



Clinical trial results:

Randomized, double-blind, placebo-controlled, multicenter study comparing ciprofloxacin DPI 32.5 mg BID intermittently administered for 28 days on / 28 days off or 14 days on / 14 days off versus placebo to evaluate the time to first pulmonary exacerbation and frequency of exacerbations in subjects with non-cystic fibrosis bronchiectasis

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2011-004208-39 |
| Trial protocol | DE ES GB IT DK FR LV SK |
| Global end of trial date | 09 March 2016 |

Results information

| | |
|--------------------------------|---|
| Result version number | v4 (current) |
| This version publication date | 24 December 2017 |
| First version publication date | 11 March 2017 |
| Version creation reason | • Correction of full data set update in SAE section |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | BAYQ3939/15625 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01764841 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 March 2016 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 09 March 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary objectives: 1) To evaluate the efficacy of ciprofloxacin dry powder for inhalation (DPI) administered twice daily (BID) intermittently for 28 days on/off treatment or 14 days on/off treatment to prolong the time to first exacerbation requiring an intervention with systemic antibiotics in subjects with non-cystic fibrosis bronchiectasis (non-CF BE) within 48 weeks after start of treatment. 2) To evaluate the efficacy of ciprofloxacin DPI administered BID intermittently for 28 days on/off treatment or 14 days on/off treatment in reducing the frequency of pulmonary exacerbation requiring an intervention with systemic antibiotics in subjects with non-CF BE within 48 weeks after start of treatment. The tests for the efficacy variables will be performed hierarchically. The comparisons ciprofloxacin DPI vs. placebo (matching or pooled according to statistical analysis plan defined for EU registration) will be performed in parallel for the regimen 28 days on/off and 14 days on/off.

Protection of trial subjects:

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

Background therapy:

Subjects were allowed to stay on their non-antibiotic standard treatment.

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 02 May 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Argentina: 6 |
| Country: Number of subjects enrolled | Israel: 53 |
| Country: Number of subjects enrolled | Australia: 52 |
| Country: Number of subjects enrolled | Japan: 33 |
| Country: Number of subjects enrolled | New Zealand: 51 |
| Country: Number of subjects enrolled | United States: 44 |
| Country: Number of subjects enrolled | Slovakia: 2 |
| Country: Number of subjects enrolled | Spain: 49 |
| Country: Number of subjects enrolled | United Kingdom: 27 |
| Country: Number of subjects enrolled | Denmark: 1 |

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | France: 14 |
| Country: Number of subjects enrolled | Germany: 47 |
| Country: Number of subjects enrolled | Italy: 21 |
| Country: Number of subjects enrolled | Latvia: 16 |
| Worldwide total number of subjects | 416 |
| EEA total number of subjects | 177 |

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) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 166 |
| From 65 to 84 years | 243 |
| 85 years and over | 7 |

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 124 study centers in 14 countries (Argentina, Australia, Denmark, France, Germany, Israel, Italy, Japan, Latvia, New Zealand, Slovakia, Spain, UK and US) between 02 May 2013 (first subject first visit) and 09 March 2016 (last subject last visit).

Pre-assignment

Screening details:

Overall 902 subjects were screened, of them 486 were screen failures, and 416 were randomized, out of which 414 subjects were assigned to the treatment. One subject from Ciprofloxacin 14 Days on/off group and one subject from Placebo 28 Days on/off group did not receive the study treatment after initial screening.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Ciprofloxacin DPI 28 Days on/off (Cipro 28) |

Arm description:

Subjects received ciprofloxacin (BAYQ3939) 32.5 milligram (mg) corresponding to 50 mg DPI administered BID (every 12 hours); a treatment cycle consisted of a 28-day on-treatment phase followed by a 28-day off-treatment phase (48 weeks treatment phase = 6 active cycles).

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ciprofloxacin DPI |
| Investigational medicinal product code | BAYQ3939 |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Subjects received 32.5 mg ciprofloxacin hydrated (corresponding to 50 mg dry powder) administered BID (every 12 hours) using T-326 powder inhaler device.

| | |
|------------------|---|
| Arm title | Ciprofloxacin DPI 14 Days on/off (Cipro 14) |
|------------------|---|

Arm description:

Subjects received ciprofloxacin 32.5 mg corresponding to 50 mg DPI administered BID (every 12 hours); a treatment cycle consisted of a 14-day on-treatment phase followed by a 14-day off-treatment phase (48 weeks treatment phase = 12 active cycles).

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ciprofloxacin DPI |
| Investigational medicinal product code | BAYQ3939 |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Subjects received 32.5 mg ciprofloxacin hydrated (corresponding to 50 mg dry powder) administered BID (every 12 hours) using T-326 powder inhaler device.

| | |
|------------------|-------------------------------------|
| Arm title | Placebo 28 Days on/off (Placebo 28) |
|------------------|-------------------------------------|

Arm description:

Subjects received placebo matched to ciprofloxacin 32.5 mg powder (containing 40 mg dry powder) administered BID (every 12 hours); a treatment cycle consisted of a 28-day on-treatment phase followed by a 28-day off-treatment phase (48 weeks treatment phase = 6 cycles).

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Subjects received placebo matched to ciprofloxacin 32.5 mg powder (containing 40 mg dry powder) administered BID (every 12 hours) using T-326 powder inhaler device.

| | |
|------------------|-------------------------------------|
| Arm title | Placebo 14 Days on/off (Placebo 14) |
|------------------|-------------------------------------|

Arm description:

Subjects received placebo matched to ciprofloxacin 32.5 mg powder (containing 40 mg dry powder) administered BID (every 12 hours); a treatment cycle consisted of a 14-day on-treatment phase followed by a 14-day off-treatment phase (48 weeks treatment phase = 12 cycles).

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

Subjects received placebo matched to ciprofloxacin 32.5 mg powder (containing 40 mg dry powder) administered BID (every 12 hours) using T-326 powder inhaler device.

| Number of subjects in period 1 | Ciprofloxacin DPI 28 Days on/off (Cipro 28) | Ciprofloxacin DPI 14 Days on/off (Cipro 14) | Placebo 28 Days on/off (Placebo 28) |
|---------------------------------------|---|---|-------------------------------------|
| Started | 141 | 137 | 70 |
| Treated | 141 | 136 | 69 |
| Completed | 118 | 111 | 56 |
| Not completed | 23 | 26 | 14 |
| Consent withdrawn by subject | 16 | 24 | 11 |
| Logistical Difficulties | - | 1 | - |
| Death | 3 | - | 1 |
| Protocol Violation | - | 1 | - |
| Lost to follow-up | 3 | - | 1 |
| No Follow Up | 1 | - | 1 |

| Number of subjects in period 1 | Placebo 14 Days on/off (Placebo 14) |
|---------------------------------------|-------------------------------------|
| Started | 68 |
| Treated | 68 |
| Completed | 49 |
| Not completed | 19 |

| | |
|------------------------------|----|
| Consent withdrawn by subject | 15 |
| Logistical Difficulties | - |
| Death | 4 |
| Protocol Violation | - |
| Lost to follow-up | - |
| No Follow Up | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Ciprofloxacin DPI 28 Days on/off (Cipro 28) |
|-----------------------|---|

Reporting group description:

Subjects received ciprofloxacin (BAYQ3939) 32.5 milligram (mg) corresponding to 50 mg DPI administered BID (every 12 hours); a treatment cycle consisted of a 28-day on-treatment phase followed by a 28-day off-treatment phase (48 weeks treatment phase = 6 active cycles).

| | |
|-----------------------|---|
| Reporting group title | Ciprofloxacin DPI 14 Days on/off (Cipro 14) |
|-----------------------|---|

Reporting group description:

Subjects received ciprofloxacin 32.5 mg corresponding to 50 mg DPI administered BID (every 12 hours); a treatment cycle consisted of a 14-day on-treatment phase followed by a 14-day off-treatment phase (48 weeks treatment phase = 12 active cycles).

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Placebo 28 Days on/off (Placebo 28) |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects received placebo matched to ciprofloxacin 32.5 mg powder (containing 40 mg dry powder) administered BID (every 12 hours); a treatment cycle consisted of a 28-day on-treatment phase followed by a 28-day off-treatment phase (48 weeks treatment phase = 6 cycles).

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Placebo 14 Days on/off (Placebo 14) |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects received placebo matched to ciprofloxacin 32.5 mg powder (containing 40 mg dry powder) administered BID (every 12 hours); a treatment cycle consisted of a 14-day on-treatment phase followed by a 14-day off-treatment phase (48 weeks treatment phase = 12 cycles).

| Reporting group values | Ciprofloxacin DPI 28 Days on/off (Cipro 28) | Ciprofloxacin DPI 14 Days on/off (Cipro 14) | Placebo 28 Days on/off (Placebo 28) |
|------------------------------------|---|---|-------------------------------------|
| Number of subjects | 141 | 137 | 70 |
| Age categorical Units: Subjects | | | |

| | | | |
|---|---------|---------|---------|
| Age continuous Units: years | | | |
| arithmetic mean | 64.2 | 65.2 | 64 |
| standard deviation | ± 12.1 | ± 13.5 | ± 13.5 |
| Gender categorical Units: Subjects | | | |
| Female | 101 | 88 | 52 |
| Male | 40 | 49 | 18 |
| Saint George's Respiratory Questionnaire (SGRQ) Symptoms Component Score (n=135, 129, 67, 66) | | | |
| The SGRQ was a validated, disease-specific instrument that measures health-related quality of life (HRQoL) in adults with chronic obstructive pulmonary disease (COPD) and asthma and was later validated for use in bronchiectasis. The SGRQ covers 3 dimensions: symptoms, activity and impact on daily life. To determine the outcome, a score ranging from 1 to 100 was calculated for each individual domain and for the total score, and smaller scores indicate better health status. For this outcome measure, the symptoms component score was reported. | | | |
| Units: score on a scale | | | |
| arithmetic mean | 60.72 | 52.51 | 55.52 |
| standard deviation | ± 19.47 | ± 21.48 | ± 22.07 |
| QoL-B Respiratory Symptoms Domain Score (n= 128, 120, 63, 65) | | | |
| The Quality of Life Questionnaire for Bronchiectasis (QoL-B) was a disease-specific questionnaire developed for non-Cystic fibrosis Bronchiectasis. It covers 8 dimensions: physical functioning, role | | | |

functioning, emotional functioning, social functioning, vitality, treatment burden, health perceptions, and respiratory symptoms. Each dimension was scored separately on a scale of 0 to 100, and higher scores represent better outcomes. For this outcome measure, the respiratory symptoms domain score was reported.

| | | | |
|--|---------|---------|---------|
| Units: score on a scale | | | |
| arithmetic mean | 53.01 | 57.69 | 55.82 |
| standard deviation | ± 18.71 | ± 18.72 | ± 18.04 |
| Forced Expiratory Volume in One Second (FEV1) | | | |
| FEV1 was the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in liters at body temperature and ambient pressure saturated with water vapor (BTPS). | | | |
| Units: liter | | | |
| arithmetic mean | 1.521 | 1.528 | 1.577 |
| standard deviation | ± 0.521 | ± 0.625 | ± 0.651 |

| Reporting group values | Placebo 14 Days on/off (Placebo 14) | Total | |
|------------------------|-------------------------------------|-------|--|
| Number of subjects | 68 | 416 | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|---|---------|-----|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 65.5 | | |
| standard deviation | ± 12.9 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 44 | 285 | |
| Male | 24 | 131 | |
| Saint George's Respiratory Questionnaire (SGRQ) Symptoms Component Score (n=135, 129, 67, 66) | | | |
| The SGRQ was a validated, disease-specific instrument that measures health-related quality of life (HRQoL) in adults with chronic obstructive pulmonary disease (COPD) and asthma and was later validated for use in bronchiectasis. The SGRQ covers 3 dimensions: symptoms, activity and impact on daily life. To determine the outcome, a score ranging from 1 to 100 was calculated for each individual domain and for the total score, and smaller scores indicate better health status. For this outcome measure, the symptoms component score was reported. | | | |
| Units: score on a scale | | | |
| arithmetic mean | 58.72 | | |
| standard deviation | ± 20.4 | - | |
| QoL-B Respiratory Symptoms Domain Score (n= 128, 120, 63, 65) | | | |
| The Quality of Life Questionnaire for Bronchiectasis (QoL-B) was a disease-specific questionnaire developed for non-Cystic fibrosis Bronchiectasis. It covers 8 dimensions: physical functioning, role functioning, emotional functioning, social functioning, vitality, treatment burden, health perceptions, and respiratory symptoms. Each dimension was scored separately on a scale of 0 to 100, and higher scores represent better outcomes. For this outcome measure, the respiratory symptoms domain score was reported. | | | |
| Units: score on a scale | | | |
| arithmetic mean | 50.67 | | |
| standard deviation | ± 19.59 | - | |
| Forced Expiratory Volume in One Second (FEV1) | | | |
| FEV1 was the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in liters at body temperature and ambient pressure saturated with water vapor (BTPS). | | | |

| | | | |
|--------------------|-------------|---|--|
| Units: liter | | | |
| arithmetic mean | 1.468 | | |
| standard deviation | ± 0.574 | - | |

End points

End points reporting groups

| | |
|-----------------------|---|
| Reporting group title | Ciprofloxacin DPI 28 Days on/off (Cipro 28) |
|-----------------------|---|

Reporting group description:

Subjects received ciprofloxacin (BAYQ3939) 32.5 milligram (mg) corresponding to 50 mg DPI administered BID (every 12 hours); a treatment cycle consisted of a 28-day on-treatment phase followed by a 28-day off-treatment phase (48 weeks treatment phase = 6 active cycles).

| | |
|-----------------------|---|
| Reporting group title | Ciprofloxacin DPI 14 Days on/off (Cipro 14) |
|-----------------------|---|

Reporting group description:

Subjects received ciprofloxacin 32.5 mg corresponding to 50 mg DPI administered BID (every 12 hours); a treatment cycle consisted of a 14-day on-treatment phase followed by a 14-day off-treatment phase (48 weeks treatment phase = 12 active cycles).

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Placebo 28 Days on/off (Placebo 28) |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects received placebo matched to ciprofloxacin 32.5 mg powder (containing 40 mg dry powder) administered BID (every 12 hours); a treatment cycle consisted of a 28-day on-treatment phase followed by a 28-day off-treatment phase (48 weeks treatment phase = 6 cycles).

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Placebo 14 Days on/off (Placebo 14) |
|-----------------------|-------------------------------------|

Reporting group description:

Subjects received placebo matched to ciprofloxacin 32.5 mg powder (containing 40 mg dry powder) administered BID (every 12 hours); a treatment cycle consisted of a 14-day on-treatment phase followed by a 14-day off-treatment phase (48 weeks treatment phase = 12 cycles).

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Full analysis set (FAS) |
|----------------------------|-------------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

FAS (N=416) included subjects who were randomized.

| | |
|----------------------------|---------------------------|
| Subject analysis set title | Safety analysis set (SAF) |
|----------------------------|---------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

SAF (N=414) included subjects who were randomized and received study medication.

| | |
|----------------------------|----------------|
| Subject analysis set title | Pooled Placebo |
|----------------------------|----------------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Subjects (N=138) received matching placebo matched to ciprofloxacin 32.5 mg powder (containing 40 mg dry powder) administered BID (every 12 hours); a treatment cycle consisted of either a 28-day on-treatment phase followed by 28-day off-treatment phase or 14-day on-treatment phase followed by 14-day off treatment phase (48 weeks treatment phase = 6 cycles and 12 cycles, respectively).

Primary: Number of subjects with exacerbation events with worsening of at least three signs/symptoms over 48 weeks

| | |
|-----------------|---|
| End point title | Number of subjects with exacerbation events with worsening of at least three signs/symptoms over 48 weeks |
|-----------------|---|

End point description:

For this outcome measure, exacerbation events were defined as exacerbations with systemic antibiotic use and presence of fever or malaise / fatigue and worsening of at least three signs/symptoms over 48 weeks.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Up to Week 48

| End point values | Ciprofloxacin DPI 28 Days on/off (Cipro 28) | Ciprofloxacin DPI 14 Days on/off (Cipro 14) | Placebo 28 Days on/off (Placebo 28) | Placebo 14 Days on/off (Placebo 14) |
|--|--|--|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 141 ^[1] | 137 ^[2] | 70 ^[3] | 68 ^[4] |
| Units: subjects with exacerbation events | | | | |
| Number of exacerbations: 0 | 74 | 84 | 33 | 26 |
| Number of exacerbations: 1 | 39 | 33 | 27 | 23 |
| Number of exacerbations: 2 | 13 | 11 | 4 | 12 |
| Number of exacerbations: 3 | 12 | 6 | 4 | 4 |
| Number of exacerbations: 4 | 1 | 2 | 2 | 3 |
| Number of exacerbations: 5 | 1 | 1 | 0 | 0 |
| Number of exacerbations: 6 | 1 | 0 | 0 | 0 |

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

[4] - FAS

Statistical analyses

| Statistical analysis title | Cipro 28 vs Placebo 28 |
|--|---|
| Statistical analysis description: | |
| A Poisson regression with adjustment for over-/under dispersion was used to analyze the number of exacerbation events over 48 weeks and to test the difference in the frequency of exacerbation between Ciprofloxacin DPI 28 and the matching placebo 28. P-value was analysed using Wald-type test along with the incidence rate ratio of the comparison. | |
| Comparison groups | Placebo 28 Days on/off (Placebo 28) v Ciprofloxacin DPI 28 Days on/off (Cipro 28) |
| Number of subjects included in analysis | 211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8946 |
| Method | Poisson regression |
| Parameter estimate | Incidence Rate Ratio |
| Point estimate | 0.9757 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.6434 |
| upper limit | 1.4796 |

| Statistical analysis title | Cipro 14 vs Placebo 14 |
|-----------------------------------|------------------------|
|-----------------------------------|------------------------|

Statistical analysis description:

A Poisson regression with adjustment for over-/under dispersion was used to analyze the number of exacerbation events over 48 weeks and to test the difference in the frequency of exacerbation between Ciprofloxacin DPI 14 and the matching placebo 14. P-value was analysed using Wald-type test along

with the incidence rate ratio of the comparison.

| | |
|---|---|
| Comparison groups | Ciprofloxacin DPI 14 Days on/off (Cipro 14) v Placebo 14 Days on/off (Placebo 14) |
| Number of subjects included in analysis | 205 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0061 |
| Method | Poisson regression |
| Parameter estimate | Incidence Rate Ratio |
| Point estimate | 0.6076 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.4043 |
| upper limit | 0.9131 |

Secondary: Time to First Exacerbation Event Within 48 Weeks

| | |
|---|---|
| End point title | Time to First Exacerbation Event Within 48 Weeks ^[5] |
| End point description: | |
| Time to first exacerbation was defined as the time from randomization until the visit at which the first qualifying exacerbation is recorded by the investigator. Exacerbation events are defined as exacerbations with systemic antibiotic use and presence of fever or malaise / fatigue and worsening of at least three signs/symptoms. An entry of '99999' indicates that the value could not be estimated due to too many censored observations. | |
| End point type | Secondary |
| End point timeframe: | |
| Up to Week 48 | |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pooled placebo group data were reported in place of individual placebo groups.

| End point values | Ciprofloxacin DPI 28 Days on/off (Cipro 28) | Ciprofloxacin DPI 14 Days on/off (Cipro 14) | Pooled Placebo | |
|------------------------------------|---|---|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 141 ^[6] | 137 ^[7] | 138 ^[8] | |
| Units: Days | | | | |
| median (confidence interval 97.5%) | 336 (206 to 99999) | 99999 (290 to 99999) | 186 (136 to 282) | |

Notes:

[6] - FAS

[7] - FAS

[8] - FAS

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | Cipro 28 vs Pooled Placebo |
|----------------------------|----------------------------|

Statistical analysis description:

The hazard ratio for time to first exacerbation event within 48 weeks and 97.5% CI was calculated by using Cox proportional hazards model by comparison of Cipro 28/Pooled Placebo reporting groups. P-value was analysed using Wald-type test.

| | |
|---|--|
| Comparison groups | Ciprofloxacin DPI 28 Days on/off (Cipro 28) v Pooled Placebo |
| Number of subjects included in analysis | 279 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.065 |
| Method | Wald-type test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.7331 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.5027 |
| upper limit | 1.069 |

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Cipro 14 vs Pooled Placebo |
|-----------------------------------|----------------------------|

Statistical analysis description:

The hazard ratio for time to first exacerbation event within 48 weeks and 97.5% CI was calculated by using Cox proportional hazards model by comparison of Cipro 14/Pooled Placebo reporting groups. P-value was analysed using Wald-type test.

| | |
|---|--|
| Comparison groups | Ciprofloxacin DPI 14 Days on/off (Cipro 14) v Pooled Placebo |
| Number of subjects included in analysis | 275 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0005 |
| Method | Wald-type test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.5333 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.3568 |
| upper limit | 0.7971 |

Secondary: Number of subjects with exacerbation events with worsening of at least one sign/symptom over 48 weeks

| | |
|-----------------|---|
| End point title | Number of subjects with exacerbation events with worsening of at least one sign/symptom over 48 weeks |
|-----------------|---|

End point description:

For this outcome measure, exacerbation events were defined as exacerbations with systemic antibiotic use and worsening of at least one sign/symptom over 48 weeks.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Week 48

| End point values | Ciprofloxacin DPI 28 Days on/off (Cipro 28) | Ciprofloxacin DPI 14 Days on/off (Cipro 14) | Placebo 28 Days on/off (Placebo 28) | Placebo 14 Days on/off (Placebo 14) |
|--|---|---|-------------------------------------|-------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 141 ^[9] | 137 ^[10] | 70 ^[11] | 68 ^[12] |
| Units: Subjects with exacerbation events | | | | |
| Number of exacerbations: 0 | 58 | 68 | 25 | 21 |
| Number of exacerbations: 1 | 47 | 42 | 26 | 17 |
| Number of exacerbations: 2 | 12 | 15 | 11 | 20 |
| Number of exacerbations: 3 | 14 | 5 | 5 | 6 |
| Number of exacerbations: 4 | 4 | 2 | 3 | 2 |
| Number of exacerbations: 5 | 4 | 3 | 0 | 2 |
| Number of exacerbations: 6 | 2 | 2 | 0 | 0 |

Notes:

[9] - FAS

[10] - FAS

[11] - FAS

[12] - FAS

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Cipro 28 vs Placebo 28 |
| Statistical analysis description: | |
| A Poisson regression with adjustment for over-/under dispersion was used to analyze the number of exacerbation events over 48 weeks and to test the difference in the frequency of exacerbation between Ciprofloxacin DPI 28 and the matching placebo 28. P-value was analysed using Wald-type test along with the incidence rate ratio of the comparison. | |
| Comparison groups | Ciprofloxacin DPI 28 Days on/off (Cipro 28) v Placebo 28 Days on/off (Placebo 28) |
| Number of subjects included in analysis | 211 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8628 |
| Method | Wald-type test |
| Parameter estimate | Incidence rate ratio |
| Point estimate | 0.9715 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.6674 |
| upper limit | 1.4141 |

| | |
|--|---|
| Statistical analysis title | Cipro 14 vs Placebo 14 |
| Statistical analysis description: | |
| A Poisson regression with adjustment for over-/under dispersion was used to analyze the number of exacerbation events over 48 weeks and to test the difference in the frequency of exacerbation between Ciprofloxacin DPI 14 and the matching placebo 14. P-value was analysed using Wald-type test along with the incidence rate ratio of the comparison. | |
| Comparison groups | Ciprofloxacin DPI 14 Days on/off (Cipro 14) v Placebo 14 Days on/off (Placebo 14) |

| | |
|---|----------------------|
| Number of subjects included in analysis | 205 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.011 |
| Method | Wald-type test |
| Parameter estimate | Incidence rate ratio |
| Point estimate | 0.6573 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 2-sided |
| lower limit | 0.4542 |
| upper limit | 0.9513 |

Secondary: Percentage of Subjects With Pathogen Eradication at End of Treatment (Week 44/46)

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Pathogen Eradication at End of Treatment (Week 44/46) ^[13] |
|-----------------|---|

End point description:

Pathogen eradication was defined as a negative culture result for all pre-specified pathogens at end of treatment (week 44 or 46 depending on treatment regimen) that were present in the subject at baseline. There was no imputation for subjects who discontinued the study prematurely.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

End of treatment (Week 44/46)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pooled placebo group data were reported in place of individual placebo groups.

| End point values | Ciprofloxacin DPI 28 Days on/off (Cipro 28) | Ciprofloxacin DPI 14 Days on/off (Cipro 14) | Pooled Placebo | |
|-------------------------------|---|---|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 141 ^[14] | 137 ^[15] | 138 ^[16] | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| No | 39 | 26.3 | 33.3 | |
| Yes | 24.1 | 28.5 | 16.7 | |

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | Cipro 28 vs Pooled Placebo |
|----------------------------|----------------------------|

Statistical analysis description:

A Cochran-Mantel-Haenszel test was used to analyse the P-value by comparing cipro 28 and pooled placebo treatments with no imputation method.

| | |
|-------------------|--|
| Comparison groups | Ciprofloxacin DPI 28 Days on/off (Cipro 28) v Pooled Placebo |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 279 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[17] |
| P-value | = 0.6723 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[17] - Odds ratio (OR) = 1.162

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Cipro 14 vs Pooled Placebo |
|-----------------------------------|----------------------------|

Statistical analysis description:

A Cochran-Mantel-Haenszel test was used to analyse the P-value by comparing cipro 14 and pooled placebo treatments with no imputation method.

| | |
|---|--|
| Comparison groups | Ciprofloxacin DPI 14 Days on/off (Cipro 14) v Pooled Placebo |
| Number of subjects included in analysis | 275 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[18] |
| P-value | = 0.0182 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[18] - Odds ratio (OR) = 2.35

Secondary: Mean Change From Baseline in Patient Reported Outcome Saint George's Respiratory Questionnaire (SGRQ) Symptoms Component Score at End of Treatment (Week 44/46)

| | |
|-----------------|---|
| End point title | Mean Change From Baseline in Patient Reported Outcome Saint George's Respiratory Questionnaire (SGRQ) Symptoms Component Score at End of Treatment (Week 44/46) |
|-----------------|---|

End point description:

The SGRQ was a validated, disease-specific instrument that measures health-related quality of life (HRQoL) in adults with chronic obstructive pulmonary disease (COPD) and asthma and was later validated for use in bronchiectasis. The SGRQ covers 3 dimensions: symptoms, activity and impact on daily life. To determine the outcome, a score ranging from 1 to 100 was calculated for each individual domain and for the total score, and smaller scores indicate better health status. For this outcome measure, the symptoms component score was reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, end of treatment (Week 44/46)

| End point values | Ciprofloxacin DPI 28 Days on/off (Cipro 28) | Ciprofloxacin DPI 14 Days on/off (Cipro 14) | Placebo 28 Days on/off (Placebo 28) | Placebo 14 Days on/off (Placebo 14) |
|--------------------------------------|---|---|-------------------------------------|-------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 110 ^[19] | 97 ^[20] | 46 ^[21] | 43 ^[22] |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | -8.17 (± 22.92) | -7.2 (± 20.41) | -4.23 (± 19.55) | 2.78 (± 16.16) |

Notes:

[19] - FAS with subjects evaluable for this endpoint.

[20] - FAS with subjects evaluable for this endpoint.

[21] - FAS with subjects evaluable for this endpoint.

[22] - FAS with subjects evaluable for this endpoint.

| | |
|-----------------------------------|---|
| Attachments (see zip file) | Statistical Analysis Cipro 28 vs Pooled and Cipro 14 vs |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Occurrence of New Pathogens Present at End of Treatment (Week 44/46)

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Occurrence of New Pathogens Present at End of Treatment (Week 44/46) ^[23] |
|-----------------|--|

End point description:

New pathogens were any of the pre-specified organisms not cultured before start of study medication. There was no imputation for subjects who discontinued the study prematurely.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

End of treatment (Week 44/46)

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Pooled placebo group data were reported in place of individual placebo groups.

| End point values | Ciprofloxacin DPI 28 Days on/off (Cipro 28) | Ciprofloxacin DPI 14 Days on/off (Cipro 14) | Pooled Placebo | |
|-------------------------------|---|---|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 141 ^[24] | 137 ^[25] | 138 ^[26] | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| No | 60.3 | 49.6 | 42.8 | |
| Yes | 3.5 | 5.1 | 8 | |

Notes:

[24] - FAS

[25] - FAS

[26] - FAS

Statistical analyses

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Cipro 28 vs Pooled Placebo |
|-----------------------------------|----------------------------|

Statistical analysis description:

Cochran-Mantel-Haenszel model was used as the confirmatory analysis to test for differences in the occurrence of new pathogens present at end of treatment between the cipro 28 and pooled placebo treatment groups with no imputation method.

| | |
|-------------------|--|
| Comparison groups | Ciprofloxacin DPI 28 Days on/off (Cipro 28) v Pooled Placebo |
|-------------------|--|

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 279 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[27] |
| P-value | = 0.0582 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[27] - Odds ratio (OR) = 0.363

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Cipro 14 vs Pooled Placebo |
|-----------------------------------|----------------------------|

Statistical analysis description:

Cochran-Mantel-Haenszel model was used as the confirmatory analysis to test for differences in the occurrence of new pathogens present at end of treatment between the cipro 14 and pooled placebo treatment groups with no imputation method.

| | |
|---|--|
| Comparison groups | Ciprofloxacin DPI 14 Days on/off (Cipro 14) v Pooled Placebo |
| Number of subjects included in analysis | 275 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[28] |
| P-value | = 0.2569 |
| Method | Cochran-Mantel-Haenszel |

Notes:

[28] - Odds ratio (OR) = 0.557

Secondary: Mean Change From Baseline in Patient Reported Outcome Quality of Life Questionnaire for Bronchiectasis (QoL-B) Respiratory Symptoms Domain Score at End of Treatment (Week 44/46)

| | |
|-----------------|---|
| End point title | Mean Change From Baseline in Patient Reported Outcome Quality of Life Questionnaire for Bronchiectasis (QoL-B) Respiratory Symptoms Domain Score at End of Treatment (Week 44/46) |
|-----------------|---|

End point description:

The QoL-B was a disease-specific questionnaire developed for non-Cystic fibrosis Bronchiectasis. It covers 8 dimensions: physical functioning, role functioning, emotional functioning, social functioning, vitality, treatment burden, health perceptions, and respiratory symptoms. Each dimension was scored separately on a scale of 0 to 100, and higher scores represent better outcomes. For this outcome measure, the respiratory symptoms domain score was reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, end of treatment (Week 44/46)

| End point values | Ciprofloxacin DPI 28 Days on/off (Cipro 28) | Ciprofloxacin DPI 14 Days on/off (Cipro 14) | Placebo 28 Days on/off (Placebo 28) | Placebo 14 Days on/off (Placebo 14) |
|--------------------------------------|---|---|-------------------------------------|-------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 106 ^[29] | 89 ^[30] | 45 ^[31] | 42 ^[32] |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 7.7 (± 18.5) | 6.72 (± 17.9) | 8.22 (± 16.74) | 4.45 (± 17.78) |

Notes:

[29] - FAS with subjects evaluable for this endpoint.

[30] - FAS with subjects evaluable for this endpoint.

[31] - FAS with subjects evaluable for this endpoint.

[32] - FAS with subjects evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Forced Expiratory Volume in One Second (FEV1) at End of Treatment (Week 44/46)

| | |
|-----------------|---|
| End point title | Mean Change From Baseline in Forced Expiratory Volume in One Second (FEV1) at End of Treatment (Week 44/46) |
|-----------------|---|

End point description:

FEV1 was defined as the maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in liters at body temperature and ambient pressure saturated with water vapor (BTPS).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, end of treatment (Week 44/46)

| End point values | Ciprofloxacin DPI 28 Days on/off (Cipro 28) | Ciprofloxacin DPI 14 Days on/off (Cipro 14) | Placebo 28 Days on/off (Placebo 28) | Placebo 14 Days on/off (Placebo 14) |
|--------------------------------------|--|--|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 112 ^[33] | 98 ^[34] | 45 ^[35] | 41 ^[36] |
| Units: liter | | | | |
| arithmetic mean (standard deviation) | -0.012 (± 0.149) | -0.026 (± 0.226) | 0.024 (± 0.344) | 0.022 (± 0.352) |

Notes:

[33] - FAS with subjects evaluable for this endpoint.

[34] - FAS with subjects evaluable for this endpoint.

[35] - FAS with subjects evaluable for this endpoint.

[36] - FAS with subjects evaluable for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to 30 days after the last study drug administration

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Ciprofloxacin DPI 28 Days on/off |
|-----------------------|----------------------------------|

Reporting group description:

Subjects received ciprofloxacin (BAYQ3939) 32.5 mg corresponding to 50 mg DPI administered BID (every 12 hours); a treatment cycle consisted of a 28-day on-treatment phase followed by a 28-day off-treatment phase (48 weeks treatment phase = 6 active cycles).

| | |
|-----------------------|----------------|
| Reporting group title | Pooled Placebo |
|-----------------------|----------------|

Reporting group description:

Subjects received matching placebo matched to ciprofloxacin 32.5 mg powder (containing 40 mg dry powder) administered BID (every 12 hours); a treatment cycle consisted of either a 28-day day on-treatment phase followed by 28-day off-treatment phase or 14-day on-treatment phase followed by 14-day off treatment phase (48 weeks treatment phase = 6 cycles and 12 cycles, respectively).

| | |
|-----------------------|----------------------------------|
| Reporting group title | Ciprofloxacin DPI 14 Days on/off |
|-----------------------|----------------------------------|

Reporting group description:

Subjects received ciprofloxacin 32.5 mg corresponding to 50 mg DPI administered BID (every 12 hours); a treatment cycle consisted of a 14-day on-treatment phase followed by a 14-day off-treatment phase (48 weeks treatment phase = 12 active cycles).

| Serious adverse events | Ciprofloxacin DPI 28 Days on/off | Pooled Placebo | Ciprofloxacin DPI 14 Days on/off |
|---|----------------------------------|-------------------|----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 29 / 141 (20.57%) | 32 / 137 (23.36%) | 23 / 136 (16.91%) |
| number of deaths (all causes) | 3 | 5 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Breast cancer | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malignant melanoma | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroid cancer recurrent | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive lobular breast carcinoma | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Strangulated hernia | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-------------------|-------------------|-----------------|
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypogammaglobulinaemia | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Prostatic haemorrhage | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchiectasis | | | |
| subjects affected / exposed | 16 / 141 (11.35%) | 17 / 137 (12.41%) | 8 / 136 (5.88%) |
| occurrences causally related to treatment / all | 0 / 20 | 0 / 19 | 0 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 141 (1.42%) | 2 / 137 (1.46%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Influenza A virus test positive | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complications of transplant surgery | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethral stricture traumatic | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 2 / 137 (1.46%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cor pulmonale | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral atrophy | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Normal pressure hydrocephalus | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient global amnesia | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Angle closure glaucoma | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal vasculitis | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Portal hypertension | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urethral stenosis | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Fracture nonunion | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchiolitis | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 1 / 137 (0.73%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathogen resistance | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Pneumonia | | | |
| subjects affected / exposed | 4 / 141 (2.84%) | 5 / 137 (3.65%) | 4 / 136 (2.94%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 5 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective exacerbation of bronchiectasis | | | |
| subjects affected / exposed | 2 / 141 (1.42%) | 1 / 137 (0.73%) | 1 / 136 (0.74%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyometra | | | |
| subjects affected / exposed | 1 / 141 (0.71%) | 0 / 137 (0.00%) | 0 / 136 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 141 (0.00%) | 0 / 137 (0.00%) | 1 / 136 (0.74%) |
| 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: 5 %

| Non-serious adverse events | Ciprofloxacin DPI 28 Days on/off | Pooled Placebo | Ciprofloxacin DPI 14 Days on/off |
|---|-------------------------------------|-------------------|-------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 74 / 141 (52.48%) | 62 / 137 (45.26%) | 83 / 136 (61.03%) |
| Investigations | | | |
| Aspergillus test positive | | | |
| subjects affected / exposed | 6 / 141 (4.26%) | 0 / 137 (0.00%) | 7 / 136 (5.15%) |
| occurrences (all) | 6 | 0 | 8 |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|--|-------------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 2 / 141 (1.42%) 2 | 1 / 137 (0.73%) 1 | 7 / 136 (5.15%) 7 |
| Headache subjects affected / exposed occurrences (all) | 11 / 141 (7.80%) 14 | 4 / 137 (2.92%) 6 | 14 / 136 (10.29%) 16 |
| General disorders and administration site conditions | | | |
| Chest pain subjects affected / exposed occurrences (all) | 5 / 141 (3.55%) 5 | 7 / 137 (5.11%) 7 | 7 / 136 (5.15%) 8 |
| Fatigue subjects affected / exposed occurrences (all) | 6 / 141 (4.26%) 6 | 3 / 137 (2.19%) 3 | 12 / 136 (8.82%) 14 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 141 (4.96%) 7 | 5 / 137 (3.65%) 5 | 9 / 136 (6.62%) 11 |
| Nausea subjects affected / exposed occurrences (all) | 5 / 141 (3.55%) 5 | 7 / 137 (5.11%) 7 | 10 / 136 (7.35%) 11 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasm subjects affected / exposed occurrences (all) | 6 / 141 (4.26%) 7 | 10 / 137 (7.30%) 13 | 7 / 136 (5.15%) 13 |
| Cough subjects affected / exposed occurrences (all) | 15 / 141 (10.64%) 18 | 9 / 137 (6.57%) 12 | 13 / 136 (9.56%) 18 |
| Dyspnoea subjects affected / exposed occurrences (all) | 15 / 141 (10.64%) 21 | 9 / 137 (6.57%) 11 | 16 / 136 (11.76%) 26 |
| Haemoptysis subjects affected / exposed occurrences (all) | 15 / 141 (10.64%) 34 | 8 / 137 (5.84%) 10 | 16 / 136 (11.76%) 32 |
| Sputum increased subjects affected / exposed occurrences (all) | 8 / 141 (5.67%) 9 | 3 / 137 (2.19%) 4 | 6 / 136 (4.41%) 8 |
| Oropharyngeal pain | | | |

| | | | |
|--|-------------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 3 / 141 (2.13%) 3 | 5 / 137 (3.65%) 5 | 7 / 136 (5.15%) 9 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 10 / 141 (7.09%) 13 | 6 / 137 (4.38%) 6 | 9 / 136 (6.62%) 10 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 15 / 141 (10.64%) 20 | 10 / 137 (7.30%) 15 | 16 / 136 (11.76%) 21 |
| Sinusitis subjects affected / exposed occurrences (all) | 4 / 141 (2.84%) 5 | 8 / 137 (5.84%) 10 | 10 / 136 (7.35%) 12 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 141 (2.84%) 5 | 10 / 137 (7.30%) 13 | 9 / 136 (6.62%) 9 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 14 February 2013 | Following modifications were done in this amendment: -Pregnancy tests before each cycles were accommodated by phone calls for more frequent AE inquiries. -Follow-up time was harmonized to 8 weeks after last dose for both regimens were improved. -Separate statistical analysis plan were to be provided for European Medicines Agency and Food and Drug Administration. -The questionnaire QOL-B is now available in all participating countries. Inclusion and exclusion criteria were checked, added, or rephrased. |
| 28 October 2013 | Following modifications were done in this amendment: -Harmonized several passages of the protocol with that of the protocol of the twin study. -Inclusion only after proven and documented diagnosis of non-CF idiopathic or post-infectious bronchiectasis by high resolution computed tomography (HRCT) was changed into diagnosis "by computer tomography (CT)" -In the 14 days on/off regimen the urine pregnancy testing was deleted from flow chart at Visit 7 and 11. |
| 18 August 2014 | Following modifications were done in this amendment: -Adjusted the sample size. -The criteria or exacerbations that qualify for the primary endpoint of this study were clarified. |
| 24 August 2015 | Deleted one criterion for exclusion from the per-protocol analysis set (PPS) (minimal treatment duration of 168 days). |
| 16 December 2015 | Following modifications were done in this amendment: -Introduced an additional secondary efficacy endpoint (i.e. exacerbation events are defined as events with systemic antibiotic use and worsening of at least one sign/symptom). -Inclusion of the patient reported outcome (PRO) endpoint QoL-B (questionnaire's respiratory symptom domain) into the panel of secondary (confirmatory) efficacy endpoints (from previously "other" efficacy variable). -Clarification of the observational period for the endpoint time to first exacerbation qualifying as event according to the protocol as "within 48 weeks after start of treatment". |

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 autogenerated and cannot be deleted. '99999' in the posting indicates that values were not estimated due to censored data. Decimal places were automatically truncated if last decimal equals zero.

Notes: