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	2013-004659-19
Trial protocol	DE NL LT AT CZ PT BG LV SK
Global end of trial date	19 October 2016

Results information

Result version number	v1 (current)
This version publication date	19 August 2017
First version publication date	19 August 2017

Trial information

Trial identification

Sponsor protocol code	BAYQ3939/15626

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02106832
WHO universal trial number (UTN)	U1111-1150-8425

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
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	19 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were
• To evaluate the efficacy of ciprofloxacin DPI administered 2 times a day (BID) intermittently for 28 days on study treatment / 28 days off study treatment or 14 days on study treatment / 14 days off study treatment to prolong the time to first pulmonary exacerbation requiring an intervention with systemic antibiotics (oral/i.v.) in subjects with non–CF BE within 48 weeks after start of treatment (as agreed with the US FDA [Food and Drug Administration]).
• To evaluate the efficacy of ciprofloxacin DPI administered 2 times a day (BID) intermittently for 28 days on study treatment / 28 days off study treatment or 14 days on study treatment / 14 days off study treatment in reducing the frequency of pulmonary exacerbation requiring an intervention with systemic antibiotics (oral/i.v.) in subjects with non–CF BE within 48 weeks after start of treatment.

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	30 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 39
Country: Number of subjects enrolled	Portugal: 14
Country: Number of subjects enrolled	Romania: 32
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	Bulgaria: 54
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Latvia: 45
Country: Number of subjects enrolled	Lithuania: 6

Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	China: 33
Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Korea, Republic of: 34
Country: Number of subjects enrolled	Philippines: 10
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	Serbia: 33
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Thailand: 13
Country: Number of subjects enrolled	Turkey: 30
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	521
EEA total number of subjects	233

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)	299
From 65 to 84 years	218
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 164 study centers in 25 countries between 30 April 2014 (first subject first visit) and 19 October 2016 (last subject last visit).

Pre-assignment

Screening details:

A total of 1123 subjects were screened and 521 subjects were randomized. The randomized subjects were allocated to treatment groups, and 2 subjects in the Cipro 14 group did not receive study medication.

Period 1

Period 1 title	Overall Study (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 dry powder for inhalation (DPI) administered twice daily (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:

Ciprofloxacin dry powder for inhalation (DPI) 32.5 mg inhaled twice daily in cycles of 28 days on-treatment and 28 days off-treatment.

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:

Ciprofloxacin DPI 32.5 mg inhaled twice daily in cycles of 14 days on-treatment and 14 days off-treatment.

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	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Matching placebo inhaled twice daily intermittently for 28 days on / 28 days off.

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	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Matching placebo inhaled twice daily intermittently for 14 days on / 14 days off.

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	171	176	86
Treated	171	174	86
Completed	148	151	70
Not completed	23	25	16
Physician decision	1	-	-
Consent withdrawn by subject	17	17	10
Deterioration of general conditions	-	-	1
Adverse event, non-fatal	1	2	3
Technical problems	-	1	-
Death	4	4	1
Lost to follow-up	-	1	1
Protocol deviation	-	-	-

Number of subjects in period 1	Placebo 14 Days on/off (Placebo 14)
Started	88
Treated	88
Completed	73
Not completed	15
Physician decision	-

Consent withdrawn by subject	7
Deterioration of general conditions	-
Adverse event, non-fatal	-
Technical problems	-
Death	4
Lost to follow-up	3
Protocol deviation	1

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 dry powder for inhalation (DPI) administered twice daily (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	171	176	86
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.3	60.4	60.6
standard deviation	± 14.2	± 13.7	± 13.7
Gender categorical Units: Subjects			
Female	92	96	52
Male	79	80	34
Saint George's Respiratory Questionnaire (SGRQ) Symptoms Component Score (n=169, 170, 85, 83)			
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	60.75	61.26	58.56
standard deviation	± 20.61	± 19.54	± 19.17
QoL-B Respiratory Symptoms Domain Score (n= 104, 115, 56, 59)			
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	50.14	52.17	53.95
standard deviation	± 19.07	± 18.49	± 16
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	1.569	1.519	1.56
standard deviation	± 0.602	± 0.617	± 0.692

Reporting group values	Placebo 14 Days on/off (Placebo 14)	Total	
Number of subjects	88	521	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	60.4		
standard deviation	± 15	-	
Gender categorical			
Units: Subjects			
Female	62	302	
Male	26	219	
Saint George's Respiratory Questionnaire (SGRQ) Symptoms Component Score (n=169, 170, 85, 83)			
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	63.47		
standard deviation	± 19.48	-	
QoL-B Respiratory Symptoms Domain Score (n= 104, 115, 56, 59)			
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	48.67		
standard deviation	± 17.72	-	
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	1.477		
standard deviation	± 0.558	-	

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 dry powder for inhalation (DPI) administered twice daily (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:	
included subjects who were randomized.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
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 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	171[1]	176[2]	86[3]	88[4]
Units: Subjects with exacerbation events				
number (not applicable)				
Number of exacerbations: 0	115	108	51	50
Number of exacerbations: 1	46	40	18	23
Number of exacerbations: 2	8	23	10	9
Number of exacerbations: 3	2	4	5	5
Number of exacerbations: 4	0	1	1	1
Number of exacerbations: 5	0	0	1	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	Ciprofloxacin DPI 28 Days on/off (Cipro 28) v Placebo 28 Days on/off (Placebo 28)
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	Poisson regression
Parameter estimate	Incidence Rate Ratio
Point estimate	0.5493
Confidence interval	
level	Other: 99.9 %
sides	2-sided
lower limit	0.2968
upper limit	1.0164

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	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2862
Method	Poisson regression
Parameter estimate	Incidence Rate Ratio
Point estimate	0.8313
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	0.5911
upper limit	1.1691

Secondary: Time to First Exacerbation Event Within 48 Weeks - Cipro 28 vs. Pooled Placebo

End point title	Time to First Exacerbation Event Within 48 Weeks - Cipro 28 vs. Pooled Placebo[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)	Pooled Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	171[6]	174[7]		
Units: Days				
median (confidence interval 99.9%)	99999 (99999 to 99999)	99999 (211 to 99999)		

Notes:

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Exacerbation Event Within 48 Weeks - Cipro 14 vs. Pooled Placebo

End point title	Time to First Exacerbation Event Within 48 Weeks - Cipro 14 vs. Pooled Placebo[8]

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:

[8] - 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 14 Days on/off (Cipro 14)	Pooled Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	176[9]	174[10]		
Units: Days				
median (confidence interval 95.1%)	99999 (99999 to 99999)	99999 (278 to 99999)		

Notes:

[9] - FAS

[10] - FAS

Statistical analyses

No statistical analyses for this end point

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	171[11]	176[12]	86[13]	88[14]
Units: Subjects with exacerbation events				
number (not applicable)				
Number of exacerbations: 0	102	96	44	46
Number of exacerbations: 1	51	46	21	24
Number of exacerbations: 2	14	26	13	9

Number of exacerbations: 3	3	4	5	6
Number of exacerbations: 4	1	3	2	2
Number of exacerbations: 5	0	1	1	1

Notes:

[11] - FAS

[12] - FAS

[13] - FAS

[14] - FAS

Statistical analyses

No statistical analyses for this end point

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)[15]

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:

[15] - 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	171[16]	176[17]	174[18]	
Units: Percentage of subjects				
number (not applicable)				
No	35.1	35.8	40.2	
Yes	31.6	35.8	31.6	

Notes:

[16] - Full analysis set (FAS) included participants who were randomized.

[17] - Full analysis set (FAS) included participants who were randomized.

[18] - Full analysis set (FAS) included participants who were randomized.

Statistical analyses

No statistical analyses for this end point

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 and 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	142[19]	142[20]	67[21]	72[22]
Units: Score on a scale				
arithmetic mean (standard deviation)	-8.92 (± 21.06)	-9.02 (± 20.1)	-2.91 (± 24.48)	-11.5 (± 18.54)

Notes:

[19] - FAS with participants evaluable for this outcome measure.

[20] - FAS with participants evaluable for this outcome measure.

[21] - FAS with participants evaluable for this outcome measure.

[22] - FAS with participants evaluable for this outcome measure.

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	171[24]	176[25]	174[26]	
Units: Percentage of subjects				
number (not applicable)				

No	62.6	67.6	61.5	
Yes	4.1	4	10.3	

Notes:

[24] - Full analysis set (FAS) included participants who were randomized.

[25] - Full analysis set (FAS) included participants who were randomized.

[26] - Full analysis set (FAS) included participants who were randomized.

Statistical analyses

No statistical analyses for this end point

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 and 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	85[27]	94[28]	43[29]	49[30]
Units: Score on a scale				
arithmetic mean (standard deviation)	11.57 (± 17.49)	10.9 (± 18.07)	7.08 (± 17)	10.7 (± 15.58)

Notes:

[27] - FAS with participants evaluable for this outcome measure.

[28] - FAS with participants evaluable for this outcome measure.

[29] - FAS with participants evaluable for this outcome measure.

[30] - FAS with participants evaluable for this outcome measure.

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 and 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	138[31]	140[32]	62[33]	71[34]
Units: Liter				
arithmetic mean (standard deviation)	0.038 (± 0.336)	-0.037 (± 0.287)	-0.038 (± 0.272)	0.037 (± 0.299)

Notes:

[31] - FAS with participants evaluable for this outcome measure.

[32] - FAS with participants evaluable for this outcome measure.

[33] - FAS with participants evaluable for this outcome measure.

[34] - FAS with participants evaluable for this outcome measure.

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	19.0

Reporting groups	
Reporting group title	Ciprofloxacin DPI 28 Days on/off (Cipro 28)
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 (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	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 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).	

Serious adverse events	Ciprofloxacin DPI 28 Days on/off (Cipro 28)	Ciprofloxacin DPI 14 Days on/off (Cipro 14)	Pooled Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 171 (16.37%)	45 / 174 (25.86%)	41 / 174 (23.56%)
number of deaths (all causes)	4	5	5
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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
Colon cancer			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glottis carcinoma			

subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioma			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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
Oesophageal carcinoma			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
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			
Hypertensive crisis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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			
Adenomyosis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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	17 / 171 (9.94%)	24 / 174 (13.79%)	21 / 174 (12.07%)
occurrences causally related to treatment / all	0 / 20	0 / 27	0 / 31
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 2
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 171 (0.00%)	3 / 174 (1.72%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
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 / 171 (1.17%)	3 / 174 (1.72%)	4 / 174 (2.30%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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 failure			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
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 disorders			
Atrial flutter			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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
Cor pulmonale			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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
Congestive cardiomyopathy			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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
Carotid artery occlusion			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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
Ischaemic stroke			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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			
Febrile neutropenia			

subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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			
Vitreous detachment			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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
Inguinal hernia			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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
Oesophageal obstruction			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
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 disorder			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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			
Cholangitis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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			
Arthralgia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 171 (0.00%)	1 / 174 (0.57%)	0 / 174 (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
Infections and infestations			
Chronic sinusitis			

subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
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			
subjects affected / exposed	3 / 171 (1.75%)	2 / 174 (1.15%)	2 / 174 (1.15%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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
Bronchitis bacterial			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
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 tract infection viral			

subjects affected / exposed	1 / 171 (0.58%)	0 / 174 (0.00%)	0 / 174 (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	0 / 171 (0.00%)	3 / 174 (1.72%)	2 / 174 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoproteinaemia			
subjects affected / exposed	0 / 171 (0.00%)	0 / 174 (0.00%)	1 / 174 (0.57%)
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 (Cipro 28)	Ciprofloxacin DPI 14 Days on/off (Cipro 14)	Pooled Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 171 (29.82%)	60 / 174 (34.48%)	55 / 174 (31.61%)
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	9 / 171 (5.26%)	8 / 174 (4.60%)	2 / 174 (1.15%)
occurrences (all)	13	16	2
Headache			
subjects affected / exposed	10 / 171 (5.85%)	10 / 174 (5.75%)	5 / 174 (2.87%)
occurrences (all)	15	11	5
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	3 / 171 (1.75%)	7 / 174 (4.02%)	9 / 174 (5.17%)
occurrences (all)	3	7	9
Cough			
subjects affected / exposed	5 / 171 (2.92%)	7 / 174 (4.02%)	11 / 174 (6.32%)
occurrences (all)	9	7	12
Dyspnoea			

subjects affected / exposed	4 / 171 (2.34%)	10 / 174 (5.75%)	3 / 174 (1.72%)
occurrences (all)	5	11	6
Haemoptysis			
subjects affected / exposed	11 / 171 (6.43%)	15 / 174 (8.62%)	20 / 174 (11.49%)
occurrences (all)	19	22	41
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 171 (5.85%)	16 / 174 (9.20%)	14 / 174 (8.05%)
occurrences (all)	11	19	18
Upper respiratory tract infection			
subjects affected / exposed	10 / 171 (5.85%)	8 / 174 (4.60%)	5 / 174 (2.87%)
occurrences (all)	13	10	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2014	Sample size calculation was clarified and generalized to take into account potential deviations from the original assumptions; Exclusion criterion #18 was changed to comply with an ethics committee request not to allow participation in both this study and sister study Respire 1.
02 September 2015	Deletion of one criterion for exclusion from the per-protocol analysis set (PPS) ("minimal treatment duration of 168 days").
29 February 2016	Introduction of an additional secondary efficacy endpoint related to the frequency of exacerbations with the broader definition "event with systemic antibiotic use and worsening of at least 1 sign/symptom"; inclusion of the efficacy endpoint related to QoL-B respiratory symptoms domain score into the confirmatory testing hierarchy as secondary efficacy variable.
15 July 2016	The originally planned alpha split of 0.025 for each treatment regimen was changed to α=0.049 for the 14 days on/off regimen and α=0.001 for the 28 days on/off regimen; omission of the data extrapolation procedure for the primary analysis of exacerbation events as originally initially required by the FDA and, alternatively, inclusion of the subjects' time on study as an offset variable in the main model.

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: