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	v3
This version publication date	28 June 2017
First version publication date	11 March 2017
Version creation reason	• Correction of full data set update measure descriptions.

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 days 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 participants with exacerbation events with worsening of at least three signs/symptoms over 48 weeks

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

End point title	Number of participants 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 Participants With Pathogen Eradication at End of Treatment (Week 44/46)

End point title	Percentage of Participants 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 participant at baseline. There was no imputation for participants 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 participants 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	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).	
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).	

Serious adverse events	Ciprofloxacin DPI 28 Days on/off	Ciprofloxacin DPI 14 Days on/off	Pooled Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 141 (19.86%)	23 / 136 (16.91%)	32 / 137 (23.36%)
number of deaths (all causes)	3	1	5
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%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer recurrent			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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
Orthostatic hypotension			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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%)	1 / 136 (0.74%)	0 / 137 (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

Peripheral swelling			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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%)	1 / 136 (0.74%)	0 / 137 (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
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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%)	1 / 136 (0.74%)	0 / 137 (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
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	16 / 141 (11.35%)	8 / 136 (5.88%)	17 / 137 (12.41%)
occurrences causally related to treatment / all	0 / 20	0 / 9	0 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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 / 136 (0.00%)	0 / 137 (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%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	2 / 141 (1.42%)	1 / 136 (0.74%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	1 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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
Pulmonary embolism			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	1 / 137 (0.73%)
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 / 136 (0.00%)	0 / 137 (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%)	1 / 136 (0.74%)	0 / 137 (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
Complications of transplant surgery			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Femoral neck fracture			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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
Fibula fracture			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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
Urethral stricture traumatic			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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
Meniscus injury			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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%)	1 / 136 (0.74%)	0 / 137 (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
Atrial flutter			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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%)	1 / 136 (0.74%)	2 / 137 (1.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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%)	1 / 136 (0.74%)	0 / 137 (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
Nervous system disorders			
Cerebral atrophy			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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
Normal pressure hydrocephalus			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient global amnesia			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 / 136 (0.00%)	0 / 137 (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%)	1 / 136 (0.74%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Ascites			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Portal hypertension			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
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 and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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 failure			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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
Urinary retention			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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
Urethral stenosis			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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 / 136 (0.00%)	0 / 137 (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%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis clostridial			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 141 (0.00%)	0 / 136 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathogen resistance			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 141 (2.84%)	4 / 136 (2.94%)	5 / 137 (3.65%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1

Urosepsis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 136 (0.00%)	0 / 137 (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 / 136 (0.74%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 136 (0.74%)	0 / 137 (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

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ciprofloxacin DPI 28 Days on/off	Ciprofloxacin DPI 14 Days on/off	Pooled Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 141 (52.48%)	83 / 136 (61.03%)	62 / 137 (45.26%)
Investigations			
Aspergillus test positive			
subjects affected / exposed	6 / 141 (4.26%)	7 / 136 (5.15%)	0 / 137 (0.00%)
occurrences (all)	6	8	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 141 (1.42%)	7 / 136 (5.15%)	1 / 137 (0.73%)
occurrences (all)	2	7	1
Headache			
subjects affected / exposed	11 / 141 (7.80%)	14 / 136 (10.29%)	4 / 137 (2.92%)
occurrences (all)	14	16	6
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	5 / 141 (3.55%)	7 / 136 (5.15%)	7 / 137 (5.11%)
occurrences (all)	5	8	7
Fatigue			

subjects affected / exposed	6 / 141 (4.26%)	12 / 136 (8.82%)	3 / 137 (2.19%)
occurrences (all)	6	14	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 141 (4.96%)	9 / 136 (6.62%)	5 / 137 (3.65%)
occurrences (all)	7	11	5
Nausea			
subjects affected / exposed	5 / 141 (3.55%)	10 / 136 (7.35%)	7 / 137 (5.11%)
occurrences (all)	5	11	7
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	6 / 141 (4.26%)	7 / 136 (5.15%)	10 / 137 (7.30%)
occurrences (all)	7	13	13
Cough			
subjects affected / exposed	15 / 141 (10.64%)	13 / 136 (9.56%)	9 / 137 (6.57%)
occurrences (all)	18	18	12
Dyspnoea			
subjects affected / exposed	15 / 141 (10.64%)	16 / 136 (11.76%)	9 / 137 (6.57%)
occurrences (all)	21	26	11
Haemoptysis			
subjects affected / exposed	15 / 141 (10.64%)	16 / 136 (11.76%)	8 / 137 (5.84%)
occurrences (all)	34	32	10
Sputum increased			
subjects affected / exposed	8 / 141 (5.67%)	6 / 136 (4.41%)	3 / 137 (2.19%)
occurrences (all)	9	8	4
Oropharyngeal pain			
subjects affected / exposed	3 / 141 (2.13%)	7 / 136 (5.15%)	5 / 137 (3.65%)
occurrences (all)	3	9	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	10 / 141 (7.09%)	9 / 136 (6.62%)	6 / 137 (4.38%)
occurrences (all)	13	10	6
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 141 (10.64%)	16 / 136 (11.76%)	10 / 137 (7.30%)
occurrences (all)	20	21	15

Sinusitis			
subjects affected / exposed	4 / 141 (2.84%)	10 / 136 (7.35%)	8 / 137 (5.84%)
occurrences (all)	5	12	10
Upper respiratory tract infection			
subjects affected / exposed	4 / 141 (2.84%)	9 / 136 (6.62%)	10 / 137 (7.30%)
occurrences (all)	5	9	13

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: