Clinical trial results:
Safety, Tolerability and Pharmacokinetics of Single Dose Intravenous Moxifloxacin in Pediatric Patients

Summary

EudraCT number	2012-000737-40
Trial protocol	Outside EU/EEA
Global end of trial date	12 August 2013

Results information

Result version number	v1
This version publication date	12 July 2016
First version publication date	26 June 2015

Trial information

Trial identification

Sponsor protocol code	BAY12-8039/11826

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01049022
WHO universal trial number (UTN)	-
Other trial identifiers	Project ID: 1962

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000288-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to describe the pharmacokinetics (PK) of moxifloxacin in children of different ages, in order to determine a dose which will provide a similar exposure as seen in adults treated with the approved therapeutic dose of 400 milligram (mg).

Protection of trial subjects:

All clinical work conducted in this study was subjected to the rules of Good Clinical Practice and under the guidelines of Declaration of Helsinki. Participating subjects or their legally authorized representative 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. Since the study was conducted in children, both parents or legal guardian may have provided informed consent, in addition to the child assenting to participation in the study, when possible. Only children requiring antibiotic therapy were included in the study, as Moxifloxacin may provide some clinical benefit for these subjects, in addition to that of their prescribed medication.
The study was following a stepwise staggered enrollment concept to allow for dose adjustment if deemed necessary due to safety reasons with dose not exceeding 10 milligram per kilogram (mg/kg) or 400 mg. Dosage predictions were based on a stepwise evaluation of the clinical PK information and safety results from group to group as well as from older to younger children.

Background therapy:

All subjects received antibiotic (Non-quinolone) therapy for a suspected or proven infection at the time of study treatment.

Evidence for comparator: -

Actual start date of recruitment	24 May 2010
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: 31
Worldwide total number of subjects	31
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	7
Children (2-11 years)	22
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 6 study centers in the United States of America (USA) with first patient first visit (FPFV) on 24 May 2010 and last patient last visit (LPLV) as 12 August 2013.

Pre-assignment

Screening details:

A total of 44 subjects were screened, out of which 13 subjects had screening failure. Six subjects withdrew consent, 6 subjects were in violation of the protocol and 1 subject qualified for study entry but was not needed. Therefore, 31 subjects were assigned to treatment and received a dose of Moxifloxacin according to their assigned dose level.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Moxifloxacin (Avelox, BAY12-8039), Cohort 1

Arm description:

Single intravenous (IV) infusion of moxifloxacin administered over 60 minutes, at an initial dosage of 5 milligram per kilogram per body weight (mg/kg/BW) with dose escalation to 6 mg/kg in subjects of age 6 years (yrs) to less than or equal to (<=) 14 years.

Arm type	Experimental
Investigational medicinal product name	Moxifloxacin
Investigational medicinal product code	BAY12-8039
Other name	Avelox
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single IV infusion of moxifloxacin administered over 60 minutes, at an initial dosage of 5 mg/kg/BW with dose escalation to 6 mg/kg in subjects.

Arm title	Moxifloxacin (Avelox, BAY12-8039), Cohort 2

Arm description:

Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 7 mg/kg/BW with dose escalation to 8 mg/kg in subjects of age 2 years to less than (<) 6 years; dose escalation was based on evaluations of the PK and safety data from the subjects in a preceding cohort.

Arm type	Experimental
Investigational medicinal product name	Moxifloxacin
Investigational medicinal product code	BAY12-8039
Other name	Avelox
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single IV infusion of moxifloxacin administered over 60 minutes, at an initial dosage of 7 - 8 mg/kg/BW in subjects.

Arm title	Moxifloxacin (Avelox, BAY12-8039), Cohort 3

Arm description:

Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 9 mg/kg/BW with dose escalation to 10 mg/kg in subjects of age 3 months to <2 years; dose escalation was based on evaluations of the PK and safety data from the subjects in a preceding cohort.

Arm type	Experimental
Investigational medicinal product name	Moxifloxacin
Investigational medicinal product code	BAY12-8039
Other name	Avelox
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 9 - 10 mg/kg/BW in subjects.

Number of subjects in period 1	Moxifloxacin (Avelox, BAY12-8039), Cohort 1	Moxifloxacin (Avelox, BAY12-8039), Cohort 2	Moxifloxacin (Avelox, BAY12-8039), Cohort 3
Started	12	12	7
Completed	8	11	6
Not completed	4	1	1
Lost to follow-up	4	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Moxifloxacin (Avelox, BAY12-8039), Cohort 1
Reporting group description:	
Single intravenous (IV) infusion of moxifloxacin administered over 60 minutes, at an initial dosage of 5 milligram per kilogram per body weight (mg/kg/BW) with dose escalation to 6 mg/kg in subjects of age 6 years (yrs) to less than or equal to (<=) 14 years.	
Reporting group title	Moxifloxacin (Avelox, BAY12-8039), Cohort 2
Reporting group description:	
Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 7 mg/kg/BW with dose escalation to 8 mg/kg in subjects of age 2 years to less than (<) 6 years; dose escalation was based on evaluations of the PK and safety data from the subjects in a preceding cohort.	
Reporting group title	Moxifloxacin (Avelox, BAY12-8039), Cohort 3
Reporting group description:	
Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 9 mg/kg/BW with dose escalation to 10 mg/kg in subjects of age 3 months to <2 years; dose escalation was based on evaluations of the PK and safety data from the subjects in a preceding cohort.	

Reporting group values	Moxifloxacin (Avelox, BAY12-8039), Cohort 1	Moxifloxacin (Avelox, BAY12-8039), Cohort 2	Moxifloxacin (Avelox, BAY12-8039), Cohort 3
Number of subjects	12	12	7
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	7
Children (2-11 years)	10	12	0
Adolescents (12-17 years)	2	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	9.2	3.9	1.1
standard deviation	± 2.4	± 1.1	± 0.6
Gender categorical			
Units: Subjects			
Female	3	3	1
Male	9	9	6
Findings on Medical History			
All subjects who were enrolled and treated in the study had a pre-existing condition for which they were already receiving antibiotics for suspected or proven infection and for which treatment with a fluoroquinolone antibiotic infusion (such as moxifloxacin) was indicated. The variety of pre-existing medical conditions within the subject population confounds and limits the value in interpretation of the medical history across cohorts and in the overall subject population.			
Units: Subjects			
Any findings	12	12	7
Prior Medication			

Subjects received prior medications due to the enrollment requirement for a pre-existing condition and the inclusion criteria, which required all subjects to receive antibiotics for a suspected or proven infection at the time of study treatment. Prior medications that were used to treat pre-existing or treatment-emergent adverse events (TEAEs) were summarized by Anatomical Therapeutic Chemical code (ATC) generic name.			
Units: Subjects			
Any finding	12	12	7

Reporting group values	Total		
Number of subjects	31		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	7		
Children (2-11 years)	22		
Adolescents (12-17 years)	2		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	7		
Male	24		
Findings on Medical History			
All subjects who were enrolled and treated in the study had a pre-existing condition for which they were already receiving antibiotics for suspected or proven infection and for which treatment with a fluoroquinolone antibiotic infusion (such as moxifloxacin) was indicated. The variety of pre-existing medical conditions within the subject population confounds and limits the value in interpretation of the medical history across cohorts and in the overall subject population.			
Units: Subjects			
Any findings	31		
Prior Medication			
Subjects received prior medications due to the enrollment requirement for a pre-existing condition and the inclusion criteria, which required all subjects to receive antibiotics for a suspected or proven infection at the time of study treatment. Prior medications that were used to treat pre-existing or treatment-emergent adverse events (TEAEs) were summarized by Anatomical Therapeutic Chemical code (ATC) generic name.			
Units: Subjects			
Any finding	31		

End points

End points reporting groups

Reporting group title	Moxifloxacin (Avelox, BAY12-8039), Cohort 1
Reporting group description:	
Single intravenous (IV) infusion of moxifloxacin administered over 60 minutes, at an initial dosage of 5 milligram per kilogram per body weight (mg/kg/BW) with dose escalation to 6 mg/kg in subjects of age 6 years (yrs) to less than or equal to (<=) 14 years.	
Reporting group title	Moxifloxacin (Avelox, BAY12-8039), Cohort 2
Reporting group description:	
Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 7 mg/kg/BW with dose escalation to 8 mg/kg in subjects of age 2 years to less than (<) 6 years; dose escalation was based on evaluations of the PK and safety data from the subjects in a preceding cohort.	
Reporting group title	Moxifloxacin (Avelox, BAY12-8039), Cohort 3
Reporting group description:	
Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 9 mg/kg/BW with dose escalation to 10 mg/kg in subjects of age 3 months to <2 years; dose escalation was based on evaluations of the PK and safety data from the subjects in a preceding cohort.	
Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), 5.0 mg/kg, 6 to <=14 yrs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Single IV infusion of Moxifloxacin administered over 60 minutes, at a dosage of 5.0 mg/kg per body weight in subjects of age 6 years to <=14 years.	
Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), 6.0 mg/kg, 6 to <=14 yrs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Single IV infusion of Moxifloxacin administered over 60 minutes, at a dosage of 6.0 mg/kg per body weight in subjects of age 6 years to <=14 years.	
Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), 7.0 mg/kg, 2 to <6 yrs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Single IV infusion of Moxifloxacin administered over 60 minutes, at a dosage of 7.0 mg/kg per body weight in subjects of age 2 years to <6 years.	
Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), 8.0 mg/kg, 2 to <6 yrs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Single IV infusion of Moxifloxacin administered over 60 minutes, at a dosage of 8.0 mg/kg per body weight in subjects of age 2 years to <6 years.	
Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), 9.0 mg/kg, 3months to <2yrs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Single IV infusion of Moxifloxacin administered over 60 minutes, at a dosage of 9.0 mg/kg per body weight in subjects of age 3 months to <2 years.	
Subject analysis set title	Moxifloxacin(Avelox, BAY12-8039), 10.0 mg/kg, 3months to <2yrs
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Single IV infusion of Moxifloxacin administered over 60 minutes, at a dosage of 10.0 mg/kg per body weight in subjects of age 3 months to <2 years.	
Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), Cohort 1, Male
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Single IV infusion of moxifloxacin administered over 60 minutes, at an initial dosage of 5 mg/kg/BW with dose escalation to 6 mg/kg in male subjects of age 6 years to <=14 years.	

Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), Cohort 1, Female
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Single IV infusion of moxifloxacin administered over 60 minutes, at an initial dosage of 5 mg/kg/BW with dose escalation to 6 mg/kg in female subjects of age 6 years to <=14 years.

Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), Cohort 2, Male
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 7 mg/kg/BW with dose escalation to 8 mg/kg in male subjects of age 2 years to <6 years; dose escalation was based on evaluations of the PK data from the subjects in a preceding cohort.

Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), Cohort 2, Female
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 7 mg/kg/BW with dose escalation to 8 mg/kg in female subjects of age 2 years to <6 years; dose escalation was based on evaluations of the PK data from the subjects in a preceding cohort.

Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), Cohort 3, Male
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 9 mg/kg/BW with dose escalation to 10 mg/kg in male subjects of age 3 months to <2 years; dose escalation was based on evaluations of the PK data from the subjects in a preceding cohort.

Subject analysis set title	Moxifloxacin (Avelox, BAY12-8039), Cohort 3, Female
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 9 mg/kg/BW with dose escalation to 10 mg/kg in female subjects of age 3 months to <2 years; dose escalation was based on evaluations of the PK data from the subjects in a preceding cohort.

Subject analysis set title	Pharmacokinetic Analysis Set (PKS) population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PKS population included any subject who received moxifloxacin (BAY12-8039) and had an adequate number of PK samples collected.

Subject analysis set title	Safety Analysis Set (SAF) population
Subject analysis set type	Safety analysis

Subject analysis set description:

SAF population included all subjects who was assigned to treatment received at least 1 dose of study drug and had post-treatment safety data.

Primary: Area under the Concentration-Time Curve (AUC) of Moxifloxacin and its Metabolites

End point title	Area under the Concentration-Time Curve (AUC) of Moxifloxacin and its Metabolites[1]

End point description:

The AUC is a measure of systemic drug exposure, which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. '99999' in the reported data indicates that geometric coefficient of variation was not calculated as only 1 subject was evaluable.

End point type	Primary

End point timeframe:

Pre-dose, 1 hour (end of infusion), 1.5, 4, 8, 12 and 24 hours (Day 2) after start of infusion (samples at 36 h and 48 h were optional)

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: No inferential statistics done. Descriptive statistics evaluation of the parameters was

performed in order to select the dose in children.

End point values	Moxifloxacin (Avelox, BAY12-8039), 5.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 6.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 7.0 mg/kg, 2 to <6 yrs	Moxifloxacin (Avelox, BAY12-8039), 8.0 mg/kg, 2 to <6 yrs
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7[2]	5[3]	7[4]	5[5]
Units: milligram*hour per liter				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039) (N=7, 5, 7, 5, 6, 1)	19.73 (± 30.53)	24.04 (± 24.11)	28.21 (± 42.75)	27.18 (± 19.29)
Metabolite M-1 (BAY31-8061) (N=6, 4, 7, 5, 6, 1)	0.5648 (± 67.66)	0.9838 (± 47.59)	1.4482 (± 35.37)	1.1104 (± 54.27)
Metabolite M-2 (BAY58-8178) (N=7, 5, 7, 5, 6, 1)	7.602 (± 43.51)	6.995 (± 88.27)	15.05 (± 41.66)	10.517 (± 47.2)

Notes:

[2] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[3] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[4] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[5] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

End point values	Moxifloxacin (Avelox, BAY12-8039), 9.0 mg/kg, 3months to <2yrs	Moxifloxacin(Avelox, BAY12-8039), 10.0 mg/kg, 3months to <2yrs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[6]	1[7]		
Units: milligram*hour per liter				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039) (N=7, 5, 7, 5, 6, 1)	25.52 (± 17.26)	40.51 (± 99999)		
Metabolite M-1 (BAY31-8061) (N=6, 4, 7, 5, 6, 1)	2.0205 (± 56.78)	3.6234 (± 99999)		
Metabolite M-2 (BAY58-8178) (N=7, 5, 7, 5, 6, 1)	17.593 (± 47.61)	20.515 (± 99999)		

Notes:

[6] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[7] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Drug Concentration in Plasma (Cmax) of Moxifloxacin and its Metabolites

End point title	Maximum Observed Drug Concentration in Plasma (Cmax) of Moxifloxacin and its Metabolites[8]

End point description:

Cmax refers to the highest measured drug concentration which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. Geometric mean and

percentage geometric coefficient of variation (%CV) were reported. '99999' in the reported data indicates that geometric coefficient of variation was not calculated as only 1 subject was evaluable.

End point type	Primary

End point timeframe:

Pre-dose, 1 hour (end of infusion), 1.5, 4, 8, 12 and 24 hours (Day 2) after start of infusion (samples at 36 h and 48 h were optional)

Notes:

[8] - 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: No inferential statistics done. Descriptive statistics evaluation of the parameters was performed in order to select the dose in children.

End point values	Moxifloxacin (Avelox, BAY12-8039), 5.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 6.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 7.0 mg/kg, 2 to <6 yrs	Moxifloxacin (Avelox, BAY12-8039), 8.0 mg/kg, 2 to <6 yrs
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7[9]	5[10]	7[11]	5[12]
Units: milligram per liter				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039)	3.159 (± 33.33)	4.607 (± 17.1)	6.514 (± 43.54)	5.644 (± 10.71)
Metabolite M-1 (BAY31-8061)	0.0761 (± 43.52)	0.1158 (± 115.01)	0.2573 (± 44.12)	0.2142 (± 90.21)
Metabolite M-2 (BAY58-8178)	0.6661 (± 41.21)	0.8072 (± 98.07)	1.5942 (± 53.26)	1.3184 (± 74.63)

Notes:

[9] - PKS

[10] - PKS

[11] - PKS

[12] - PKS

End point values	Moxifloxacin (Avelox, BAY12-8039), 9.0 mg/kg, 3months to <2yrs	Moxifloxacin(Avelox, BAY12-8039), 10.0 mg/kg, 3months to <2yrs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[13]	1[14]		
Units: milligram per liter				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039)	5.308 (± 14.67)	5.964 (± 99999)		
Metabolite M-1 (BAY31-8061)	0.3236 (± 40.05)	0.5005 (± 99999)		
Metabolite M-2 (BAY58-8178)	2.0927 (± 48.26)	1.9228 (± 99999)		

Notes:

[13] - PKS

[14] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment Emergent Findings on Joint Assessment: Baseline

End point title	Number of Subjects With Treatment Emergent Findings on Joint Assessment: Baseline[15]

End point description:

Joint assessment included formal physical examination of all joints with special care and attention to the weight-bearing joints (such as, knees, hips, and ankles) and to the shoulder girdle. All joints were examined for pain/tenderness, evidence of inflammation (i.e., redness, warmth, deformity, swelling or ballotable fluid), loss of function (to the extent this could be assessed in younger children and infants), and any restrictions to expected active/passive range of motion. Both active and passive range of motion were assessed. An incidence count was reported as the number of subjects with at least one finding at baseline, regardless of side.

End point type	Primary

End point timeframe:

Baseline

Notes:

[15] - 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: No inferential statistics done. Descriptive statistics evaluation of the parameters was performed in order to select the dose in children.

End point values	Moxifloxacin (Avelox, BAY12-8039), Cohort 1	Moxifloxacin (Avelox, BAY12-8039), Cohort 2	Moxifloxacin (Avelox, BAY12-8039), Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12[16]	12[17]	7[18]	
Units: subjects				
Achilles tendon: Any findings	0	0	1	
Elbow: Any findings	1	2	0	
Wrist: Any findings	0	1	1	

Notes:

[16] - SAF

[17] - SAF

[18] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment Emergent Findings on Joint Assessment : At any Time During Treatment

End point title	Number of Subjects With Treatment Emergent Findings on Joint Assessment : At any Time During Treatment[19]

End point description:

Joint assessment included formal physical examination of all joints with special care and attention to the weight-bearing joints (such as, knees, hips, and ankles) and to the shoulder girdle. All joints were examined for pain/tenderness, evidence of inflammation (i.e., redness, warmth, deformity, swelling or ballotable fluid), loss of function (to the extent this could be assessed in younger children and infants), and any restrictions to expected active/passive range of motion. Both active and passive range of motion were assessed. An incidence count was reported as the number of subjects with at least one finding at any time during treatment, regardless of side.

End point type	Primary

End point timeframe:

Day 1 up to Year 5 (follow-up)

Notes:

[19] - 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: No inferential statistics done. Descriptive statistics evaluation of the parameters was performed in order to select the dose in children.

End point values	Moxifloxacin (Avelox, BAY12-8039), Cohort 1	Moxifloxacin (Avelox, BAY12-8039), Cohort 2	Moxifloxacin (Avelox, BAY12-8039), Cohort 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12[20]	12[21]	7[22]	
Units: subjects				
Elbow: Any findings	1	2	0	
Wrist: Any findings	0	3	1	

Notes:

[20] - SAF

[21] - SAF

[22] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Drug Concentration in Plasma (tmax) of Moxifloxacin and its Metabolites

End point title	Time to Reach Maximum Drug Concentration in Plasma (tmax) of Moxifloxacin and its Metabolites

End point description:

tmax refers to the time after dosing when a drug attains its highest measurable concentration (Cmax). It is obtained by collecting a series of blood samples at various times after dosing, and measuring them for drug content.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour (end of infusion), 1.5, 4, 8, 12 and 24 hours (Day 2) after start of infusion (samples at 36 h and 48 h were optional)

End point values	Moxifloxacin (Avelox, BAY12-8039), Cohort 1, Male	Moxifloxacin (Avelox, BAY12-8039), Cohort 1, Female	Moxifloxacin (Avelox, BAY12-8039), Cohort 2, Male	Moxifloxacin (Avelox, BAY12-8039), Cohort 2, Female
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9[23]	3[24]	9[25]	3[26]
Units: hour				
median (full range (min-max))				
Moxifloxacin (BAY12-8039)	1.0333 (1 to 1.5)	1.0333 (1.017 to 1.283)	1.0333 (1.017 to 1.217)	1.1667 (1 to 1.2)
Metabolite M-1 (BAY31-8061)	1.0333 (1 to 1.5)	1.0333 (1.017 to 1.283)	1.0333 (1.017 to 1.217)	1.1667 (1 to 1.2)
Metabolite M-2 (BAY58-8178)	1.5167 (1.1 to 3.5)	3.8667 (1.283 to 4)	1.5667 (1.217 to 4.033)	1.2 (1.167 to 1.5)

Notes:

[23] - PKS

[24] - PKS

[25] - PKS

[26] - PKS

End point values	Moxifloxacin (Avelox, BAY12-8039), Cohort 3, Male	Moxifloxacin (Avelox, BAY12-8039), Cohort 3, Female		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[27]	1[28]		
Units: hour				
median (full range (min-max))				
Moxifloxacin (BAY12-8039)	1.0917 (1 to 1.567)	1.0667 (1.0667 to 1.0667)		
Metabolite M-1 (BAY31-8061)	1.0917 (1 to 1.567)	1.0667 (1.0667 to 1.0667)		
Metabolite M-2 (BAY58-8178)	1.525 (1.5 to 4)	1.4833 (1.4833 to 1.4833)		

Notes:

[27] - PKS

[28] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Half Life Associated With Terminal Slope (t1/2) of Moxifloxacin and its Metabolites

End point title	Half Life Associated With Terminal Slope (t1/2) of Moxifloxacin and its Metabolites

End point description:

Half life associated with terminal slope refers to the elimination of the drug. It is the time taken for the blood plasma concentration to reach half the concentration in the terminal phase of elimination. It is expressed in hours (h) and derived from the terminal slope of the concentration versus time curve. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. '99999' in the reported data indicates that geometric coefficient of variation was not calculated as only 1 subject was evaluable.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour (end of infusion), 1.5, 4, 8, 12 and 24 hours (Day 2) after start of infusion (samples at 36 h and 48 h were optional)

End point values	Moxifloxacin (Avelox, BAY12-8039), 5.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 6.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 7.0 mg/kg, 2 to <6 yrs	Moxifloxacin (Avelox, BAY12-8039), 8.0 mg/kg, 2 to <6 yrs
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7[29]	5[30]	7[31]	5[32]

Units: hour				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039) (N=7, 5, 7, 5, 6, 1)	7.887 (± 34.32)	6.164 (± 23.99)	5.66 (± 18.79)	6.031 (± 24.78)
Metabolite M-1 (BAY31-8061) (N=6, 4, 7, 5, 6, 1)	6.181 (± 80.62)	6.724 (± 43.26)	4.714 (± 47.04)	4.741 (± 41.41)
Metabolite M-2 (BAY58-8178) (N=7, 5, 7, 5, 6, 1)	7.015 (± 22.14)	5.79 (± 25.16)	5.26 (± 21.61)	5.171 (± 22.22)

Notes:

[29] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[30] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[31] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[32] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

End point values	Moxifloxacin (Avelox, BAY12-8039), 9.0 mg/kg, 3months to <2yrs	Moxifloxacin(Avelox, BAY12-8039), 10.0 mg/kg, 3months to <2yrs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[33]	1[34]		
Units: hour				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039) (N=7, 5, 7, 5, 6, 1)	6.817 (± 35.1)	5.938 (± 99999)		
Metabolite M-1 (BAY31-8061) (N=6, 4, 7, 5, 6, 1)	7.043 (± 106.68)	6.546 (± 99999)		
Metabolite M-2 (BAY58-8178) (N=7, 5, 7, 5, 6, 1)	5.928 (± 32.83)	5.704 (± 99999)		

Notes:

[33] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[34] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Amount Excreted in the Urine (Aeur) of Moxifloxacin and its Metabolites

End point title	Total Amount Excreted in the Urine (Aeur) of Moxifloxacin and its Metabolites

End point description:

Aeur refers to the total amount of moxifloxacin excreted in urine. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Secondary

End point timeframe:

Baseline up to 36 hour post-infusion

End point values	Moxifloxacin (Avelox, BAY12-8039), 5.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 6.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 7.0 mg/kg, 2 to <6 yrs	Moxifloxacin (Avelox, BAY12-8039), 8.0 mg/kg, 2 to <6 yrs
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7[35]	5[36]	7[37]	5[38]
Units: milligram				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039) (N=6, 5, 3, 3)	22.9 (± 33.23)	25.4 (± 27.5)	31.3 (± 32.38)	24.7 (± 54.41)
Metabolite M-1 (BAY31-8061) (N=6, 5, 3, 3)	3.692 (± 79.22)	3.257 (± 126.05)	6.41 (± 90)	7.998 (± 26.85)
Metabolite M-2 (BAY58-8178) (N=6, 5, 3, 3)	28.65 (± 57.74)	19.85 (± 100.61)	32.03 (± 25.89)	28.5 (± 35.69)

Notes:

[35] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[36] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[37] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[38] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss) of Moxifloxacin and its Metabolites

End point title	Volume of Distribution at Steady State (Vss) of Moxifloxacin and its Metabolites

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. Vss is the apparent volume of distribution at steady-state.
Geometric mean and percentage geometric coefficient of variation (%CV) were reported. '99999' in the reported data indicates that geometric coefficient of variation was not calculated as only 1 subject was evaluable.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour (end of infusion), 1.5, 4, 8, 12 and 24 hours (Day 2) after start of infusion (samples at 36 h and 48 h were optional)

End point values	Moxifloxacin (Avelox, BAY12-8039), 5.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 6.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 7.0 mg/kg, 2 to <6 yrs	Moxifloxacin (Avelox, BAY12-8039), 8.0 mg/kg, 2 to <6 yrs
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7[39]	5[40]	7[41]	5[42]
Units: liter				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039) (N=7, 5, 7, 5, 6, 1)	73.8 (± 49.67)	45 (± 10.55)	26.8 (± 20.3)	28.46 (± 26.61)
Metabolite M-1 (BAY31-8061) (N=6, 4, 7, 5, 6, 1)	2805.3 (± 54.15)	1513.3 (± 65.08)	639 (± 54.86)	803.3 (± 90.5)

Metabolite M-2 (BAY58-8178) (N=7, 5, 7, 5, 6, 1)	302.47 (± 61.45)	249.51 (± 95.67)	90.03 (± 61.44)	117.84 (± 90.15)

Notes:

[39] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[40] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[41] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[42] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

End point values	Moxifloxacin (Avelox, BAY12-8039), 9.0 mg/kg, 3months to <2yrs	Moxifloxacin(Avelox, BAY12-8039), 10.0 mg/kg, 3months to <2yrs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[43]	1[44]		
Units: liter				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039) (N=7, 5, 7, 5, 6, 1)	23.45 (± 31.35)	16.74 (± 99999)		
Metabolite M-1 (BAY31-8061) (N=6, 4, 7, 5, 6, 1)	461.7 (± 55.73)	244.1 (± 99999)		
Metabolite M-2 (BAY58-8178) (N=7, 5, 7, 5, 6, 1)	55.46 (± 59.89)	53.36 (± 99999)		

Notes:

[43] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[44] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Clearance (CL) of Moxifloxacin and its Metabolites

End point title	Plasma Clearance (CL) of Moxifloxacin and its Metabolites

End point description:

Total body clearance of drug in plasma is expressed in litres per hour. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. '99999' in the reported data indicates that geometric coefficient of variation was not calculated as only 1 subject was evaluable.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour (end of infusion), 1.5, 4, 8, 12 and 24 hours (Day 2) after start of infusion (samples at 36 h and 48 h were optional)

End point values	Moxifloxacin (Avelox, BAY12-8039), 5.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 6.0 mg/kg, 6 to <=14 yrs	Moxifloxacin (Avelox, BAY12-8039), 7.0 mg/kg, 2 to <6 yrs	Moxifloxacin (Avelox, BAY12-8039), 8.0 mg/kg, 2 to <6 yrs
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7[45]	5[46]	7[47]	5[48]
Units: liters per hour				
geometric mean (geometric coefficient of variation)				

Moxifloxacin (BAY12-8039) (N=7, 5, 7, 5, 6, 1)	8.111 (± 40.08)	6.238 (± 32.37)	4.361 (± 26.19)	4.505 (± 21.75)
Metabolite M-1 (BAY31-8061) (N=6, 4, 7, 5, 6, 1)	330.82 (± 76.81)	177.25 (± 58.86)	101.92 (± 16.64)	132.31 (± 65.25)
Metabolite M-2 (BAY58-8178) (N=7, 5, 7, 5, 6, 1)	30.295 (± 52.2)	30.85 (± 81.39)	11.764 (± 36.83)	16.757 (± 56.87)

Notes:

[45] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[46] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[47] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[48] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

End point values	Moxifloxacin (Avelox, BAY12-8039), 9.0 mg/kg, 3months to <2yrs	Moxifloxacin(Avelox, BAY12-8039), 10.0 mg/kg, 3months to <2yrs		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[49]	1[50]		
Units: liters per hour				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039) (N=7, 5, 7, 5, 6, 1)	3.675 (± 27.1)	2.197 (± 99999)		
Metabolite M-1 (BAY31-8061) (N=6, 4, 7, 5, 6, 1)	55.7 (± 59.98)	29.46 (± 99999)		
Metabolite M-2 (BAY58-8178) (N=7, 5, 7, 5, 6, 1)	7.673 (± 56.9)	6.241 (± 99999)		

Notes:

[49] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[50] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration Versus Time Curve From Zero to Infinity Divided by Dose Per kilogram Body Weight (AUCnorm) of Moxifloxacin and its Metabolites

End point title	Area Under the Plasma Concentration Versus Time Curve From Zero to Infinity Divided by Dose Per kilogram Body Weight (AUCnorm) of Moxifloxacin and its Metabolites

End point description:

AUC is a measure of the serum concentration of the drug over time. It is used to characterize drug absorption. AUCnorm is defined as AUC divided by dose per kg body weight. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. '99999' in the reported data indicates that geometric coefficient of variation was not calculated as only 1 subject was evaluable.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour (end of infusion), 1.5, 4, 8, 12 and 24 hours (Day 2) after start of infusion (samples at 36 h and 48 h were optional)

End point values	Moxifloxacin (Avelox, BAY12-8039), Cohort 1, Male	Moxifloxacin (Avelox, BAY12-8039), Cohort 1, Female	Moxifloxacin (Avelox, BAY12-8039), Cohort 2, Male	Moxifloxacin (Avelox, BAY12-8039), Cohort 2, Female
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9[51]	3[52]	9[53]	3[54]
Units: kilogram*hour per liters				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039) (N=9, 3, 9, 3, 6, 1)	3.7 (± 25.52)	4.911 (± 19.86)	3.871 (± 37.6)	3.409 (± 28.25)
Metabolite M-1 (BAY31-8061) (N=7, 3, 9, 3, 6, 1)	0.1311 (± 42.42)	0.07153 (± 83.93)	0.14791 (± 54.14)	0.13998 (± 27.13)
Metabolite M-2 (BAY58-8178) (N=9, 3, 9, 3, 6, 1)	0.9596 (± 62.79)	0.9065 (± 74.62)	1.1536 (± 55.86)	1.4244 (± 31.76)

Notes:

[51] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[52] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[53] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[54] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

End point values	Moxifloxacin (Avelox, BAY12-8039), Cohort 3, Male	Moxifloxacin (Avelox, BAY12-8039), Cohort 3, Female		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[55]	1[56]		
Units: kilogram*hour per liters				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039) (N=9, 3, 9, 3, 6, 1)	3.035 (± 22.4)	2.721 (± 99999)		
Metabolite M-1 (BAY31-8061) (N=7, 3, 9, 3, 6, 1)	0.20152 (± 61.28)	0.19579 (± 99999)		
Metabolite M-2 (BAY58-8178) (N=9, 3, 9, 3, 6, 1)	1.4073 (± 46.74)	1.1655 (± 99999)		

Notes:

[55] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

[56] - PKS. Here "N" signifies subjects who were evaluable for the specified category.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration Divided by Dose Per kilogram Body Weight (Cmax,Norm) of Moxifloxacin and its Metabolites

End point title	Maximum Observed Plasma Concentration Divided by Dose Per kilogram Body Weight (Cmax,Norm) of Moxifloxacin and its Metabolites

End point description:

Cmax refers to the highest measured drug concentration which is obtained by collecting a series of blood samples and measuring the concentrations of drug in each sample. Cmax,norm is defined as Cmax divided by dose (mg) per kg body weight. Geometric mean and percentage geometric coefficient of variation (%CV) were reported. '99999' in the reported data indicates that geometric coefficient of variation was not calculated as only 1 subject was evaluable.

End point type	Secondary

End point timeframe:

Pre-dose, 1 hour (end of infusion), 1.5, 4, 8, 12 and 24 hours (Day 2) after start of infusion (samples at 36 h and 48 h were optional)

End point values	Moxifloxacin (Avelox, BAY12-8039), Cohort 1, Male	Moxifloxacin (Avelox, BAY12-8039), Cohort 1, Female	Moxifloxacin (Avelox, BAY12-8039), Cohort 2, Male	Moxifloxacin (Avelox, BAY12-8039), Cohort 2, Female
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	9[57]	3[58]	9[59]	3[60]
Units: kilogram(s)/liter				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039)	0.6679 (± 32.32)	0.7397 (± 14.21)	0.8671 (± 40.7)	0.7219 (± 7.49)
Metabolite M-1 (BAY31-8061)	0.015601 (± 78.9)	0.01017 (± 39.81)	0.025204 (± 69.35)	0.032342 (± 50.02)
Metabolite M-2 (BAY58-8178)	0.09804 (± 66.31)	0.07926 (± 60.23)	0.12784 (± 59.33)	0.17447 (± 76.73)

Notes:

[57] - PKS

[58] - PKS

[59] - PKS

[60] - PKS

End point values	Moxifloxacin (Avelox, BAY12-8039), Cohort 3, Male	Moxifloxacin (Avelox, BAY12-8039), Cohort 3, Female		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6[61]	1[62]		
Units: kilogram(s)/liter				
geometric mean (geometric coefficient of variation)				
Moxifloxacin (BAY12-8039)	0.5953 (± 14.6)	0.5693 (± 99999)		
Metabolite M-1 (BAY31-8061)	0.03079 (± 42.26)	0.035878 (± 99999)		
Metabolite M-2 (BAY58-8178)	0.16201 (± 48.07)	0.13292 (± 99999)		

Notes:

[61] - PKS

[62] - PKS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 1 year (follow up) (Joint abnormalities followed until resolution, up to 5 years)

Adverse event reporting additional description:

Treatment-emergent adverse events were defined as adverse events/serious adverse events that started or worsened after the study drug treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Moxifloxacin (Avelox, BAY12-8039), Cohort 1

Reporting group description:

Single IV infusion of moxifloxacin administered over 60 minutes, at an initial dosage of 5 mg/kg/BW with dose escalation to 6 mg/kg in subjects of age 6 years to <= 14 years.

Reporting group title	Moxifloxacin (Avelox, BAY12-8039), Cohort 2

Reporting group description:

Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 7 mg/kg/BW with dose escalation to 8 mg/kg in subjects of age 2 years to < 6 years; dose escalation was based on evaluations of the PK data from the subjects in a preceding cohort.

Reporting group title	Moxifloxacin (Avelox, BAY12-8039), Cohort 3

Reporting group description:

Single IV infusion of moxifloxacin administered over 60 minutes, at a dosage of 9 mg/kg/BW with dose escalation to 10 mg/kg in subjects of age 3 months to < 2 years; dose escalation was based on evaluations of the PK data from the subjects in a preceding cohort.

Serious adverse events	Moxifloxacin (Avelox, BAY12-8039), Cohort 1	Moxifloxacin (Avelox, BAY12-8039), Cohort 2	Moxifloxacin (Avelox, BAY12-8039), Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Biopsy bone			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Histiocytosis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Moxifloxacin (Avelox, BAY12-8039), Cohort 1	Moxifloxacin (Avelox, BAY12-8039), Cohort 2	Moxifloxacin (Avelox, BAY12-8039), Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 12 (50.00%)	6 / 12 (50.00%)	5 / 7 (71.43%)
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Abscess drainage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Application site urticaria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Chest discomfort			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Device occlusion			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infusion site erythema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pain			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vessel puncture site pruritus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Pneumothorax			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Investigations			
Blood cholesterol increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood urea decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Fibrin D dimer increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Oxygen saturation decreased			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Cardiac disorders			
Defect conduction intraventricular			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Left atrial dilatation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Right ventricular hypertrophy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Leukocytosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Thrombocytosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Frequent bowel movements			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	3 / 12 (25.00%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Rash			

subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Rash papular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Pyuria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Fluid overload			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypoproteinaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2010	The amendment reflected changes to the timing of the follow-up joint assessments. The original protocol included a 30 day follow-up. However, the Written Request Letter from the Food and Drug Administration (FDA) stipulated that additional assessments were to be made at 3 months, and 1 year after dosing. If any subjects have a musculoskeletal abnormality, they were to be followed at yearly intervals for 5 years or until resolution of the event.
23 March 2010	The amendment was specified the following modifications: - Defined the primary completion date as 3-month follow-up - Clarified exclusion criteria for renal and hepatic disease and musculoskeletal abnormalities - Removed the requirement for weighing dose administration materials - Clarified that use of concomitant medications up to Day 10 of the study were to be documented on the CRF - Added the exclusion criteria that subjects could not have participated in another clinical trial within 30 days (changed from 3 months) - Changed the documentation period of previous medication history to 4 weeks prior to dosing (changed from rather than 10 weeks) - Restricted the requirement for PK urine collection to subjects who were toilet trained or catheterized - Added vital signs and ECG at all PK sample time points up to 24 hours - Added PK parameters AUCnorm and Cmax, norm - Clarified the of systems covered by the complete physical exam - Revised the timeframe for following AEs - Gamma glutamyl transferase (GGT) was added to the clinical lab tests (blood chemistry) - Revised the Study Flow Chart to clarify PK sampling on Days 1 – 3 and to add vital signs and ECG evaluations
14 June 2011	Amendment 3 addressed issues of particular concern to Cohort 3 (ages 3 months to < 2 years) regarding breastfeeding, i.e., medications that the mother may have been taking, and the enrollment of premature infants. The amendment specified the following modifications: - ALT up to 3X ULN was allowed if not considered related to hepatic disease (i.e., elevation may be secondary to infection). This change was suggested by investigators, who felt subjects were being unnecessarily excluded, since elevated ALT could have been be related to the infection, rather than hepatic disease. - Added exclusion of subjects with a history of myasthenia gravis (to reflect the updated labeling of quinolones) - Incorporated items addressed in Administrative letter 2 and removed the coordinating investigator (thought not to be needed because the study was conducted only in the USA). This measure was not enacted. - Deleted procedures that were either not relevant to the protocol (e.g., body mass index [BMI]), or inconsistent with the actual study conduct (e.g., temperature not being measured), and clarified inconsistencies (e.g., discrepancies in urine PK volume between the PK manual and the protocol)

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.

Occurrence of "±” in relation with geometric CV is auto-generated and cannot be deleted. '99999' in the posting indicates data were not calculated. Decimal places were automatically truncated if last decimal equals zero.

Notes: