



## Clinical trial results:

**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 followed by oral therapy or purely IV therapy) or a non-quinolone antibiotic (either as oral suspension, oral tablets or sequential IV followed by oral therapy or purely IV therapy) in the treatment of pediatric patients with infectious diagnoses**

### Summary

EudraCT number	2014-004622-18
Trial protocol	Outside EU/EEA
Global end of trial date	03 January 2008

### Results information

Result version number	v2 (current)
This version publication date	02 September 2016
First version publication date	19 July 2015
Version creation reason	<ul style="list-style-type: none"><li>• New data added to full data set</li><li>• Correction of full data set</li></ul> Bayer sponsor contact information to be updated

### Trial information

#### Trial identification

Sponsor protocol code	BAY O 9867/100201
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00761462
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368, Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@baye.com

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 January 2008
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 January 2008
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

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 (that is [i.e.], pathology of the joint) and other musculoskeletal sequelae (i.e., articular cartilage, tendon, and ligament), if any, of intravenous (IV), sequential (IV followed by oral), and purely oral ciprofloxacin therapy or non-quinolone antibiotic therapy in pediatric subjects with various infectious conditions.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or their legally authorized representative. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 October 1999
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 979
Country: Number of subjects enrolled	Canada: 15
Worldwide total number of subjects	994
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	185
Children (2-11 years)	732
Adolescents (12-17 years)	77
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Observational study in which subjects were recruited between 1999 and 2002, and followed up for 5 years (ciprofloxacin subjects) or 2 years (non-ciprofloxacin subjects), monitoring the occurrence of musculoskeletal and central nervous system events.

### Pre-assignment

Screening details:

The decision to treat with ciprofloxacin or a non-quinolone antibiotic was made prior to a subject's enrolment in the study and was based on the particular infection, type of subject, medical history, and the clinical evaluation by the prescribing physician. The study was not randomized.

### Period 1

Period 1 title	Treatment Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Ciprofloxacin

Arm description:

Subjects receiving Ciprofloxacin (group followed-up for 5 years).

Arm type	Experimental
Investigational medicinal product name	Ciprofloxacin
Investigational medicinal product code	BAY O 9867
Other name	
Pharmaceutical forms	Injection, Oral suspension, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Either as oral suspension, oral tablets or sequential IV - oral therapy or purely IV therapy according to label. Dose and duration of ciprofloxacin was at the discretion of the pediatric investigator. The maximum permissible doses of ciprofloxacin were 750 milligram (mg) twice daily orally (that is, total daily dose 1500 mg) or 400 mg three times daily intravenously (that is, total daily dose 1200 mg).

<b>Arm title</b>	Non-quinolone Antibiotic
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Arm description:

Subjects receiving non-quinolone antibiotic (group followed-up for 2 years).

Arm type	Active comparator
Investigational medicinal product name	Non-quinolone antibiotic
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Oral suspension, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Either as oral suspension, oral tablets or sequential IV - oral therapy or purely IV therapy according to label. Dose and duration of non-quinolone antibiotic was at the discretion of the pediatric investigator. Investigators used the approved product labeling for the selected antibiotic for their respective maximum dosages and frequency of administration within a 24-hour period.

Number of subjects in period 1	Ciprofloxacin	Non-quinolone Antibiotic
Started	510	519
Subjects received treatment	487	507
Completed	487	507
Not completed	23	12
Subjects never received study medication	23	12

## Period 2

Period 2 title	2 or 5 years long-term safety Follow-up
Is this the baseline period?	Yes <sup>[1]</sup>
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Ciprofloxacin

### Arm description:

Subjects receiving Ciprofloxacin entered in the long term safety evaluation (group followed-up for 5 years).

Arm type	Experimental
Investigational medicinal product name	Ciprofloxacin
Investigational medicinal product code	BAY O 9867
Other name	
Pharmaceutical forms	Injection, Oral suspension, Tablet
Routes of administration	Intravenous use, Oral use

### Dosage and administration details:

Either as oral suspension, oral tablets or sequential IV - oral therapy or purely IV therapy according to label. Dose and duration of ciprofloxacin was at the discretion of the pediatric investigator. The maximum permissible doses of ciprofloxacin were 750 mg twice daily orally (that is, total daily dose 1500 mg) or 400 mg three times daily intravenously (that is, total daily dose 1200 mg).

<b>Arm title</b>	Non-quinolone antibiotic
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### Arm description:

Subjects receiving non-quinolone antibiotic entered in the long term safety evaluation (group followed-up for 2 years).

Arm type	Active comparator
Investigational medicinal product name	Non-quinolone antibiotic
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Oral suspension, Tablet
Routes of administration	Intravenous use, Oral use

### Dosage and administration details:

Either as oral suspension, oral tablets or sequential IV - oral therapy or purely IV therapy according to label. Dose and duration of non-quinolone antibiotic was at the discretion of the pediatric investigator. Investigators used the approved product labeling for the selected antibiotic for their respective maximum dosages and frequency of administration within a 24-hour period.

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Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: It was planned that only subjects in safety population who received at least 1 dose of study drug were to be included in baseline period.

<b>Number of subjects in period 2</b>	Ciprofloxacin	Non-quinolone antibiotic
Started	487	507
4-6 Weeks Post Treatment	487	507
1 Year Follow-up	485	507
Completed	333	456
Not completed	154	51
Consent withdrawn by subject	75	21
Death	4	-
Lost to follow-up	75	30

## Baseline characteristics

### Reporting groups

Reporting group title	Ciprofloxacin
Reporting group description:	
Subjects receiving Ciprofloxacin entered in the long term safety evaluation (group followed-up for 5 years).	
Reporting group title	Non-quinolone antibiotic
Reporting group description:	
Subjects receiving non-quinolone antibiotic entered in the long term safety evaluation (group followed-up for 2 years).	

Reporting group values	Ciprofloxacin	Non-quinolone antibiotic	Total
Number of subjects	487	507	994
Age categorical			
Units: subjects			
>= 2 months through 12 month	37	48	85
>=13 months through 23 month	48	52	100
>=2 years through 5 years	150	165	315
>= 6 years through 11 years	194	223	417
>=12 years through 16 years	58	19	77
Gender categorical			
Units: subjects			
Female	269	242	511
Male	218	265	483
Type of infection, pre-treatment			
Type of infection, pre-treatment, which qualified subjects for long term safety evaluation			
Units: Subjects			
Category 1, Otitis Media	143	207	350
Category 2, Pharyngitis / Tonsillitis	39	148	187
Category 3, Urinary Tract	105	12	117
Category 4, Sinusitis	39	47	86
Category 5, Pyelonephritis	24	8	32
Category 6, Pneumonia	12	17	29
Category 7, Bronchitis	7	7	14
Category 8, Abscess	7	6	13
Category 9, Skin Infection	6	7	13
Category 10, External Otitis	10	1	11
Category 11, Wound Infection	7	2	9
Category 12, Other Respiratory Tract Infection	2	6	8
Category 13, Bacteremia	6	1	7
Category 14, Shigellosis	7	0	7
Category 15, Acute Bronchitis	2	5	7
Category 16, Pseudomonas Infections	6	0	6
Category 17, Abscess with cellulitis	2	4	6
Category 18, Mastoiditis	5	0	5
Category 19, Cystitis	5	0	5
Category 20, Other	53	29	82





## End points

### End points reporting groups

Reporting group title	Ciprofloxacin
Reporting group description: Subjects receiving Ciprofloxacin (group followed-up for 5 years).	
Reporting group title	Non-quinolone Antibiotic
Reporting group description: Subjects receiving non-quinolone antibiotic (group followed-up for 2 years).	
Reporting group title	Ciprofloxacin
Reporting group description: Subjects receiving Ciprofloxacin entered in the long term safety evaluation (group followed-up for 5 years).	
Reporting group title	Non-quinolone antibiotic
Reporting group description: Subjects receiving non-quinolone antibiotic entered in the long term safety evaluation (group followed-up for 2 years).	

### Primary: Incidence of Arthropathy (cumulative)

End point title	Incidence of Arthropathy (cumulative) <sup>[1]</sup>
End point description: Arthropathy, as assessed by independent safety committee. The committee, after reviewing data related to musculoskeletal events, decided whether each subject had arthropathy or not. Each incidence includes number shown at previous time point, plus any new subjects with the event. The 112/20 arthropathies were mentioned in the other Adverse Events section as well.	
End point type	Primary
End point timeframe: 4-6 weeks after treatment / 1 year after treatment / 2 or 5 years after treatment	

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was non-randomized, and the treatment groups were not comparable in their background infection types or demographics. Subjects in the ciprofloxacin group were enrolled with much more severe infections than those in the control group. Further, subjects were not enrolled into the control group until well after enrolment into the ciprofloxacin group had started. Since, the groups were not comparable and there was no randomization; no inferential statistical analyses were performed.

End point values	Ciprofloxacin	Non-quinolone antibiotic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	487 <sup>[2]</sup>	507 <sup>[3]</sup>		
Units: subjects				
number (not applicable)				
4-6 weeks after treatment	39	9		
1 year after treatment	64	16		
2 or 5 years after treatment	112	20		

#### Notes:

[2] - Subjects valid for safety (all subjects confirmed to have received at least one dose of study drug).

[3] - Subjects valid for safety (all subjects confirmed to have received at least one dose of study drug).

### Statistical analyses

No statistical analyses for this end point

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**Primary: Incidence of Nervous System Events (cumulative)**

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End point title	Incidence of Nervous System Events (cumulative) <sup>[4]</sup>
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End point description:

Any event within the Medical Dictionary for Drug Regulatory Affairs (MedDRA) system organ class 'Nervous System disorders'. Each incidence includes number shown at the previous time point, plus any new subjects with the event.

End point type	Primary
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End point timeframe:

4-6 weeks after treatment / 1 year after treatment / 2 or 5 years after treatment

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This study was non-randomized, and the treatment groups were not comparable in their background infection types or demographics. Subjects in the ciprofloxacin group were enrolled with much more severe infections than those in the control group. Further, subjects were not enrolled into the control group until well after enrolment into the ciprofloxacin group had started. Since, the groups were not comparable and there was no randomization; no inferential statistical analyses were performed.

End point values	Ciprofloxacin	Non-quinolone antibiotic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	487 <sup>[5]</sup>	507 <sup>[6]</sup>		
Units: subjects				
number (not applicable)				
4-6 weeks after treatment	38	10		
1 year after treatment	49	13		
2 or 5 years after treatment	56	17		

Notes:

[5] - Subjects valid for safety (all subjects confirmed to have received at least one dose of study drug).

[6] - Subjects valid for safety (all subjects confirmed to have received at least one dose of study drug).

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Day 28 to 42 up to 2 or 5 years after study drug administration

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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### Reporting groups

Reporting group title	Non-quinolone antibiotic
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Reporting group description:

Subjects receiving non-quinolone antibiotic (group followed-up for 2 years).

Reporting group title	Ciprofloxacin
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Reporting group description:

Subjects receiving Ciprofloxacin (group followed-up for 5 years).

Serious adverse events	Non-quinolone antibiotic	Ciprofloxacin	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 507 (1.18%)	25 / 487 (5.13%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 507 (0.00%)	3 / 487 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Astrocytoma			
subjects affected / exposed	1 / 507 (0.20%)	0 / 487 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system leukaemia			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Subclavian vein thrombosis			

subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 507 (0.00%)	4 / 487 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 507 (0.39%)	0 / 487 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial thrombosis			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 507 (0.00%)	3 / 487 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 507 (0.20%)	0 / 487 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Neurogenic bladder			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nephropathy			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvi-ureteric obstruction			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicoureteric reflux			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 507 (0.00%)	2 / 487 (0.41%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Empyema			
subjects affected / exposed	1 / 507 (0.20%)	0 / 487 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 507 (0.00%)	2 / 487 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perianal abscess			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 507 (0.20%)	0 / 487 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 507 (0.00%)	2 / 487 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 507 (0.00%)	1 / 487 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

<b>Non-serious adverse events</b>	Non-quinolone antibiotic	Ciprofloxacin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 507 (13.81%)	192 / 487 (39.43%)	
Injury, poisoning and procedural complications			
Joint sprain			
subjects affected / exposed	5 / 507 (0.99%)	13 / 487 (2.67%)	
occurrences (all)	6	16	
Contusion			
subjects affected / exposed	8 / 507 (1.58%)	11 / 487 (2.26%)	
occurrences (all)	11	11	
Nervous system disorders			



Headache subjects affected / exposed occurrences (all)	8 / 507 (1.58%) 11	31 / 487 (6.37%) 38	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Pyrexia subjects affected / exposed occurrences (all)	0 / 507 (0.00%) 0  7 / 507 (1.38%) 7	18 / 487 (3.70%) 19  19 / 487 (3.90%) 19	
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	5 / 507 (0.99%) 5  2 / 507 (0.39%) 2  5 / 507 (0.99%) 5	12 / 487 (2.46%) 12  14 / 487 (2.87%) 14  18 / 487 (3.70%) 20	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 507 (0.59%) 3	16 / 487 (3.29%) 16	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	4 / 507 (0.79%) 4	17 / 487 (3.49%) 18	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)  Arthralgia subjects affected / exposed occurrences (all)	7 / 507 (1.38%) 7  14 / 507 (2.76%) 15	36 / 487 (7.39%) 44  85 / 487 (17.45%) 152	
Infections and infestations			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	8 / 507 (1.58%) 8	17 / 487 (3.49%) 17	
Otitis media subjects affected / exposed occurrences (all)	15 / 507 (2.96%) 16	20 / 487 (4.11%) 23	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 1999	<p>The amendment was added:</p> <ul style="list-style-type: none"><li>- To clarify the timing interval between ciprofloxacin and infant formula (2 hours before or after)</li><li>- To correct discrepancies among the age groups referred to</li><li>- To delete a reference to a data collection instrument other than a care report form</li><li>- To provide clarification on performance of required gait/joint examinations and the category of professional (i.e., evaluator) required to perform the exams (physical therapist or rheumatologist)</li><li>- To specify the type of intervention (i.e., imaging) to evaluate cases presenting with signs and/or symptoms suggestive of arthropathy</li><li>- To add a cap on enrollment of subjects in the adolescent age group (a single center should not have enrolled more than two subjects aged 12 to 16 years of age)</li><li>- To clarify the categorization and reporting of adverse events during the long term follow-up</li></ul>
20 July 2000	<p>The second amendment provided for the following:</p> <ul style="list-style-type: none"><li>- Extended the permissible window for a subject'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.</li><li>- Allowed for enrollment of children reliant on infant formula provided they were treated with IV medication only;</li><li>- Corrected a typographical error in the dose strength of the 5 percent (%) suspension;</li><li>- 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;</li><li>- Clarified that subjects enrolled into the 100169 complicated urinary tract infection study could be enrolled into the observational study provided informed consent was provided to allow for retrospective collection of the initial year's data.</li></ul>
23 January 2001	<p>The purpose of the third amendment was to:</p> <ul style="list-style-type: none"><li>- Allow for enrollment of subjects up to 72 hours after initiation of study drug treatment;</li><li>- Specify provisions for performance of the gait/joint examination when a certified physical therapist was not available;</li><li>- Clarify the expectation for documentation of the Range of motion examination within the case report form;</li><li>- Allow for enrollment of children with febrile neutropenia receiving ciprofloxacin prophylaxis pending recovery of white blood cell (WBC) count to greater than or equal to (<math>\geq</math>) 500 cells per millimeter<sup>3</sup>;</li><li>- Clarify the exclusion of children with cystic fibrosis from the protocol;</li><li>- To provide a gait/joint examination flow diagram.</li></ul>

30 October 2001	<p>The purpose of the fourth amendment was to incorporate the following changes, as requested by the Food and Drugs Administration (FDA):</p> <ul style="list-style-type: none"> <li>- Add 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 subjects.</li> <li>- Shorten 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. Subjects who experienced a musculoskeletal adverse event during therapy were to be followed for 5 years regardless of their stage of pubescence.</li> <li>- Revise downward the total number of subjects to be enrolled from 3,000 to approximately 900 subjects. Approximately half (450) of these 900 subjects 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 was based on combining these 900 subjects with at least 600 subjects available from another pediatric ciprofloxacin trial.</li> <li>- Demographic and baseline characteristics were to be summarized by treatment group as well as type of ciprofloxacin treatment (IV versus oral), age group (<math>\geq</math> 2 months to less than [<math>&lt;</math>] 24 months; 2 years to <math>&lt;</math> 6 years; <math>\geq</math> 6 years to <math>&lt;</math> 12 years; <math>\geq</math> 12 years to <math>&lt;</math> 17 years).</li> <li>- The decision to treat with ciprofloxacin or a non-quinolone antibiotic was made prior to a subject's enrollment in the study and was based on the particular infection, type of subject, medical history and the clinical evaluation by the prescribing physician.</li> </ul>
03 November 2004	<p>The purpose of the fifth amendment was to incorporate the following change, as requested by the FDA:</p> <p>Shorten the follow-up period for the non-quinolone arm from five years to up to two years. This change was made because the FDA no longer required a follow-up for musculoskeletal events in pediatric subjects receiving non-quinolone treatment. At the time of this amendment, the study dataset included data collected for subjects up to two years, so this data was analyzed.</p>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was not randomized or blinded; the demographic and baseline infection characteristics were not comparable for the treatment groups; the long term follow-up times were different for the two groups (5 year versus 2 years).

Notes: