by the IPSC. Of these, 7/35 ciprofloxacin patients and none (0/9) of the comparator patients had an event(s) occurring by Day +42 as well as an event(s) occurring between Day +42 and one year.*

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

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

The Division requested the applicant include a description of the patient with fibrocartilage tear in the Adverse Reactions section of the package insert. The following is a narrative of the patient cited on Form 483: Patient 250033 was a 13 year old female who was enrolled in the observational study on November 6, 2000 and prescribed ciprofloxacin for "sinus problems" (sinusitis and cervical adenitis). Patient history is significant for back pain. She was active in gymnastics in the summer of 2000, but quit because of the back pain. At that time an MRI showed swollen discs. She was also active in volleyball from September to November 2000. The patient reported mild right wrist pain on the third day of taking ciprofloxacin (November 9, 2000). Study drug was discontinued due to the adverse event on November 13, 2000, after 7 days of treatment. The wrist pain improved, but did not completely resolve. An MRI performed on _____ showed an intrasubstance tear of the triangular fibrocartilage in the right wrist (21 days following treatment with ciprofloxacin). The patient was referred for physical therapy and prescribed anti-inflammatory medication (prescribed Relafen®, but subsequent note says that she only took acetaminophen) and braces (both wrists) by an orthopedic surgeon. Patient was lost to follow-up for about 2 months. She did not respond to two telephone messages asking her to come back for a follow-up visit. On February 28, 2001 the patient was seen by a rheumatologist and had complaints of pain in the left wrist and left lower back. No pain in the right wrist. The rheumatologist diagnosed the patient with "probable tenosynovitis versus overuse syndrome secondary to gymnastics" and "no evidence of inflammatory arthritis." The patient was advised to take NSAIDs (ibuprofen) as needed. On May 7, 2001 the patient returned to the clinic.

She complained of a pain in her tail bone. X-ray showed inflamed tissue near the spinal cord. The patient was told to discontinue (or take time off) from gymnastics. No mention of wrist pain at this visit.

In order to understand the cases of arthralgia better, as this category of musculoskeletal events comprises the greatest proportion of the musculoskeletal events, the FDA Clinical Reviewer looked in greater detail at these patients. Table 14 lists the patients with arthralgia events occurring by Day +42 for ciprofloxacin and comparator, respectively,

TABLE 14
ARTHRALGIA Cases Occurring by Day +42

Ciprofloxacin			Comparator		
27 patients (38 events)/56 = 48%			3 patients (3 events)/13 = 23%		
Pt. #/Sex/Age in years	Description	Duration	Pt. #/Sex/ Age in years	Description	Duration
80006/F/14	Shoulder pain	8	70085/M/11	R wrist pain	5
90014/F/4	L knee pain	1	70101/M/11	R knee pain	88
170001/M/2	L ankle tenderness	9	70104/F/5	Knee pain	236
	L knee tenderness	9			
210005/M/2 [2 additional events after Day 42]	Intermittent jaw pain	633			
290023/F/3	Bilateral knee pain	ongoing			
350022/F/11 [1 additional event after Day 42]	Bilateral elbow pain	Unknown			
	Bilateral wrist pain	unknown			
350023/M/8	Ankle pain	Ongoing			
	Knee pain	Ongoing			
	Shoulder pain	Ongoing			
380006/F/10	Jaw pain	5			
400049/F/11	Intermittent L shoulder pain	6			
610001/M/8 [1 additional event after Day 42]	Knee pain	2			
760005/F/14	Hip pain	unknown			
920005/F/9	L knee pain	2			
220001/F/2	Elbow pain	7			
250003/M/9*	L wrist pain	3			

Ciprofloxacin			Comparator		
27 patients (38 events)/56 = 48%			3 patients (3 events)/13 = 23%		
Pt. #/Sex/Age in years	Description	Duration	Pt. #/Sex/ Age in years	Description	Duration
250033/F/13	R wrist pain	Unknown			
	L wrist pain	unknown			
270017/F/8 [2 additional events after Day 42]	Bilateral knee pain	66			
	Bilateral ankle pain	66			
290007/F/13	L shoulder pain	23			
400033/M/11	R knee pain	22			
460001/F/10	L wrist pain	8			
	R knee pain	8			
870056/M/5	Aching in knees	16			
80003/F/9*	L ankle pain	8			
210004/F/11**	L elbow pain	3			
	L shoulder pain	2			
	L elbow pain	7			
	L elbow pain	3			
30001/M/6	L elbow pain	1			
320002/F/11	Soreness in knees	1			
350015/F/12**	R ankle pain	3			
	R ankle pain	6			
370010/M/3*	R knee pain	7			
790011/M/16**	R knee pain	12			

*** associated with "accidental trauma"**
** IPSC inadvertently unblinded to study drug

The incidence rates of drug-related musculoskeletal or CNS events occurring in > 1% of patients, through the 42-day follow-up period for ciprofloxacin and control are shown in Table 15. The incidence rates of any drug-related musculoskeletal or CNS events were 8% for ciprofloxacin and 2% for control, and the incidence rate of drug-related arthropathy was 6% for ciprofloxacin and 2% for control.

TABLE 15
Drug-Related Musculoskeletal or CNS Events by Day +42 Occurring in ≥1% of Ciprofloxacin Patients
Ciprofloxacin (N=487) and Control (N=507) Patients

	Ciprofloxacin	95% Confidence Interval	Control	95% Confidence Interval
Any Musculoskeletal or CNS Event	37 (8%)	(5.4%, 10.3%)	9 (2%)	(0.8%, 3.3%)
Any Musculoskeletal Event	28 (6%)	(3.9%, 8.2%)	8 (2%)	(0.7%, 3.1%)
Arthropathy (assessed by IPSC)	27 (6%)	(3.7%, 8.0%)	8 (2%)	(0.7%, 3.1%)
Any CNS Event	9 (2%)	(0.8%, 3.5%)	1 (<1%)	(< 0.1%, 1.1%)
Insomnia	5 (1%)	(0.3%, 2.4%)	1 (<1%)	(< 0.1%, 1.1%)

12.15.10 All Adverse Events Through Day +42

Tables 16 and 17 shows adverse events, for all adverse events and those related to study drug, respectively, for all body systems through the Day +42 follow-up period for ciprofloxacin and control patients. The results for events, regardless of relationship to study drug that occurred in at least 2% of patients are shown in Table 14.

TABLE 16
Incidence Rates of Adverse Events by Body System Through Day +42
Ciprofloxacin (N=487) and Control (N=507) Patients

Body System	Ciprofloxacin		Control	
Any event	210	(43%)	134	(26%)
Body as a Whole	89	(18%)	50	(10%)
Cardiovascular	11	(2%)	1	(<1%)
Digestive	44	(9%)	17	(3%)
Endocrine	1	(<1%)	0	(0%)
Hemic and Lymphatic	11	(2%)	3	(<1%)
Metabolic & Nutritional	6	(1%)	2	(< 1%)
Musculoskeletal	42	(9%)	9	(2%)
Nervous	28	(6%)	9	(2%)
Respiratory	68	(14%)	50	(10%)
Skin & Appendages	27	(6%)	22	(4%)
Special Senses	35	(7%)	27	(5%)
Urogenital	18	(4%)	4	(<1%)

Through the 42-day follow-up period, 43% of ciprofloxacin patients experienced at least one adverse event. Most of the events were in the

Body as a Whole and Respiratory body systems (18% [89/487] and 14% [68/487] incidence rates, respectively). The most common events (other than musculoskeletal events) were otitis media and pharyngitis (5% each [25/487] and [24/487], respectively).

Through 42-day follow-up period, 26% (134/507) of control patients experienced at least one adverse event. Most of the events were in the Body as a Whole and Respiratory body systems (10% each [50/507] and [50/507], respectively). The most common event was pharyngitis (4% [20/507]).

TABLE 17
Incidence Rates of Drug-Related Adverse Events by Body System Through Day +42
Ciprofloxacin (N=487) and Control (N=507) Patients

Body System	Ciprofloxacin		Control	
Any event	70	(14%)	20	(4%)
Body as a Whole	16	(3%)	4	(<1%)
Cardiovascular	1	(<1%)	0	(0%)
Digestive	21	(4%)	3	(<1%)
Musculoskeletal	28	(6%)	8	(2%)
Nervous	9	(2%)	1	(<1%)
Respiratory	1	(<1%)	0	(0%)
Skin & Appendages	4	(<1%)	6	(1%)
Special Senses	1	(<1%)	0	(0%)
Urogenital	2	(<1%)	0	(0%)

Most of the adverse events reported through the 42-day follow-up period were not considered drug-related. The incidence rate of any drug-related adverse event was 14% (70/487) in the ciprofloxacin group and 4% (20/507) in the control group. Specific drug-related adverse events (other than musculoskeletal events) with drug-related incidence rates of 1% or higher for ciprofloxacin were abdominal pain (2%; 8/487), diarrhea (2%; 9/487), and vomiting (2%; 9/487). All events (other than musculoskeletal events) with drug-related incidence rates were 1% or less in the control group.

Specific adverse events reported through the 42-day follow-up period, other than those affecting the musculoskeletal and central nervous systems, are shown in Table 18, if incidence was at least 2% of patients in either group.

TABLE 18
Incidence Rates of Adverse Events Through Day +42 (Other than Musculoskeletal and CNS) Occurring in at Least 2% of Patients (Regardless of Relationship to Study Drug) in Either Group Ciprofloxacin (N=487) and Control (N=507) Patients

Adverse Event	Ciprofloxacin		Control	
Any event	210	(43%)	134	(26%)
Otitis Media	25	(5%)	14	(3%)
Pharyngitis	24	(5%)	20	(4%)
Fever	21	(4%)	7	(1%)
Accidental Injury	18	(4%)	14	(3%)
Vomiting	18	(4%)	5	(<1%)
Rhinitis	18	(4%)	15	(3%)
Asthenia	17	(3%)	0	(0%)
Rash	17	(3%)	13	(3%)
Abdominal Pain	15	(3%)	6	(1%)
Headache	14	(3%)	4	(<1%)
Cough Increased	14	(3%)	3	(<1%)
Diarrhea	14	(3%)	2	(<1%)
Leg Pain	8	(2%)	4	(<1%)
Sinusitis	8	(2%)	7	(1%)

12.15.11 Severe Adverse Events Through Day +42

Severe adverse events were experienced by 7% (33/487) of ciprofloxacin patients and 3% (15/507) of control patients through the 42-day follow-up period. The most common severe adverse events in the ciprofloxacin group were sepsis and fever (4 patients each). Three ciprofloxacin patients experienced severe musculoskeletal events; 2 had severe arthralgia, and 1 had severe osteomyelitis. There were no severe nervous system events in the ciprofloxacin group.

The most common severe adverse event in the control group was asthma (2 patients). No other event was considered severe in more than one control patient. No control patient experienced a severe musculoskeletal event. Two control patients experienced severe nervous system events (1 convulsion and 1 vertigo).

12.15.12 Outcomes for Adverse Events Through Day +42

Outcomes for adverse events through the 42-day follow-up period for ciprofloxacin patients were reported as follows: 135 patients had events that resolved, 11 improved, 24 were unchanged, 5 patients worsened (2 patients with rash, 1 with heart failure, 1 with thrombosis, and 1 with asthma), and 24 patients had insufficient follow-up to assess resolution.

Outcomes for adverse events through the 42-day follow-up period for control patients were reported as follows: 95 patients had events that

resolved, 3 improved, 25 were unchanged, 2 patients worsened (1 patient with infection, and 1 with pharyngitis and rhinitis) and 3 had insufficient follow-up to assess resolution.

12.15.13 Overview of Adverse Events Through One Year

Table 19 displays a brief summary of the rates of death, any adverse event, any drug-related adverse event, any serious adverse event, and premature discontinuations due to adverse events, for ciprofloxacin patients valid for safety through the on year follow-up time point. No additional patients died between Day +42 and the 1-year follow-up time point.

TABLE 19
Summary of Adverse Events by Day +42
Ciprofloxacin Treated Patients (N=487)

	Ciprofloxacin
Deaths	1 (<1%)*
Adverse Events	252 (52%)
Drug-Related Adverse Events	88 (18%)
Serious Adverse Events	22 (5%)
Premature Discontinuations due to Adverse Events	14 (3%)

* One ciprofloxacin-treated patient died (Patient 49-0055) due to right atrial thrombosis with deterioration in cardiac function during the Day +42 follow-up period.

12.15.14 Serious Adverse Events Through One Year

Only one additional serious adverse event was reported after the 42-day follow-up period (fever). This event was not thought to be drug-related. Therefore, there were no serious drug-related adverse events reported after the initial 42-day follow-up period.

12.15.15 Musculoskeletal and CNS Adverse Events Through One Year

The incidence rates of musculoskeletal or CNS events occurring in ≥ 1% of ciprofloxacin patients, including arthropathy, through the 1-year follow-up period for ciprofloxacin and control patients valid for safety are shown in Table 17. The overall rate of any musculoskeletal or CNS event through the 1-year follow-up period for ciprofloxacin was 21%, with a corresponding 95% confidence interval of (17.8%, 25.3%) and 5%, with a corresponding 95% confidence interval of (3.2%, 7.2%) for control. The incidence rate of arthropathy for ciprofloxacin was 11%, with a 95% confidence interval of (8.8%, 14.7%) and 3%, with a corresponding 95% confidence interval of (1.4%, 4.3%) for control.

The only musculoskeletal event occurring in ≥1% of ciprofloxacin patients was arthralgia (9%; 46 patients). Arthrosis occurred in 3 patients (0.6%) and myalgia in 2 patients(0.4%). Tendon disorder was reported in one

patient (0.3%). The incidence of convulsions was the same in both treatment arms (3 patients each, 0.6%).

TABLE 20
Musculoskeletal or CNS Events Through One Year of Follow-Up
Occurring in ≥1% of Ciprofloxacin Patients
Ciprofloxacin (N=487) and Control (N=507) Patients

	Ciprofloxacin	95% Confidence Interval	Control	95% Confidence Interval
Any Musculoskeletal or CNS Event	104 (21%)	(17.8%, 25.3%)	25 (5%)	(3.2%, 7.2%)
Any Musculoskeletal Event	64 (13%)	(10.3%, 16.5%)	14 (3%)	(1.5%, 4.6%)
Arthropathy (assessed by IPSC)	56 (11%)	(8.8%, 14.7%)	13 (3%)	(1.4%, 4.3%)
Arthralgia	46 (9%)	(7.0%, 12.4%)	6 (1%)	(0.4%, 2.6%)
Any CNS Event	56 (11%)	(8.8%, 14.7%)	11 (2%)	(1.1%, 3.9%)
Insomnia	21 (4%)	(2.7%, 6.5%)	4 (<1%)	(0.2%, 2.0%)
Dizziness	9 (2%)	(0.8%, 3.5%)	1 (<1%)	(<0.1%, 1.1%)
Abnormal Dreams	6 (1%)	(0.5%, 2.7%)	0	--
Anxiety	5 (1%)	(0.3%, 2.4%)	0	--
Abnormal Gait	5 (1%)	(0.3%, 2.4%)	0	--

Clinical Reviewer's Comment: ***Tables 21 and 22 Appendix 1 were*** *created by the reviewer and list the ciprofloxacin and control patients, respectively, with arthropathy occurring between Day +42 and 1-year of follow-up, as assessed by the IPSC. Of these, 7 ciprofloxacin patients and none of the control patients had an event(s) occurring between Day +42 and one year as well as an event(s) occurring by Day +42.*

In order to understand the cases of arthralgia better, as this category of musculoskeletal events comprises the greatest proportion of the musculoskeletal events, the FDA Clinical Reviewer looked in greater detail at these patients. Table 23 lists the patients with arthralgia events occurring between Day +42 and 1-year of follow-up for ciprofloxacin and control, respectively.

TABLE 23
ARTHRALGIA Cases Occurring between Day +42 and 1 Year of Follow-up

Ciprofloxacin		Comparator	
15 patients (22 events)/56 = 27%		2 patients (2 events)/13 = 15%	
Pt. #/Sex/Age in years	Description	Pt. #/Sex/ Age in years	Description
210005/M/7 [2 events prior]	Unable to bend second toe on R foot	320036/F/8	Bilateral knee pain
	Intermittent bilateral knee pain (back of knees)	830028/F/9	R knee pain
300001/M/12	R knee pain		
	L knee pain		
310011/F/4	Bilateral knee pain		
	Hip pain		
310016/F/4	R ankle pain		
	R knee pain		
320004/F/3	Joint pains in knees		
320032/F/11	Knee pain		
350022/F/11 [2 earlier events]	R hip pain		
610001/M/8 [1 earlier event]	Knee pain		
630005/F/10	Pain in fingers and back		
640008/F/5	Bilateral knee pain		
270017/F/8 [2 earlier events]	Pains on ankles		
	Knee pains		
270024/M/5**	Knee pain		
320029/M/11	Joint pain in knees		
	Joint pain		
	Bilateral joint pain in knees		
210015/M/11**	Jaw pain		
9930010/M/8	Hip pain		

** IPSC inadvertently unblinded to study drug

Table 24 displays the incidence rates of drug-related musculoskeletal or CNS events occurring in ≥1% of ciprofloxacin patients through the 1-year follow-up period for ciprofloxacin and control patients valid for safety. The incidence rate of any drug-related musculoskeletal or CNS event at this time point was 11% for ciprofloxacin and 3% for control. The incidence rate of drug-related arthropathy was 8% for ciprofloxacin and 2% for control.

TABLE 24
Drug-Related Musculoskeletal or CNS Events
Through One Year of Follow-Up
Occurring in ≥1% of Ciprofloxacin Treated Patients (N=487)

	Ciprofloxacin	95% Confidence Interval	Control	95% Confidence Interval
Any Musculoskeletal or CNS Event	53 (11%)	(8.3%, 14.0%)	10 (3%)	(1.0%, 3.6%)
Any Musculoskeletal Event	41 (8%)	(6.1%, 11.2%)	9 (2%)	(0.8%, 3.3%)
Arthropathy (assessed by IPSC)	40 (8%)	(5.9%, 11.0%)	9 (2%)	(0.8%, 3.3%)
Arthralgia	8 (2%)	(0.7%, 3.2%)	0	--
Any CNS Event	12 (2%)	(1.3%, 4.3%)	1 (<1%)	(<0.1%, 1.1%)
Insomnia	6 (1%)	(0.5%, 2.7%)	1 (<1%)	(<0.1%, 1.1%)
Dizziness	9 (2%)	(0.8%, 3.5%)	0	--

12.15.16 Analysis of Arthropathy Adverse Events Through One Year

At the end of the study (i.e., through one year of follow-up) there were 128 patients identified using the arthropathy algorithm. Of note, 1 patient (60001) did not appear on the algorithm at the end of the study. The patient had arthralgia as an initial adverse event, which was later clarified **as an adverse event of neck pain. The patient's case was also reviewed** by the IPSC.

Of the 129 patients reviewed by the IPSC, 70 patients were deemed by the IPSC to have possible, probable, or definite arthropathy. The information for these cases, with one exception, was included in the **applicant's statistical analyses for the study. One patient (350008) was** not considered to be valid for safety by the applicant and thus was not included in the statistical analyses.

Clinical Reviewer's Comment: ***It could not be confirmed by the applicant*** *that Patient 350008 received at least one dose of study drug, therefore the reviewer agrees with the removal of this patient from the statistical analyses. A breakdown of the remaining 69 cases by treatment received can be found in Tables 25 and 26 in Appendix 1. There were 56 cases of arthropathy in the ciprofloxacin arm and 13 in the comparator arm by one year of follow-up.*

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

Rates of arthropathy were slightly higher among patients who received IV or sequential ciprofloxacin therapy (18%; 7/39) than among those who received oral therapy (11%; 48/487). Rates of arthropathy were higher in the IV or sequential therapy groups (8%; 2/26) than among those that received oral therapy (2%; 11/474).

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

Of Note: The IPSC was inadvertently unblinded to the results of 7 patients in the ciprofloxacin arm: 870053/M/7; 270024/M/5; 350014/M/6; 210004/F/11; 210015/M/11; 350015/F/12; and 790011/M/16.

***Clinical Reviewer's Comment: Tables 27 through 36 were created by the** reviewer.*

Table 27 shows the arthropathy rates by sex of the patient. Overall enrollment into the study was about 51% female (55% for ciprofloxacin and 48% for control). The incidence of arthropathy in the overall valid for safety population for the ciprofloxacin group was 12.3% (33/269) in females and 10.5% (23/218%) in males.

TABLE 27
Sex Distribution of Patients with Arthropathy

	Ciprofloxacin N= 56	Control N= 13
Females	33 (59%)	5 (38%)
Males	23 (41%)	8 (62%)

Table 28 shows the age distribution of patients with arthropathy. In both groups, the about 38% of cases of arthropathy occurred in patients between 9 to 12 years of age.

Clinical Reviewer's Comment: The age breakdown in Table 28 is similar, but not identical to the applicant's grouping of patients by age.

TABLE 28
Age Distribution of Patients with Arthropathy

	Ciprofloxacin N= 56	Control N= 13
≤ 2 years	2 (4%)	3 (23%)
3 to 5 years	10 (18%)	1 (8%)
6 to 8 years	11 (20%)	3 (23%)
9 to 12 years	21 (37%)	5 (38%)
13 to 17 years	12 (21%)	1 (8%)

The breakdown of the arthropathy assessment by the IPSC (i.e., definite, probable, or possible arthropathy) is shown in Table 29 for ciprofloxacin

and control. In addition, for each arthropathy classification, it is noted the number of cases which were probably, possibly, or not related to study drug. The arthropathy cases in the both groups were predominantly possible arthropathies.

TABLE 29
Arthropathy Classification and Corresponding Relationship to Study Drug (as determined by IPSC)

Classification	Ciprofloxacin N= 56	Control N= 13
Definite	13 (23%) 1 probable association with study drug, 6 possible, and 6 not related	2 (15%) both were not related to study drug
Probable	13 (23%) 4 probable associations with study drug, 7 possible, and 2 not related	1 (8%) probable association with study drug
Possible	30 (54%) no probable associations with study drug, 22 possible, and 8 not related	10 (77%) 8 were possibly related to study drug and 2 were not related

Table 30 shows the reverse relationship as shown in Table 23. In Table 24 the cases for ciprofloxacin and control are grouped by relationship to study drug (i.e., probably, possibly, or not related) and then the corresponding arthropathy classification is given (i.e., definite, probable, or possible arthropathy). The majority of cases in each treatment group were possibly related to study drug.

TABLE 30
Relationship to Study Drug and Corresponding Arthropathy Classification (as determined by IPSC)

Relationship	Ciprofloxacin N= 56	Control N= 13
Probable	5 (9%) 1 was a definite arthropathy, and 4 were probable	1 (8%) probable arthropathy
Possible	35 (63%) 6 were definite arthropathies, 7 were probable, and 22 were possible	8 (61%) all possible arthropathies
None	16 (28%) 6 were definite arthropathies, 2 were probable, and 8 were	4 (31%) 2 definite arthropathies and 2 possible

Relationship	Ciprofloxacin N= 56	Control N= 13
	possible	

The severity of arthropathy events is shown in Table 31. Since many patients had more than one event, they were classified by the reviewer based upon the most severe event.

TABLE 31
Severity of Arthropathy Events

Severity of Event	Ciprofloxacin N= 56	Control N= 13
Mild	29 (52%)	3 (23%)
Moderate	16 (29%)	4 (31%)
Severe	4 (7%) 70062/M/14: myalgia, bilateral knee pain and bilateral shoulder muscle pain (associated with exercising in the pool) 210005/M/7:arthralgia, intermittent jaw pain and intermittent bilateral knee pain (back of knees) 760005/F/14: arthralgia, hip pain; back pain [serious event, resulted in hospitalization] 210015/M/11: arthralgia, jaw pain	1 (8%) 830028/F/9: arthralgia, R knee pain (patient doesn't stretch before running)
No information	7 (12%)	5 (38%)

* a patient may have had more than one event

There was only one serious arthropathy which occurred in a ciprofloxacin patient, as shown in Table 32. The event was classified by the IPSC as a possible arthropathy. The patient was being treated with chemotherapy (vincristine) and the IPSC thought the event could possibly be related to the vincristine.

TABLE 32
Serious Arthropathy Adverse Events

Ciprofloxacin N= 56	Control N= 13
One patient	No patients
760005/F/14: arthralgia, hip pain; back pain [serious event, resulted in hospitalization] IPSC: myopthy or neuropathy, could be related to vincristine toxicity	

There were two tendon disorders noted in the study, one in each treatment group, as shown in Table 33. Patient 350011 in the ciprofloxacin group had a pre-existing tendonitis in his right elbow which continued during the study and was exacerbated by pitching baseball. The IPSC classified the event as a possible arthropathy with no relationship to study drug.

TABLE 33
Tendon-Related Adverse Events

Ciprofloxacin N= 56	Control N= 13
One patient	One patient
350011/M/13: R elbow tendonitis, present at baseline, exacerbated by pitching baseball possible arthropathy, no relationship to study drug	280018/F/14: bilateral Achillean tendonitis IPSC: not warming up in sports, spondyloarthritis Probable arthropathy, probable relationship to study drug

Table 34 shows the arthropathy events which developed while the patient was still receiving study medication. Of the patients with arthropathy, similar percentages (37% for ciprofloxacin and 38% for control) developed arthropathy before the end of treatment with study drug.

TABLE 34
Patients with Arthropathy Developing During Study Drug Administration

Ciprofloxacin N= 56		Control N= 13	
21/56 (37%)		5/13 (38%)	
Pt. Number	COSTART term /Description	Pt. Number	COSTART term/ Description
80006/F/14	Arthralgia/shoulder pain	500026/M/1	--/R hip pain and tenderness on joint exam
170001/M/2	Arthralgia/L ankle tenderness	500032/M/15	--/R hip pain and tenderness on joint exam
	Arthralgia/L knee tenderness		

Ciprofloxacin N= 56		Control N= 13	
21/56 (37%)		5/13 (38%)	
Pt. Number	COSTART term /Description	Pt. Number	COSTART term/ Description
210005/M/7	Arthralgia/intermittent jaw pain	870025/M/2	--/bilateral knee tenderness on joint exam
350012/M/15	--/bilateral ankle and foot swelling	280018/F/14	Tendon disorder/bilateral Achillean tendonitis
350013/F/9	Peripheral edema/bilateral ankle swelling		
350020/F/7	--/L shoulder pain		
380006/F/10	Arthralgia/jaw pain		
400049/F/11	Arthralgia/intermittent L shoulder pain		
490054/F/15	--/L shoulder pain and tenderness on joint exam		
	--/R ankle and foot pain on joint exam		
580001/F/6*	--/R shoulder tenderness on joint exam		
9930001/F/10	--/bilateral hip pain on joint exam (pre-existing)		
220001/F/2	Arthralgia/elbow pain		
250033/F/13	Arthralgia/R wrist pain		
270017/F/8	Arthralgia/bilateral knee pain		
	Arthralgia/bilateral ankle pain		
460001/F/10	Arthralgia/L wrist pain		
	Arthralgia/R knee pain		
210004/F/11**	Arthralgia/L elbow pain		
	Arthralgia/L shoulder pain		
	Arthralgia/L elbow pain		
210015/M/11**	Joint disorder/stiffness in hands and fingers		
30011/M/6	Arthralgia/L elbow		