



## 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)                          | EMA-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:

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**Results analysis stage**

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

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

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Notes:

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**General information about the trial**

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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).

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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.

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Background therapy:

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

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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         |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 31 |
| Worldwide total number of subjects   | 31                |
| EEA total number of subjects         | 0                 |

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Notes:

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**Subjects enrolled per age group**

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|          |   |
|----------|---|
| 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)  | 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   |
| <b>Arm title</b>             | 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 ( $\leq$ ) 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.

|                  |   |
|------------------|---|
| <b>Arm title</b> | 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.

|                  |   |
|------------------|---|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | Moxifloxacin<br>(Avelox, BAY12-8039), Cohort 1 | Moxifloxacin<br>(Avelox, BAY12-8039), Cohort 2 | Moxifloxacin<br>(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 ( $\leq$ ) 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<br>(Avelox, BAY12-8039), Cohort 1 | Moxifloxacin<br>(Avelox, BAY12-8039), Cohort 2 | Moxifloxacin<br>(Avelox, BAY12-8039), Cohort 3 |
|--|--|--|--|
| Number of subjects   | 12   | 12   | 7  |
| Age categorical  |  |  |  |
| Units: Subjects  |  |  |  |
| In utero   | 0  | 0  | 0  |
| Preterm newborn infants<br>(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   | $\pm 2.4$                                      | $\pm 1.1$                                      | $\pm 0.6$                                      |
| 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:<br>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 ( $\leq$ ) 14 years.                       |   |
| Reporting group title   | Moxifloxacin (Avelox, BAY12-8039), Cohort 2                       |
| Reporting group description:<br>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:<br>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 $\leq 14$ yrs  |
| Subject analysis set type   | Sub-group analysis  |
| Subject analysis set description:<br>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 $\leq 14$ years.   |   |
| Subject analysis set title  | Moxifloxacin (Avelox, BAY12-8039), 6.0 mg/kg, 6 to $\leq 14$ yrs  |
| Subject analysis set type   | Sub-group analysis  |
| Subject analysis set description:<br>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 $\leq 14$ 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:<br>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:<br>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 $<2$ yrs |
| Subject analysis set type   | Sub-group analysis  |
| Subject analysis set description:<br>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 $<2$ yrs |
| Subject analysis set type   | Sub-group analysis  |
| Subject analysis set description:<br>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:<br>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 $\leq 14$ 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 <sup>[1]</sup> |
| 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 <sup>[2]</sup>  | 5 <sup>[3]</sup>  | 7 <sup>[4]</sup>  | 5 <sup>[5]</sup>  |
| 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 <sup>[6]</sup>   | 1 <sup>[7]</sup>   |  |  |
| 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 <sup>[8]</sup> |
|-----------------|---|

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 <sup>[9]</sup>  | 5 <sup>[10]</sup>   | 7 <sup>[11]</sup>   | 5 <sup>[12]</sup>   |
| 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 <sup>[13]</sup>  | 1 <sup>[14]</sup>  |  |  |
| 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**

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|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Treatment Emergent Findings on Joint Assessment: Baseline <sup>[15]</sup> |
|-----------------|---|

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 <sup>[16]</sup>                          | 12 <sup>[17]</sup>                          | 7 <sup>[18]</sup>                           |  |
| 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 <sup>[19]</sup> |
|-----------------|--|

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 <sup>[20]</sup>                          | 12 <sup>[21]</sup>                          | 7 <sup>[22]</sup>                           |  |
| 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 <sup>[23]</sup>                                 | 3 <sup>[24]</sup>                                   | 9 <sup>[25]</sup>                                 | 3 <sup>[26]</sup>                                   |
| 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 <sup>[27]</sup>                                 | 1 <sup>[28]</sup>                                   |  |  |
| 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 (t<sub>1/2</sub>) of Moxifloxacin and its Metabolites

|                 |  |
|-----------------|--|
| End point title | Half Life Associated With Terminal Slope (t <sub>1/2</sub> ) 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 <sup>[29]</sup>  | 5 <sup>[30]</sup>  | 7 <sup>[31]</sup>   | 5 <sup>[32]</sup>   |

|   |                 |                 |                 |                 |
|---|-----------------|-----------------|-----------------|-----------------|
| 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.

|   |  |  |  |  |
|---|--|--|--|--|
| <b>End point values</b>                             | 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 <sup>[33]</sup>  | 1 <sup>[34]</sup>  |  |  |
| 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:<br>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:<br>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 <sup>[35]</sup>   | 5 <sup>[36]</sup>   | 7 <sup>[37]</sup>   | 5 <sup>[38]</sup>   |
| 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 <sup>[39]</sup>   | 5 <sup>[40]</sup>   | 7 <sup>[41]</sup>   | 5 <sup>[42]</sup>   |
| 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 ( $\pm$ 61.45) | 249.51 ( $\pm$ 95.67) | 90.03 ( $\pm$ 61.44) | 117.84 ( $\pm$ 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 <sup>[43]</sup>  | 1 <sup>[44]</sup>  |  |  |
| Units: liter  |  |  |  |  |
| geometric mean (geometric coefficient of variation) |  |  |  |  |
| Moxifloxacin (BAY12-8039) (N=7, 5, 7, 5, 6, 1)      | 23.45 ( $\pm$ 31.35)   | 16.74 ( $\pm$ 99999)   |  |  |
| Metabolite M-1 (BAY31-8061) (N=6, 4, 7, 5, 6, 1)    | 461.7 ( $\pm$ 55.73)   | 244.1 ( $\pm$ 99999)   |  |  |
| Metabolite M-2 (BAY58-8178) (N=7, 5, 7, 5, 6, 1)    | 55.46 ( $\pm$ 59.89)   | 53.36 ( $\pm$ 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 <sup>[45]</sup>   | 5 <sup>[46]</sup>   | 7 <sup>[47]</sup>   | 5 <sup>[48]</sup>   |
| 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 <sup>[49]</sup>  | 1 <sup>[50]</sup>  |  |  |
| 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 <sup>[51]</sup>                                 | 3 <sup>[52]</sup>                                   | 9 <sup>[53]</sup>                                 | 3 <sup>[54]</sup>                                   |
| 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 <sup>[55]</sup>                                 | 1 <sup>[56]</sup>                                   |  |  |
| 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 (C<sub>max</sub>,Norm) of Moxifloxacin and its Metabolites

|                 |   |
|-----------------|---|
| End point title | Maximum Observed Plasma Concentration Divided by Dose Per kilogram Body Weight (C <sub>max</sub> ,Norm) of Moxifloxacin and its Metabolites |
|-----------------|---|

End point description:

C<sub>max</sub> 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. C<sub>max</sub>,norm is defined as C<sub>max</sub> 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 <sup>[57]</sup>                                 | 3 <sup>[58]</sup>                                   | 9 <sup>[59]</sup>                                 | 3 <sup>[60]</sup>                                   |
| 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 <sup>[61]</sup>                                 | 1 <sup>[62]</sup>                                   |  |  |
| 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<br>(Avelox, BAY12-8039), Cohort 1 | Moxifloxacin<br>(Avelox, BAY12-8039), Cohort 2 | Moxifloxacin<br>(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 %

| <b>Non-serious adverse events</b>                     | Moxifloxacin<br>(Avelox, BAY12-8039), Cohort 1 | Moxifloxacin<br>(Avelox, BAY12-8039), Cohort 2 | Moxifloxacin<br>(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<br>occurrences (all)   | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 0 / 7 (0.00%)<br>0  |
| Vessel puncture site pain<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 12 (8.33%)<br>1 | 0 / 12 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |
| Vessel puncture site pruritus<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 12 (8.33%)<br>1 | 0 / 12 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>2 | 0 / 12 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |
| Pneumothorax<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 0 / 7 (0.00%)<br>0  |
| Investigations<br>Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 0 / 7 (0.00%)<br>0  |
| Blood urea decreased<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 |
| C-reactive protein increased<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 12 (8.33%)<br>1 | 0 / 12 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |
| Fibrin D dimer increased<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 |
| Oxygen saturation decreased  |                     |                     |                     |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>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<br>occurrences (all)  | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 1 / 7 (14.29%)<br>1 |
| Rash papular<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 12 (8.33%)<br>1 | 0 / 12 (0.00%)<br>0 | 0 / 7 (0.00%)<br>0  |
| Renal and urinary disorders<br>Pyuria<br>subjects affected / exposed<br>occurrences (all)             | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 0 / 7 (0.00%)<br>0  |
| Infections and infestations<br>Abdominal abscess<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>2 | 0 / 7 (0.00%)<br>0  |
| Metabolism and nutrition disorders<br>Dehydration<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 |
| Fluid overload<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 |
| Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>1 |
| Hypoproteinaemia<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 12 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 7 (14.29%)<br>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: <ul style="list-style-type: none"><li>- Defined the primary completion date as 3-month follow-up</li><li>- Clarified exclusion criteria for renal and hepatic disease and musculoskeletal abnormalities</li><li>- Removed the requirement for weighing dose administration materials</li><li>- Clarified that use of concomitant medications up to Day 10 of the study were to be documented on the CRF</li><li>- Added the exclusion criteria that subjects could not have participated in another clinical trial within 30 days (changed from 3 months)</li><li>- Changed the documentation period of previous medication history to 4 weeks prior to dosing (changed from rather than 10 weeks)</li><li>- Restricted the requirement for PK urine collection to subjects who were toilet trained or catheterized</li><li>- Added vital signs and ECG at all PK sample time points up to 24 hours</li><li>- Added PK parameters AUC<sub>norm</sub> and C<sub>max, norm</sub></li><li>- Clarified the of systems covered by the complete physical exam</li><li>- Revised the timeframe for following AEs</li><li>- Gamma glutamyl transferase (GGT) was added to the clinical lab tests (blood chemistry)</li><li>- Revised the Study Flow Chart to clarify PK sampling on Days 1 – 3 and to add vital signs and ECG evaluations</li></ul> |
| 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: <ul style="list-style-type: none"><li>- 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.</li><li>- Added exclusion of subjects with a history of myasthenia gravis (to reflect the updated labeling of quinolones)</li><li>- 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.</li><li>- 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)</li></ul>  |

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: