Clinical trial results:
A randomised, double-blind, placebo-controlled parallel-group trial to confirm the efficacy after 12 weeks and the safety of tiotropium 5 mcg administered once daily via the Respimat® device in patients with cystic fibrosis

Summary

EudraCT number	2010-019802-17
Trial protocol	PT HU FR SK DE GB BE CZ IT AT IE ES
Global end of trial date	07 March 2012

Results information

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

Trial information

Trial identification

Sponsor protocol code	205.438

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01179347
WHO universal trial number (UTN)	-

Notes:

Sponsors

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:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000035-PIP02-09
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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 March 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 March 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this confirmatory study was to investigate the efficacy (over 12 weeks) and long-term safety (over at least 6 months [24 weeks]) of tiotropium solution for inhalation (5 mcg) delivered by the Respimat® inhaler in comparison to placebo (i.e. on top of usual care) in patients with cystic fibrosis (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. Rescue medication was not provided because the study drug was administered on top of usual maintenance therapy.

Background therapy:

Patients maintained their background therapy , including inhaled corticosteroids (ICS) as long as the dose had been stabilised for at least 2 weeks prior to study start and remained stable for the first 12 weeks of the study.

Evidence for comparator: -

Actual start date of recruitment	29 September 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	14 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Czech Republic: 22
Country: Number of subjects enrolled	France: 79
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Italy: 19

Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Portugal: 16
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	Slovakia: 26
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Switzerland: 13
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	United States: 112
Worldwide total number of subjects	567
EEA total number of subjects	332

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)	2
Children (2-11 years)	186
Adolescents (12-17 years)	117
Adults (18-64 years)	259
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) 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

Period 1 title	Double-blind period (12 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching Placebo once daily (qd) delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis.

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 puffs once daily delivered by the Respimat® inhaler.

Arm title	Tio R5 qd

Arm description:

Tiotropium 5 mcg qd delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis.

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 puffs once daily for a total dose of 5 mcg delivered by the Respimat® inhaler.

Number of subjects in period 1[1]	Placebo	Tio R5 qd
Started	155	308
Completed	147	294
Not completed	8	14
Consent withdrawn by subject	1	2
Reason other than those stated above	2	4
Adverse event, non-fatal	2	6
Lost to follow-up	1	2
Protocol deviation	2	-

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.

Period 2

Period 2 title	Open-label period (12 to 60 weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Tiotropium 5 mcg qd delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis. All patients randomised to Placebo in period 1 switched to experimental treatment in period 2.

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 puffs once daily for a total dose of 5 mcg delivered by the Respimat® inhaler.

Arm title	Tio R5 qd

Arm description:

Tiotropium 5 mcg qd delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis. All patients randomised to Tiotropium in period 1 continue experimental treatment in period 2.

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 puffs once daily for a total dose of 5 mcg delivered by the Respimat® inhaler.

Number of subjects in period 2	Placebo	Tio R5 qd
Started	147	294
Completed	132	278
Not completed	15	16
Consent withdrawn by subject	1	1
Reason other than those stated above	7	4
Adverse event, non-fatal	5	9
Lost to follow-up	1	-
Protocol deviation	1	-
Lack of efficacy	-	2

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Matching Placebo once daily (qd) delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis.	
Reporting group title	Tio R5 qd
Reporting group description:	
Tiotropium 5 mcg qd delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis.	
Reporting group title	Placebo
Reporting group description:	
Tiotropium 5 mcg qd delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis. All patients randomised to Placebo in period 1 switched to experimental treatment in period 2.	
Reporting group title	Tio R5 qd
Reporting group description:	
Tiotropium 5 mcg qd delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis. All patients randomised to Tiotropium in period 1 continue experimental treatment in period 2.	

Primary: Forced expiratory volume in 1 second (FEV1) area under the curve 0-4 hours (AUC0-4h) response

End point title	Forced expiratory volume in 1 second (FEV1) area under the curve 0-4 hours (AUC0-4h) response
End point description:	
Mixed Model Repeated Measurement (MMRM) results. Response was defined as change from baseline in percent of predicted at the end of 12-week double-blind treatment period and is therefore expressed in percent of predicted. Means are adjusted for treatment, visit, treatment-by-visit interaction, age group (<= 11, >=12), baseline and baseline-by-visit interaction. FEV1 AUC0-4h was normalised for time and was calculated using the trapezoidal rule divided by the observation time (4 h). The full analysis set (FAS) was defined as all patients in the treated set who had at least 1 baseline pulmonary function test (PFT) measurement and at least 1 post-baseline on-treatment PFT measurement. No patients <5 years of age were included in the FAS.	
End point type	Primary
End point timeframe:	
30 minutes (min) before first dosing of study drug (defined as baseline), at 1 hour (h), 2 h , 3 h, and 4 h post dosing at day 1 and at 30 min before dosing, at 1 hour, 2 h , 3 h, and 4 h post dosing after 12 weeks.	

End point values	Placebo	Tio R5 qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146[1]	292[2]		
Units: Percent of predicted				
arithmetic mean (standard error)	0.87 (± 0.8)	2.51 (± 0.57)		

Notes:

[1] - Full Analysis Set (FAS) with imputation reduced to patients with observed wash-out compliance.

[2] - Full Analysis Set (FAS) with imputation reduced to patients with observed wash-out compliance.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hierarchical testing procedure was applied for both co-primary endpoints to maintain the overall alpha level. If and only if statistical superiority of the Tio R5 qd compared to Placebo in FEV1 AUC0-4h was demonstrated at the 1 sided alpha level of 0.025, confirmatory comparison in the second co-primary endpoint, at the same alpha level of 0.025 could be done .

Comparison groups	Placebo v Tio R5 qd
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.092 [4]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	3.55
Variability estimate	Standard error of the mean
Dispersion value	0.97

Notes:

[3] - Tio R5 qd minus Placebo

[4] - Two-sided p-value.

Primary: Trough (pre-dose) FEV1 response

End point title	Trough (pre-dose) FEV1 response

End point description:

MMRM results. Response was defined as change from baseline in percent of predicted at the end of 12-week double-blind treatment period and is therefore expressed in percent of predicted. Trough FEV1 was defined as the pre-dose FEV1 measured just prior to the administration of randomised treatment. Means are adjusted for treatment, visit, treatment-by-visit interaction, age group (<= 11, >=12), baseline and baseline-by-visit interaction.

End point type	Primary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo	Tio R5 qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144[5]	287[6]		
Units: Percent of predicted				
arithmetic mean (standard error)	0.72 (± 0.8)	2.12 (± 0.58)		

Notes:

[5] - Full Analysis Set (FAS) with imputation reduced to patients with observed wash-out compliance.

[6] - Full Analysis Set (FAS) with imputation reduced to patients with observed wash-out compliance.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Hierarchical testing for co-primary endpoints, confirmatory only if previous hypotheses had been successful.	
Comparison groups	Placebo v Tio R5 qd
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.15 [8]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	3.3
Variability estimate	Standard error of the mean
Dispersion value	0.97

Notes:

[7] - Tio R5 qd minus Placebo

[8] - Two-sided p-value.

Secondary: Forced vital capacity (FVC) area under the curve 0-4 hours (AUC0-4h) response

End point title	Forced vital capacity (FVC) area under the curve 0-4 hours (AUC0-4h) response
End point description:	
MMRM results. Response was defined as change from baseline in percent of predicted at the end of 12-week double-blind treatment period and is therefore expressed in percent of predicted. Means are adjusted for treatment, visit, treatment-by-visit interaction, age group (<= 11, >=12), baseline and baseline-by-visit interaction. FVC AUC0-4h was normalised for time and was calculated using the trapezoidal rule divided by the observation time (4 h).	
End point type	Secondary
End point timeframe:	
30 minutes (min) before first dosing of study drug (defined as baseline), at 1 hour (h), 2 h , 3 h, and 4 h post dosing at day 1 and at 30 min before dosing, at 1 hour, 2 h , 3 h, and 4 h post dosing after 12 weeks.	

End point values	Placebo	Tio R5 qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137[9]	282[10]		
Units: Percent of predicted				
arithmetic mean (standard error)	0.17 (± 0.75)	1.27 (± 0.53)		

Notes:

[9] - Full Analysis Set (FAS) with imputation reduced to patients with observed wash-out compliance.

[10] - Full Analysis Set (FAS) with imputation reduced to patients with observed wash-out compliance.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed effects model with repeated measures analysis for comparing Tiotropium 5 mcg versus placebo with fixed effects of treatment, visit, treatment-by-visit interaction, age group (≤11; ≥12), baseline, baseline-by-visit interaction.

Comparison groups	Placebo v Tio R5 qd
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.23 [12]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	2.86
Variability estimate	Standard error of the mean
Dispersion value	0.9

Notes:

[11] - Tio R5 qd minus Placebo

[12] - Two-sided p-value.

Secondary: Trough (pre-dose) FVC response

End point title	Trough (pre-dose) FVC response

End point description:

MMRM results. Response was defined as change from baseline in percent of predicted at the end of 12-week double-blind treatment period and is therefore expressed in percent of predicted. Trough FCV was defined as the pre-dose FVC measured just prior to the administration of randomised treatment. Means are adjusted for treatment, visit, treatment-by-visit interaction, age group (<= 11, >=12), baseline and baseline-by-visit interaction.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo	Tio R5 qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[13]	277[14]		
Units: Percent of predicted				
arithmetic mean (standard error)	0.3 (± 0.77)	1.51 (± 0.55)		

Notes:

[13] - Full Analysis Set (FAS) with imputation reduced to patients with observed wash-out compliance.

[14] - Full Analysis Set (FAS) with imputation reduced to patients with observed wash-out compliance.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed effects model with repeated measures analysis for comparing Tiotropium 5 mcg versus placebo with fixed effects of treatment, visit, treatment-by-visit interaction, age group (≤11; ≥12), baseline,

baseline-by-visit interaction.

Comparison groups	Placebo v Tio R5 qd
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.19 [16]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	3.02
Variability estimate	Standard error of the mean
Dispersion value	0.93

Notes:

[15] - Tio R5 qd minus Placebo

[16] - Two-sided p-value.

Secondary: Pre-bronchodilator Forced expiratory flow between 25 percent and 75 percent of the FVC (FEF25−75) response

End point title	Pre-bronchodilator Forced expiratory flow between 25 percent and 75 percent of the FVC (FEF25−75) response

End point description:

MMRM results. Response was defined as change from baseline in percent of predicted at the end of 12-week double-blind treatment period and is therefore expressed in percent of predicted. FEF25−75 is also known as maximum mid-expiratory flow and was measured before bronchodilator (salbutamol) use. Means are adjusted for treatment, visit, treatment-by-visit interaction, age group (<= 11, >=12), baseline and baseline-by-visit interaction.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo	Tio R5 qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[17]	277[18]		
Units: Percent of predicted				
arithmetic mean (standard error)	2.15 (± 1.48)	3.02 (± 1.05)		

Notes:

[17] - Full Analysis Set (FAS) with imputation reduced to patients with observed wash-out compliance.

[18] - Full Analysis Set (FAS) with imputation reduced to patients with observed wash-out compliance.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed effects model with repeated measures analysis for comparing Tiotrpium 5 mcg versus placebo with fixed effects of treatment, visit, treatment-by-visit interaction, age group (<=11; >=12), baseline, baseline-by-visit interaction.

Comparison groups	Placebo v Tio R5 qd

Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.62 [20]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.59
upper limit	4.32
Variability estimate	Standard error of the mean
Dispersion value	1.76

Notes:

[19] - Tio R5 qd minus Placebo.

[20] - Two-sided p-value.

Secondary: Percentage of participants with at least 1 pulmonary exacerbation during double-blind treatment

End point title	Percentage of participants with at least 1 pulmonary exacerbation during double-blind treatment

End point description:

Selected questions from the Respiratory and Systemic Symptoms Questionnaire (RSSQ), the investigator assessment of physical findings and pulmonary function, and the use of intravenous antibiotics as a concomitant therapy were used to determine if a cystic fibrosis-related pulmonary exacerbation had occurred.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Tio R5 qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[21]	214[22]		
Units: Percentage of Participants				
number (not applicable)	7.8	8.9		

Notes:

[21] - FAS reduced to patients having RSSQ information on day 29, 57 or 85.

[22] - FAS reduced to patients having RSSQ information on day 29, 57 or 85.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Logistic regression with treatment, age group, baseline weight and baseline FEV1 percent predicted as covariates was used for the analysis of the proportion of patients with at least 1 pulmonary exacerbation.

Comparison groups	Placebo v Tio R5 qd

Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.84 [24]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.453
upper limit	2.633

Notes:

[23] - Tio R5 qd versus Placebo.

[24] - Two-sided p-value.

Secondary: Change from Baseline in Revised Cystic Fibrosis Questionnaire (CFQ-R) Score

End point title	Change from Baseline in Revised Cystic Fibrosis Questionnaire (CFQ-R) Score

End point description:

Different format of CFQ-R are used depending of the patients' age. Adolescent and adult format of CFQ-R is used for patients of 14 years and older, for younger children a parent version and a children format is used. In case parent and children questionnaires were filled out, the children questionnaire is taken into account. Scores were calculated for each domain of the CFQ-R which are presented separately. A score of 100 corresponds to the highest quality of life possible, whereas a score of 0 corresponds to the lowest quality of life possible. Increasing score indicates better health.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo	Tio R5 qd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130[25]	255[26]		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Adolescents: Physical (N=83, N=162)	-0.85 (± 14.4)	-0.15 (± 12.95)		
Adolescents: Role (N=78, N=157)	0.85 (± 12.99)	-0.42 (± 13.3)		
Adolescents: Vitality (N=82, N=161)	-1.22 (± 18.06)	0.05 (± 14.08)		
Adolescents: Emotion (N=82, N=161)	-1.54 (± 12.05)	-0.99 (± 12.96)		
Adolescents: Social (N=82, N=159)	-1.69 (± 10.09)	0.7 (± 10.19)		
Adolescents: Body Image (N=82, N=159)	0.14 (± 16.14)	3.14 (± 15.11)		
Adolescents: Eating (N=82, N=161)	-1.49 (± 14.89)	1.38 (± 10.74)		
Adolescents: Treatment burden (N=82, N=160)	0.95 (± 14.73)	0.56 (± 14.84)		
Adolescents: Health perceptions (N=82, N=159)	-0.81 (± 13.83)	0.77 (± 16.68)		

Adolescents: Weight (N=80, N=160)	-2.08 (± 29.22)	3.75 (± 26.96)		
Adolescents: Respiratory (N=80, N=159)	0.97 (± 13.83)	-0.77 (± 15.19)		
Adolescents: Digestion (N=80, N=159)	-0.83 (± 17.03)	0.49 (± 12.4)		
Children: Physical (N=47, N=93)	-2.84 (± 15.67)	1.43 (± 15.19)		
Children: Social (N=46, N=93)	2.8 (± 15.73)	1.59 (± 15.7)		
Children: Body Image (N=46, N=93)	-1.21 (± 18.48)	4.66 (± 25.71)		
Children: Emotion (N=47, N=93)	-1.24 (± 12.83)	1.12 (± 12.18)		
Children: Eating (N=47, N=93)	2.84 (± 19.03)	0.72 (± 20.18)		
Children: Treatment burden (N=46, N=93)	0.72 (± 15.43)	-0.48 (± 19.1)		
Children: Respiratory (N=46, N=93)	-0.91 (± 15.34)	-1.61 (± 16.81)		
Children: Digestion (N=46, N=92)	2.17 (± 22.66)	-1.09 (± 29.84)		

Notes:

[25] - FAS reduced to patients having CFQ-R information at baseline and at week 12.

[26] - FAS reduced to patients having CFQ-R information at baseline and at week 12.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First administration of trial medication until 30 days after last administration of trial drug, for AE analyses over open-label period and over the study. Over the double-blind period, 30 days of wash-out is only used for premature discontinued patients.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Placebo Over the Double-Blind Period

Reporting group description:

Matching Placebo once daily (qd) delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis over the double-blind period (period 1).

Reporting group title	Tio 5mcg Over the Double-Blind Period

Reporting group description:

Tiotropium 5 mcg qd delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis over the double-blind period (period 1).

Reporting group title	Placebo Over the Open-Label Period

Reporting group description:

All placebo patients in period 1 switched to Tiotropium in the open-label period.
Tiotropium 5 mcg qd delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis over the study.

Reporting group title	Tio 5mcg Over the Study

Reporting group description:

Tiotropium 5 mcg qd delivered by the Respimat® inhaler as add-on therapy to usual care in patients with cystic fibrosis over the study.

Serious adverse events	Placebo Over the Double-Blind Period	Tio 5mcg Over the Double-Blind Period	Placebo Over the Open-Label Period
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 155 (8.39%)	36 / 308 (11.69%)	24 / 147 (16.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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
Surgical and medical procedures			
Antibiotic prophylaxis			

subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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
Central venous catheter removal			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Central venous catheterisation			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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
Device occlusion			
subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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
Pyrexia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypersensitivity			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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
Cough			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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
Dyspnoea			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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	2 / 155 (1.29%)	5 / 308 (1.62%)	2 / 147 (1.36%)
occurrences causally related to treatment / all	0 / 2	0 / 5	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to			

Pulmonary congestion			
subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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
Sleep apnoea syndrome			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sputum increased			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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			
Anxiety			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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
Investigations			
Bacterial test positive			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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 creatinine increased			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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
Forced expiratory volume decreased			
subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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

Oxygen saturation decreased			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary function test decreased			
subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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
Weight decreased			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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
Foot fracture			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus lesion			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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
Wrist fracture			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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

Congenital, familial and genetic disorders			
Cystic fibrosis			
subjects affected / exposed	2 / 155 (1.29%)	6 / 308 (1.95%)	7 / 147 (4.76%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystic fibrosis lung			
subjects affected / exposed	0 / 155 (0.00%)	2 / 308 (0.65%)	3 / 147 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystic fibrosis related diabetes			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
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			
Ventricular extrasystoles			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distal intestinal obstruction syndrome			
subjects affected / exposed	1 / 155 (0.65%)	2 / 308 (0.65%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			

subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth impacted			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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
Vomiting			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Urethral stenosis			
subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspergillosis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 155 (0.00%)	2 / 308 (0.65%)	3 / 147 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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
Bronchopulmonary aspergillosis allergic			

subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic sinusitis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	2 / 155 (1.29%)	4 / 308 (1.30%)	3 / 147 (2.04%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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 / 155 (0.65%)	1 / 308 (0.32%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 155 (0.00%)	5 / 308 (1.62%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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
Pseudomonas infection			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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
Sinusitis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 308 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stenotrophomonas infection			
subjects affected / exposed	0 / 155 (0.00%)	1 / 308 (0.32%)	0 / 147 (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
Viral infection			
subjects affected / exposed	1 / 155 (0.65%)	0 / 308 (0.00%)	0 / 147 (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

Serious adverse events	Tio 5mcg Over the Study		
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 308 (20.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Antibiotic prophylaxis			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Central venous catheter removal			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Central venous catheterisation			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	2 / 308 (0.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device occlusion			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 308 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	0 / 308 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Bronchospasm				
subjects affected / exposed	1 / 308 (0.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	4 / 308 (1.30%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 308 (0.65%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 308 (0.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	9 / 308 (2.92%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Lung infiltration				
subjects affected / exposed	0 / 308 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasal polyps				

subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Productive cough			
subjects affected / exposed	2 / 308 (0.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary congestion			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sputum increased			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Bacterial test positive			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			

subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Forced expiratory volume decreased			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oxygen saturation decreased			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary function test decreased			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Weight decreased			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Meniscus lesion			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radius fracture			

subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Cystic fibrosis			
subjects affected / exposed	11 / 308 (3.57%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Cystic fibrosis lung			
subjects affected / exposed	2 / 308 (0.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cystic fibrosis related diabetes			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Distal intestinal obstruction syndrome			
subjects affected / exposed	3 / 308 (0.97%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth impacted			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

subjects affected / exposed	2 / 308 (0.65%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis allergic				
subjects affected / exposed	0 / 308 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic sinusitis				
subjects affected / exposed	0 / 308 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infective pulmonary exacerbation of cystic fibrosis				
subjects affected / exposed	10 / 308 (3.25%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 0			
Lobar pneumonia				
subjects affected / exposed	1 / 308 (0.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 308 (0.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 308 (0.32%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lung infection pseudomonal				
subjects affected / exposed	1 / 308 (0.32%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				

subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	6 / 308 (1.95%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Pneumonia staphylococcal			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pseudomonas infection			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinusitis			
subjects affected / exposed	0 / 308 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stenotrophomonas infection			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 308 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo Over the Double-Blind Period	Tio 5mcg Over the Double-Blind Period	Placebo Over the Open-Label Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 155 (32.90%)	124 / 308 (40.26%)	72 / 147 (48.98%)
Congenital, familial and genetic disorders			
Cystic fibrosis			
subjects affected / exposed	4 / 155 (2.58%)	11 / 308 (3.57%)	7 / 147 (4.76%)
occurrences (all)	5	13	10
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 155 (3.23%)	11 / 308 (3.57%)	8 / 147 (5.44%)
occurrences (all)	7	13	12
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 155 (6.45%)	15 / 308 (4.87%)	13 / 147 (8.84%)
occurrences (all)	13	17	20
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 155 (3.23%)	11 / 308 (3.57%)	5 / 147 (3.40%)
occurrences (all)	5	13	5
Nausea			
subjects affected / exposed	1 / 155 (0.65%)	6 / 308 (1.95%)	8 / 147 (5.44%)
occurrences (all)	1	6	8
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 155 (12.90%)	55 / 308 (17.86%)	30 / 147 (20.41%)
occurrences (all)	21	69	43
Lung disorder			
subjects affected / exposed	5 / 155 (3.23%)	11 / 308 (3.57%)	8 / 147 (5.44%)
occurrences (all)	6	12	16
Oropharyngeal pain			
subjects affected / exposed	2 / 155 (1.29%)	6 / 308 (1.95%)	9 / 147 (6.12%)
occurrences (all)	2	6	9
Sputum increased			

subjects affected / exposed	5 / 155 (3.23%)	13 / 308 (4.22%)	6 / 147 (4.08%)
occurrences (all)	6	14	10
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 155 (2.58%)	12 / 308 (3.90%)	10 / 147 (6.80%)
occurrences (all)	4	16	14
Nasopharyngitis			
subjects affected / exposed	4 / 155 (2.58%)	14 / 308 (4.55%)	11 / 147 (7.48%)
occurrences (all)	4	14	14
Pharyngitis			
subjects affected / exposed	2 / 155 (1.29%)	4 / 308 (1.30%)	1 / 147 (0.68%)
occurrences (all)	2	4	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 155 (2.58%)	11 / 308 (3.57%)	7 / 147 (4.76%)
occurrences (all)	4	12	8

Non-serious adverse events	Tio 5mcg Over the Study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	194 / 308 (62.99%)		
Congenital, familial and genetic disorders			
Cystic fibrosis			
subjects affected / exposed	20 / 308 (6.49%)		
occurrences (all)	37		
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 308 (7.14%)		
occurrences (all)	27		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	28 / 308 (9.09%)		
occurrences (all)	35		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	19 / 308 (6.17%)		
occurrences (all)	27		
Nausea			

subjects affected / exposed	10 / 308 (3.25%)		
occurrences (all)	16		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	84 / 308 (27.27%)		
occurrences (all)	132		
Lung disorder			
subjects affected / exposed	24 / 308 (7.79%)		
occurrences (all)	32		
Oropharyngeal pain			
subjects affected / exposed	16 / 308 (5.19%)		
occurrences (all)	18		
Sputum increased			
subjects affected / exposed	24 / 308 (7.79%)		
occurrences (all)	36		
Infections and infestations			
Bronchitis			
subjects affected / exposed	26 / 308 (8.44%)		
occurrences (all)	42		
Nasopharyngitis			
subjects affected / exposed	25 / 308 (8.12%)		
occurrences (all)	32		
Pharyngitis			
subjects affected / exposed	18 / 308 (5.84%)		
occurrences (all)	19		
Upper respiratory tract infection			
subjects affected / exposed	24 / 308 (7.79%)		
occurrences (all)	27		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 November 2010	1. Introduction of a pre-dose urine sample at Visit 5. 2. Elimination of a physical examination at Visit 13. 3. The introduction of an interactive voice and web system instead of only an IVRS. 4. Changes made to clarify inconsistencies within the text and between text and flowcharts, or to provide further description and explanation for investigations.
25 November 2011	Added a new open-label tiotropium treatment period to allow for the assessment of ECGs

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported