Clinical trial results:
A randomized, double-blind, placebo-controlled parallel group study to investigate the safety and efficacy of two doses of tiotropium bromide (2.5 µg and 5 µg) administered once daily via the Respimat device for 12 weeks in patients with cystic fibrosis.

EudraCT number	2008-001156-43
Trial protocol	FR BE DE NL GB PT IT
Global end of trial date	02 April 2010

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	17 April 2015

Sponsor protocol code	205.339

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00737100
WHO universal trial number (UTN)	-

Notes:

Sponsor organisation name	Boehringer Ingelheim Pharma GmbH & Co. KG
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000035-PIP01-07
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Analysis stage	Final
Date of interim/final analysis	27 April 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 April 2010
Was the trial ended prematurely?	No

Notes:

Main objective of the trial:

This study evaluates the effects of 12-week treatment with two doses of tiotropium bromide (2.5 µg q.d. and 5 µg q.d.) compared to placebo administered via the Respimat® device on lung function in patients with CF.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Administration of rescue medication was allowed at any point during the study as medically needed. Open-label salbutamol/albuterol MDI (100 µg per puff) was provided as rescue medication by BI.

Background therapy:

Patients maintained their background therapy , including inhaled corticosteroids (ICS).

Evidence for comparator: -

Actual start date of recruitment	23 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	United Kingdom: 49
Country: Number of subjects enrolled	Belgium: 35
Country: Number of subjects enrolled	France: 126
Country: Number of subjects enrolled	Germany: 74
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Australia: 28
Country: Number of subjects enrolled	New Zealand: 11
Country: Number of subjects enrolled	Russian Federation: 36
Country: Number of subjects enrolled	United States: 221
Worldwide total number of subjects	620
EEA total number of subjects	324

Notes:

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)	168
Adolescents (12-17 years)	100
Adults (18-64 years)	348
From 65 to 84 years	4
85 years and over	0

Recruitment details: -

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subject) met all strictly implemented inclusion/exclusion criteria. Subjects were not randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1 title	Overall trial (Treatment period) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Are arms mutually exclusive?	Yes
	Placebo

Arm description:

Patients randomised to receive matching placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations once daily at the same time of day, ideally in the morning between 6 am and 10 am.

	Tiotropium Respimat 2.5 Micrograms

Arm description:

Patients randomised to receive Tiotropium Respimat 2.5 micrograms once daily

Arm type	Experimental
Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations once daily at the same time of day, ideally in the morning between 6 am and 10 am.

	Tiotropium Respimat 5 Micrograms

Arm description:

Patients randomised to receive Tiotropium Respimat 5.0 micrograms once daily

Arm type	Experimental

Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations once daily at the same time of day, ideally in the morning between 6 am and 10 am.

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms
Started	168	166	176
Completed	161	159	169
Not completed	7	7	7
Adverse event, serious fatal	2	1	-
Consent withdrawn by subject	-	-	3
Adverse event, non-fatal	4	4	3
Reason not explained above	1	1	1
Lost to follow-up	-	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Reporting group title	Placebo
Reporting group description:	
Patients randomised to receive matching placebo	
Reporting group title	Tiotropium Respimat 2.5 Micrograms
Reporting group description:	
Patients randomised to receive Tiotropium Respimat 2.5 micrograms once daily	
Reporting group title	Tiotropium Respimat 5 Micrograms
Reporting group description:	
Patients randomised to receive Tiotropium Respimat 5.0 micrograms once daily	

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms
Number of subjects	168	166	176
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	20.4	21.5	20.7
standard deviation	± 11.6	± 12	± 11.3
Gender categorical Units: Subjects			
Female	72	81	82
Male	96	85	94
Age, Customized			

Ex-smoker	7	5	7
Currently smokes	2	4	2

Height			
Units: centimeters			
arithmetic mean	157.4	157.7	155.7
standard deviation	± 17.2	± 17	± 18.2
Weight			
Units: kilograms			
arithmetic mean	52.1	51	50.4
standard deviation	± 19	± 17.3	± 18.2
Body Mass Index			
Units: kilogram/square meter			
arithmetic mean	20.3	19.9	20
standard deviation	± 4.4	± 4	± 4.1

	Total		
Number of subjects	510		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	235		
Male	275		
Age, Customized			
Units: Subjects			
<= 11 years	138		
>= 12 years	372		
Race/Ethnicity, Customized			
Units: Subjects			
Asian	3		
Black/African American	5		
White	383		
Missing	111		
American Indian / Alaskan native	8		
Alcohol history			
Units: Subjects			
Drinks no alcohol	374		
Drinks alcohol but should not interfere with trial	135		
Drinks alcohol but could interfere with trial	1		
Smoking history			
Units: Subjects			
Never smoked	483		
Ex-smoker	19		
Currently smokes	8		

Height Units: centimeters arithmetic mean standard deviation	- -		
Weight Units: kilograms arithmetic mean standard deviation	- -		
Body Mass Index Units: kilogram/square meter arithmetic mean standard deviation	- -		

Reporting group title	Placebo
Reporting group description:	
Patients randomised to receive matching placebo	
Reporting group title	Tiotropium Respimat 2.5 Micrograms
Reporting group description:	
Patients randomised to receive Tiotropium Respimat 2.5 micrograms once daily	
Reporting group title	Tiotropium Respimat 5 Micrograms
Reporting group description:	
Patients randomised to receive Tiotropium Respimat 5.0 micrograms once daily	

End point title	Percent Predicted FEV1 AUC0-4 Response at the End of Week 12
End point description:	
Change from baseline in percent predicted Forced Expiratory Volume in one second (FEV1) Area Under the Curve from 0 to 4 hours (AUC0-4). Calculated as percent predicted at week 12 minus percent predicted at baseline.	

End point type	Primary
End point timeframe:	
Baseline, Week 12	

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163[1]	158[2]	169[3]	
Units: Percentage change				
least squares mean (standard error)	-1.74 (± 0.65)	1.2 (± 0.66)	1.65 (± 0.63)	

Notes:

[1] - FAS - only patients with endpoint values at week 12 were analysed

[2] - FAS - only patients with endpoint values at week 12 were analysed

[3] - FAS - only patients with endpoint values at week 12 were analysed

	Statistical Analysis 1
Statistical analysis description:	
Comparison of Tiotropium 2.5 microgram dose versus placebo adjusted for baseline, center, visit and age group. Analysis based on mixed effects model with repeated measures using unstructured covariance matrix.	
Comparison groups	Placebo v Tiotropium Respimat 2.5 Micrograms

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	4.7

Notes:

[4] - Hierarchical testing was applied. Comparison of 2.5 dose to be performed only if superiority of tiotropium 5.0 dose compared to placebo was shown for both primary endpoints.

	Statistical Analysis 2

Statistical analysis description:

Comparison of Tiotropium 5.0 microgram dose versus placebo adjusted for baseline, center, visit and age group. Analysis based on mixed effects model with repeated measures using unstructured covariance matrix.

Comparison groups	Placebo v Tiotropium Respimat 5 Micrograms
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.67
upper limit	5.12

Notes:

[5] - Hierarchical testing was applied. Comparison of 2.5 dose to be performed only if superiority of tiotropium 5.0 dose compared to placebo was shown for both primary endpoints.

End point title	Percent Predicted FEV1 Trough Response at the End of Week 12

End point description:

Change from baseline in percent predicted trough Forced Expiratory Volume in one second. Calculated as percent predicted at week 12 minus percent predicted at baseline.

End point type	Primary

End point timeframe:

Baseline, Week 12

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	163[6]	158[7]	169[8]	
Units: Percentage change				
least squares mean (standard error)	-1.44 (± 0.71)	0.81 (± 0.71)	0.78 (± 0.69)	

Notes:

[6] - FAS - only patients with endpoint values at week 12 were analysed

[7] - FAS - only patients with endpoint values at week 12 were analysed

[8] - FAS - only patients with endpoint values at week 12 were analysed

	Statistical Analysis 1
Statistical analysis description:	
Comparison of Tiotropium 2.5 microgram dose versus placebo adjusted for baseline, center, visit and age group. Analysis based on mixed effects model with repeated measures using unstructured covariance matrix	
Comparison groups	Tiotropium Respimat 2.5 Micrograms v Placebo
Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0184 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	4.11

Notes:

[9] - Hierarchical testing was applied. Comparison of 2.5 dose to be performed only if superiority of tiotropium 5.0 dose compared to placebo was shown for both primary endpoints.

	Statistical Analysis 2
Statistical analysis description:	
Comparison of Tiotropium 5.0 microgram dose versus placebo adjusted for baseline, center, visit and age group. Analysis based on mixed effects model with repeated measures using unstructured covariance matrix	
Comparison groups	Placebo v Tiotropium Respimat 5 Micrograms
Number of subjects included in analysis	332
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0179 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	4.06

Notes:

[10] - Hierarchical testing was applied. Comparison of 2.5 dose to be performed only if superiority of tiotropium 5.0 dose compared to placebo was shown for both primary endpoints.

End point title	Percent Predicted FVC AUC0-4 Response at the End of Week 12

End point description:

Change from baseline in percent predicted Forced Vital Capacity (FVC) Area Under the Curve from 0 to 4 hours (AUC0-4). Calculated as percent predicted at week 12 minus percent predicted at baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 12

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149[11]	150[12]	158[13]	
Units: Percentage change				
least squares mean (standard error)	-1.3 (± 0.74)	0.53 (± 0.74)	1.81 (± 0.72)	

Notes:

[11] - FAS - only patients with endpoint values at week 12 were analysed

[12] - FAS - only patients with endpoint values at week 12 were analysed

[13] - FAS - only patients with endpoint values at week 12 were analysed

	Statistical Analysis 1

Statistical analysis description:

Comparison of Tiotropium 2.5 microgram dose versus placebo adjusted for baseline, center, visit and age group. Analysis based on mixed effects model with repeated measures using unstructured covariance matrix.

Comparison groups	Tiotropium Respimat 2.5 Micrograms v Placebo
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0756
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	3.86

	Statistical Analysis 2
Statistical analysis description:	
Comparison of Tiotropium 5.0 microgram dose versus placebo adjusted for baseline, center, visit and age group	
Comparison groups	Placebo v Tiotropium Respimat 5 Micrograms
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.12
upper limit	5.12

End point title	Percent Predicted FVC Trough Response at the End of Week 12
End point description:	
Change from baseline in percent predicted trough Forced Vital Capacity (FVC). Calculated as percent predicted at week 12 minus percent predicted at baseline.	

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	149[14]	150[15]	158[16]	
Units: Percentage change				
least squares mean (standard error)	-0.39 (± 0.73)	0.47 (± 0.72)	0.81 (± 0.7)	

Notes:

[14] - FAS - only patients with endpoint values at week 12 were analysed

[15] - FAS - only patients with endpoint values at week 12 were analysed

[16] - FAS - only patients with endpoint values at week 12 were analysed

	Statistical Analysis 1
Statistical analysis description:	
Comparison of Tiotropium 2.5 microgram dose versus placebo adjusted for baseline, center, visit and age group. Analysis based on mixed effects model with repeated measures using unstructured covariance matrix.	

Comparison groups	Tiotropium Respimat 2.5 Micrograms v Placebo
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3857
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.08
upper limit	2.79

	Statistical Analysis 2
Statistical analysis description:	
Comparison of Tiotropium 5.0 microgram dose versus placebo adjusted for baseline, center, visit and age group. Analysis based on mixed effects model with repeated measures using unstructured covariance matrix	
Comparison groups	Placebo v Tiotropium Respimat 5 Micrograms
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2199
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	3.11

End point title	Pre-bronchodilator FEF25-75 Percent Predicted at the End of Week 12
End point description:	
Forced Expiratory Flow at 25-75% of vital capacity (FEF25-75). Calculated as percent predicted at week 12 minus percent predicted at baseline.	

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150[17]	152[18]	158[19]	
Units: Percentage change				
least squares mean (standard error)	-1.4 (± 1.57)	2.78 (± 1.55)	3.94 (± 1.52)	

Notes:

[17] - FAS - only patients with endpoint values at week 12 were analysed

[18] - FAS - only patients with endpoint values at week 12 were analysed

[19] - FAS - only patients with endpoint values at week 12 were analysed

	Statistical Analysis 1
Statistical analysis description:	
Comparison of Tiotropium 2.5 microgram dose versus placebo. Analysis based on mixed effects model with repeated measures with fixed effects of treatment, visit, treatment-by-visit interaction, age group, baseline, baseline-by-visit interaction, and random effect of centre.	
Comparison groups	Placebo v Tiotropium Respimat 2.5 Micrograms
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0363
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	4.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	8.11

	Statistical Analysis 2
Statistical analysis description:	
Comparison of Tiotropium 5.0 microgram dose versus placebo. Analysis based on mixed effects model with repeated measures with fixed effects of treatment, visit, treatment−by−visit interaction,age group, baseline, baseline−by−visit interaction, and random effect of centre.	
Comparison groups	Placebo v Tiotropium Respimat 5 Micrograms
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0073
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	5.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	9.23

End point title	Change From Baseline in Residual Volume/Total Lung Capacity (RV/TLC) at the End of Week 12

End point description:

Change from baseline in static lung hyperinflation as measured by RV/TLC. Calculated as percent predicted at week 12 minus percent predicted at baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 12

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53[20]	54[21]	54[22]	
Units: Percentage change				
least squares mean (standard error)	-0.01 (± 0.03)	0 (± 0.03)	0.04 (± 0.03)	

Notes:

[20] - FAS - only patients with endpoint values at week 12 were analysed

[21] - FAS - only patients with endpoint values at week 12 were analysed

[22] - FAS - only patients with endpoint values at week 12 were analysed

	Statistical Analysis 1

Statistical analysis description:

Comparison of Tiotropium 2.5 microgram dose versus placebo. Analysis based on mixed effects model adjusted for baseline, center, visit and age group.

Comparison groups	Placebo v Tiotropium Respimat 2.5 Micrograms
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7414
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.08

	Statistical Analysis 2
Statistical analysis description:	
Comparison of Tiotropium 5.0 microgram dose versus placebo. Analysis based on mixed effects model adjusted for baseline, center, visit and age group.	
Comparison groups	Placebo v Tiotropium Respimat 5 Micrograms
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1418
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.12

End point title	Respiratory and Systemic Symptoms Questionnaire (RSSQ)
End point description:	
The RSSQ questionnaire is used to determine the presence or absence of an exacerbation during the recall period. This questionnaire consists of 12 symptoms and 3 physical findings. The definition of an exacerbation requires the patient to report at least 4 of 12 symptoms plus at least one of the following: findings on chest exam (e.g., crackles), greater than a 10% decrease in FEV1 or necessity of a chest x-ray.	
End point type	Secondary
End point timeframe:	
12 weeks	

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167[23]	166[24]	175[25]	
Units: Participants				
At least one pulmonary exacerbation	16	13	12	
No pulmonary exacerbation	151	153	163	

Notes:

[23] - FAS - only patients with endpoint values at week 12 were analysed

[24] - FAS - only patients with endpoint values at week 12 were analysed

[25] - FAS - only patients with endpoint values at week 12 were analysed

	Statistical Analysis 1
Statistical analysis description:	
Comparison of Tiotropium 2.5 microgram dose versus placebo. Treatment and age group were covariates for the logistic regression analysis.	

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	168[26]	166[27]	176[28]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Physical (N=99, 102, 105)	-2.5 (± 14.8)	0 (± 14.1)	-2.9 (± 11.4)	
Role (N=94, 100, 103)	0.7 (± 12)	-2.7 (± 12)	-2.1 (± 15.1)	
Vitality (N=99, 101, 105)	-2.3 (± 15)	-1.8 (± 16.4)	-3.3 (± 17.7)	
Emotion (N=99, 101, 105)	-1.1 (± 11.5)	-1.3 (± 13.5)	0.1 (± 12.1)	
Social (N=99, 101, 106)	-1.1 (± 12.3)	-1 (± 10.7)	-0.8 (± 11.1)	
Body (N=99,101, 106)	0.4 (± 18.4)	-0.9 (± 15.3)	1.7 (± 16.4)	
Eat (N=99,101,106)	1.5 (± 9.5)	0.2 (± 10.3)	0 (± 16.4)	
Treat (N=99, 101, 106)	0.9 (± 15.5)	-1.4 (± 14.1)	-1.7 (± 12.7)	
Health (N=99, 101, 106)	-1.9 (± 15.1)	-3.2 (± 18.3)	-0.6 (± 18.1)	
Weight (N=95, 101, 103)	1.4 (± 22.2)	-3.3 (± 28.9)	0 (± 26)	
Respirat (N=93, 101, 103)	-1.3 (± 14.8)	-3.7 (± 15.8)	-1.8 (± 14.3)	
Digest (N=93, 101, 103)	0.8 (± 14.9)	-1.3 (± 13.7)	0.3 (± 14.9)	

Notes:

[26] - FAS - only patients with endpoint values at week 12 were analysed

[27] - FAS - only patients with endpoint values at week 12 were analysed

[28] - FAS - only patients with endpoint values at week 12 were analysed

No statistical analyses for this end point

End point title	Change From Baseline in CFQ Scores - Adolescents Group

End point description:

The Cystic Fibrosis questionnaire (CFQ) is a disease-specific instrument that measures health-related quality of life (HRQOL) for adolescents (age 6-13) with CF. This validation questionnaire consists of 50 items on generic and disease-specific scales. The scores range from 0 to 100, with higher scores indicating better health.

End point type	Secondary

End point timeframe:

12 weeks

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	168[29]	166[30]	176[31]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Physical (N=46, 42, 54)	1.1 (± 18)	3.2 (± 14.8)	-1.9 (± 15)	
School (N=46, 42, 55)	1.1 (± 14.3)	-1.6 (± 10.9)	-1.1 (± 13.5)	
Body (N=46, 42, 55)	2.8 (± 13.9)	-0.3 (± 16.1)	-0.1 (± 15.7)	

School2 (N=46, 42, 55)	1.2 (± 18.8)	4.2 (± 19.2)	2.4 (± 20.9)	
Eat (N=46, 42, 55)	-1.4 (± 19.7)	-2.4 (± 17.3)	1.6 (± 22.8)	
Treat (N=46, 42, 55)	0.2 (± 16.5)	-1.9 (± 20.1)	5.7 (± 19.5)	
Respirat (N=46, 42, 55)	-1.4 (± 15.2)	1.2 (± 16.7)	-3 (± 20.2)	
Digest (N=46, 42, 55)	-5.1 (± 26.3)	2.4 (± 26.9)	-3 (± 35.3)	

Notes:

[29] - FAS - only patients with endpoint values at week 12 were analysed

[30] - FAS - only patients with endpoint values at week 12 were analysed

[31] - FAS - only patients with endpoint values at week 12 were analysed

No statistical analyses for this end point

End point title	Change From Baseline in CFQ Scores - Parent Questionnaire

End point description:

The Cystic Fibrosis questionnaire (CFQ) is a disease-specific instrument that measures health-related quality of life (HRQOL) for adolescents with CF - parent questionnaire. This validation questionnaire consists of 50 items on generic and disease-specific scales. The scores range from 0 to 100, with higher scores indicating better health.

End point type	Secondary

End point timeframe:

12 weeks

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	168[32]	166[33]	176[34]	
Units: Units on a scale				
arithmetic mean (standard deviation)				
Physical (N=46, 45, 53)	-0.1 (± 15.4)	4.9 (± 15.9)	0.2 (± 12.7)	
Emotion (N=46, 45, 52)	-0.3 (± 11.2)	0 (± 16)	-0.1 (± 15.7)	
Vitality (N=46, 44, 53)	-0.1 (± 12.3)	3.3 (± 13.1)	-1.5 (± 14.9)	
School (N=46, 45, 52)	-4.8 (± 19.5)	2.2 (± 26.3)	0.4 (± 17)	
Eat (N=46, 43, 49)	-2.2 (± 23.7)	-0.8 (± 21.2)	3.4 (± 15.9)	
Body (N=46, 45, 52)	-3.9 (± 18.6)	-1.7 (± 21.7)	-3.2 (± 22.6)	
Treat (N=46, 45, 52)	-2.4 (± 18.6)	2.5 (± 16.4)	-0.2 (± 21.4)	
Health (N=46, 45, 52)	-2.7 (± 21.4)	3.5 (± 23.1)	-3 (± 20.7)	
Respirat (N=45, 43, 50)	-2.8 (± 16.4)	-2.2 (± 18.8)	-6 (± 14.2)	
Digest (N=46, 43, 50)	-0.7 (± 15.6)	-1.8 (± 17)	1.1 (± 16.8)	
Weight (N=45, 45, 49)	-5.2 (± 35.5)	1.5 (± 30.1)	4.1 (± 31.6)	

Notes:

[32] - FAS - only patients with endpoint values at week 12 were analysed

[33] - FAS - only patients with endpoint values at week 12 were analysed

[34] - FAS - only patients with endpoint values at week 12 were analysed

No statistical analyses for this end point

End point title	Amount of Tiotropium Eliminated in Urine From 0 to 4 Hours at Steady State (Ae0-4,ss)[35]

End point description:

Ae0-4,ss represents the amount of tiotropium that is eliminated in urine from time 0 to 4 hours at steady state

End point type	Secondary

End point timeframe:

pre-dose, and 5 minutes (min), 20 min, 1 hour (h), and 2 h post-dose

Notes:

[35] - 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: In this case, the amount of tiotropium that is eliminated in urine from time 0 to 4 hours is analyzed and hence, only tiotropium arms have been included in the analysis.

	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[36]	99[37]		
Units: ng				
geometric mean (geometric coefficient of variation)	114 (± 73)	245 (± 67.5)		

Notes:

[36] - FAS - only patients with endpoint values at week 12 were analysed

[37] - FAS - only patients with endpoint values at week 12 were analysed

No statistical analyses for this end point

End point title	Maximum Measured Concentration at Steady State

End point description:

Cmax,ss represents the maximum measured concentration of tiotropium in plasma at steady state.

End point type	Secondary

End point timeframe:

pre-dose, and 5 minutes (min), 20 min, 1 hour (h), and 2 h post-dose

Notes:

[38] - 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: In this case, the maximum measured concentration of tiotropium in plasma is analyzed and hence, only tiotropium arms have been included in the analysis.

	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[39]	59[40]		
Units: pg/mL				
geometric mean (geometric coefficient of variation)	6.49 (± 58.5)	9.95 (± 66.6)		

Notes:

[39] - FAS - only patients with endpoint values at week 12 were analysed

[40] - FAS - only patients with endpoint values at week 12 were analysed

No statistical analyses for this end point

End point title	Time From Dosing to the Maximum Concentration (Tmax,ss)[41]

End point description:

Tmax,ss represents the time from dosing to the maximum concentration of tiotropium in plasma

End point type	Secondary

End point timeframe:

pre-dose, and 5 minutes (min), 20 min, 1 hour (h), and 2 h post-dose

Notes:

[41] - 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: In this case, the time from dosing to the maximum concentration of tiotropium in plasma is analyzed and hence, only tiotropium arms have been included in the analysis.

	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[42]	59[43]		
Units: hours				
median (full range (min-max))	0.083 (0.033 to 0.433)	0.083 (0.033 to 0.333)		

Notes:

[42] - FAS - only patients with endpoint values at week 12 were analysed

[43] - FAS - only patients with endpoint values at week 12 were analysed.

No statistical analyses for this end point

End point title	Clinical Relevant Abnormalities for Vital Signs and Laboratory Evaluation

End point description:

Clinical Relevant Abnormalities for Vital Signs and Laboratory evaluation. Any new or clinically relevant worsening of baseline conditions was reported as Adverse Event. This analysis was conducted on the treated set which includes all randomized patients who received at least one dose of treatment.

End point type	Secondary

End point timeframe:

From first drug administration until 30 days after last drug administration (up to 121 days)

	Placebo	Tiotropium Respimat 2.5 Micrograms	Tiotropium Respimat 5 Micrograms	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	168[44]	166[45]	176[46]	
Units: Participants				
Blood chloride decreased	0	0	1	
Blood glucose increased	1	1	0	
Blood pressure increased	2	1	0	
Blood sodium decreased	0	0	1	
Eosinophil count increased	0	1	0	
Hepatic enzyme increased	2	0	0	
Oxygen saturation decreased	0	0	1	
Vitamin K decreased	1	0	0	
White blood cell count increased	0	1	0	

Notes:

[44] - Participants in the treated set were included.

[45] - Participants in the treated set were included.

[46] - Participants in the treated set were included.

No statistical analyses for this end point

Timeframe for reporting adverse events:	
From the first drug administration until 30 days after the last drug administration up to 121 days.	
Assessment type	Systematic

Dictionary name	MedDRA
Dictionary version	13.0

Reporting group title	Placebo
Reporting group description:	
Patients randomised to receive matching placebo	
Reporting group title	Tio R 2.5
Reporting group description:	
Patients randomised to receive Tiotropium Respimat 2.5 micrograms once daily	
Reporting group title	Tio R 5.0
Reporting group description:	
Patients randomised to receive Tiotropium Respimat 5.0 micrograms once daily	

	Placebo	Tio R 2.5	Tio R 5.0
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 168 (12.50%)	28 / 166 (16.87%)	21 / 176 (11.93%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Antibiotic prophylaxis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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 disorders and administration site conditions			
Application site hypersensitivity			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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
Infusion related reaction			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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

Multi-organ failure			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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			
Acute respiratory failure			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Cough			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	1 / 176 (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
Hypoxia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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
Lung disorder			

subjects affected / exposed	0 / 168 (0.00%)	0 / 166 (0.00%)	3 / 176 (1.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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 disorder			
subjects affected / exposed	0 / 168 (0.00%)	2 / 166 (1.20%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sputum increased			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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
Investigations			
Pulmonary function test decreased			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Congenital, familial and genetic disorders			
Cystic fibrosis			
subjects affected / exposed	5 / 168 (2.98%)	8 / 166 (4.82%)	8 / 176 (4.55%)
occurrences causally related to treatment / all	0 / 5	1 / 9	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystic fibrosis lung			
subjects affected / exposed	7 / 168 (4.17%)	4 / 166 (2.41%)	4 / 176 (2.27%)
occurrences causally related to treatment / all	0 / 7	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Blood and lymphatic system disorders			
Aplastic anaemia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Gastrointestinal disorder			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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 obstruction			
subjects affected / exposed	0 / 168 (0.00%)	0 / 166 (0.00%)	1 / 176 (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
Nausea			
subjects affected / exposed	0 / 168 (0.00%)	0 / 166 (0.00%)	1 / 176 (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
Pancreatitis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pancreatitis acute			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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			
Cholelithiasis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Renal and urinary disorders			
Renal disorder			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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			
Bronchitis			
subjects affected / exposed	2 / 168 (1.19%)	2 / 166 (1.20%)	0 / 176 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 168 (0.60%)	1 / 166 (0.60%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Chronic sinusitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Lung infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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
Lung infection pseudomonal			
subjects affected / exposed	1 / 168 (0.60%)	1 / 166 (0.60%)	1 / 176 (0.57%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral herpes			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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
Overgrowth bacterial			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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

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subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	1 / 176 (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
Respiratory tract infection			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Sepsis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 166 (0.00%)	0 / 176 (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
Stenotrophomonas infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 166 (0.60%)	0 / 176 (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
Metabolism and nutrition disorders			
Hyperlipasaemia			
subjects affected / exposed	0 / 168 (0.00%)	0 / 166 (0.00%)	1 / 176 (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 %

	Placebo	Tio R 2.5	Tio R 5.0
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 168 (57.74%)	88 / 166 (53.01%)	110 / 176 (62.50%)
Congenital, familial and genetic disorders			
Cystic fibrosis			
subjects affected / exposed	12 / 168 (7.14%)	15 / 166 (9.04%)	19 / 176 (10.80%)
occurrences (all)	13	20	23
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 168 (10.71%)	7 / 166 (4.22%)	14 / 176 (7.95%)
occurrences (all)	20	13	19
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	17 / 168 (10.12%)	9 / 166 (5.42%)	18 / 176 (10.23%)
occurrences (all)	20	10	20
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 168 (5.95%)	13 / 166 (7.83%)	9 / 176 (5.11%)
occurrences (all)	11	14	11
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	34 / 168 (20.24%)	34 / 166 (20.48%)	46 / 176 (26.14%)
occurrences (all)	45	47	65
Dyspnoea			
subjects affected / exposed	9 / 168 (5.36%)	8 / 166 (4.82%)	6 / 176 (3.41%)
occurrences (all)	9	9	7
Haemoptysis			
subjects affected / exposed	7 / 168 (4.17%)	12 / 166 (7.23%)	11 / 176 (6.25%)
occurrences (all)	8	13	14
Nasal congestion			
subjects affected / exposed	4 / 168 (2.38%)	9 / 166 (5.42%)	10 / 176 (5.68%)
occurrences (all)	4	9	12
Oropharyngeal pain			
subjects affected / exposed	13 / 168 (7.74%)	5 / 166 (3.01%)	11 / 176 (6.25%)
occurrences (all)	14	5	12
Rhinorrhoea			
subjects affected / exposed	9 / 168 (5.36%)	6 / 166 (3.61%)	9 / 176 (5.11%)
occurrences (all)	10	8	9
Sputum increased			
subjects affected / exposed	8 / 168 (4.76%)	11 / 166 (6.63%)	13 / 176 (7.39%)
occurrences (all)	9	12	13
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 168 (5.36%)	5 / 166 (3.01%)	4 / 176 (2.27%)
occurrences (all)	12	5	4
Infections and infestations			

Bronchitis			
subjects affected / exposed	8 / 168 (4.76%)	4 / 166 (2.41%)	10 / 176 (5.68%)
occurrences (all)	10	5	13
Nasopharyngitis			
subjects affected / exposed	14 / 168 (8.33%)	11 / 166 (6.63%)	14 / 176 (7.95%)
occurrences (all)	15	12	16
Sinusitis			
subjects affected / exposed	6 / 168 (3.57%)	3 / 166 (1.81%)	9 / 176 (5.11%)
occurrences (all)	7	3	10
Upper respiratory tract infection			
subjects affected / exposed	6 / 168 (3.57%)	8 / 166 (4.82%)	11 / 176 (6.25%)
occurrences (all)	7	10	13

Were there any global substantial amendments to the protocol? Yes

11 August 2008	1.Added a second (co-primary) endpoint. 2.Implemented administration of age-specific CFQs. The change from baseline in CFQ at the end of Week 12 was added as a secondary endpoint. 3.Restricted the collection of blood for pharmacokinetic (PK) evaluation to two subpopulations, and specified the timing of sample collection by subpopulation. This was also added as a PK endpoint. 4.Clarified Exclusion Criterion 7 5.Specified the contents of each patient treatment box 6.Required a 12-h washout of LABAs on PFT testing days 7.Permitted the use of LABA/long-acting corticosteroid fixed dose combination products 8.Allowed rescheduling of Visit 6 to comply with the permitted on-treatment TOBI regimen 9.Added instructions for urine collection for the PK analyses
07 May 2009	1.Specified that PFTs and body plethysmography should be conducted within ±10 min of the specified time. 2.Implemented new Inclusion Criterion 5c:pre-bronchodilator FEV1 at Visit 2 must have been within 15% of the value at Visit 1 3.Added an optional pre-bronchodilator forced expiratory maneuver to document the degree of reversibility.

Notes:

Were there any global interruptions to the trial? No

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A "Missing" category is unavailable for the countrywise and age group breakdown of enrolled patients. Hence, 7 patients with a missing country have been added to "United States" and 7 patients with a missing age group to "Adults (18-64 years)".

Notes: