Clinical trial results:
A phase II/III, randomised, double-blind, placebo-controlled, parallel group trial to evaluate safety and efficacy of tiotropium inhalation solution (2.5 µg and 5 µg) administered once daily in the afternoon via Respimat® Inhaler for 12 weeks in patients 1 to 5 years old with persistent asthma

Summary

EudraCT number	2011-005512-28
Trial protocol	NL LT LV FI DE BE
Global end of trial date	04 December 2014

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	06 June 2015

Trial information

Trial identification

Sponsor protocol code	205.443

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01634113
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, +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co.KG, +1 800 243 0127, 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	26 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 November 2014
Global end of trial reached?	Yes
Global end of trial date	04 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the safety and efficacy of two doses of tiotropium inhalation solution delivered via the Respimat® inhaler once daily in the afternoon in patients (1 to 5 years old) with persistent asthma on top of at least inhaled corticosteroid (ICS) treatment.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be randomised to trial treatment. 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. Salbutamol (albuterol) was provided as rescue medication for use as necessary during the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Latvia: 18
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Philippines: 4
Country: Number of subjects enrolled	Ukraine: 28
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	129
EEA total number of subjects	56

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)	23
Children (2-11 years)	106
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
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 to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Treatment period (overall period)
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 Respimat

Arm description:

Inhalation of placebo solution once daily for 12 weeks, delivered by the Respimat Inhaler.

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 actuations once daily in the afternoon. Dose not applicable.

Arm title	Tio R2.5

Arm description:

Inhalation of 2.5µg tiotropium bromide solution once daily for 12 weeks, delivered by the Respimat Inhaler.

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

Dosage and administration details:

2 actuations once daily in the afternoon, for a total dose of 2.5 µg.

Arm title	Tio R5

Arm description:

Inhalation of 5µg tiotropium bromide solution once daily for 12 weeks, delivered by the Respimat Inhaler.

One patient was randomised to the Tio R5 treatment arm, however this patient was not treated. Consequently, even though the actual number of subjects that started is 32, only 31 were reported to ensure consistent reporting with baseline characteristics which include only treated patients.

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

Dosage and administration details:

2 actuations once daily in the afternoon, for a total dose of 5 µg.

Number of subjects in period 1[1]	Placebo Respimat	Tio R2.5	Tio R5
Started	34	36	31
Completed	34	36	31

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 dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Respimat
Reporting group description:	
Inhalation of placebo solution once daily for 12 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R2.5
Reporting group description:	
Inhalation of 2.5µg tiotropium bromide solution once daily for 12 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R5
Reporting group description:	
Inhalation of 5µg tiotropium bromide solution once daily for 12 weeks, delivered by the Respimat Inhaler.	

One patient was randomised to the Tio R5 treatment arm, however this patient was not treated. Consequently, even though the actual number of subjects that started is 32, only 31 were reported to ensure consistent reporting with baseline characteristics which include only treated patients.

Reporting group values	Placebo Respimat	Tio R2.5	Tio R5
Number of subjects	34	36	31
Age categorical Units: Subjects			

Age Continuous			
Treated set (TS) which included all randomised patients who received at least one dose of trial medication represents the baseline analysis population.			
Units: years			
arithmetic mean	3.2	3.1	3.1
standard deviation	± 1.4	± 1.5	± 1.3
Gender, Male/Female Units: participants			
Female	13	17	10
Male	21	19	21

Reporting group values	Total		
Number of subjects	101		
Age categorical Units: Subjects			

Age Continuous			
Treated set (TS) which included all randomised patients who received at least one dose of trial medication represents the baseline analysis population.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: participants			
Female	40		
Male	61		

End points

End points reporting groups

Reporting group title	Placebo Respimat
Reporting group description:	
Inhalation of placebo solution once daily for 12 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R2.5
Reporting group description:	
Inhalation of 2.5µg tiotropium bromide solution once daily for 12 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R5
Reporting group description:	
Inhalation of 5µg tiotropium bromide solution once daily for 12 weeks, delivered by the Respimat Inhaler.	

One patient was randomised to the Tio R5 treatment arm, however this patient was not treated. Consequently, even though the actual number of subjects that started is 32, only 31 were reported to ensure consistent reporting with baseline characteristics which include only treated patients.

Primary: Weekly mean combined daytime asthma symptom score

End point title	Weekly mean combined daytime asthma symptom score

End point description:

Change from baseline in weekly mean combined daytime asthma symptom score as assessed by the Paediatric Asthma Caregivers Diary (PACD) in last week (wk) of 12 wk treatment period. Diary consists of 3 questions to be answered each morning and 7 questions to be answered each evening. A week was defined as 7 days. Combined daytime score is the average of scores from questions 4 – 7 which are questions regarding severity of cough, wheezing, trouble breathing and interference with activities, scores for each question range from 0 (best) to 5 (worst). The wk 12 weekly mean is mean of the responses for each day averaged over the 7 days in wk 12, so combined daytime asthma symptom scores also range from 0 (best) to 5 (worst). The measured values presented are adjusted means. Full analysis set (FAS) included all randomised patients who received at least one dose of trial medication. Missing data was imputed by available data from patient during that wk, but no imputation for wks with no data.

End point type	Primary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34[1]	36[2]	30[3]	
Units: units on a scale				
arithmetic mean (standard error)	-0.456 (± 0.084)	-0.535 (± 0.082)	-0.504 (± 0.089)	

Notes:

[1] - FAS including patients with available endpoint data at week 12

[2] - FAS including patients with available endpoint data at week 12

[3] - FAS including patients with available endpoint data at week 12

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of covariance (ANCOVA) was used. This ANCOVA model included the fixed, categorical effect of treatment as well as continuous fixed covariate of baseline.
Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.4963
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.312
upper limit	0.152
Variability estimate	Standard error of the mean
Dispersion value	0.117

Notes:

[4] - All treatment comparisons were exploratory, no formal hypothesis testing was performed.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of covariance (ANCOVA) was used. This ANCOVA model included the fixed, categorical effect of treatment as well as continuous fixed covariate of baseline.
Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.6936
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.292
upper limit	0.195
Variability estimate	Standard error of the mean
Dispersion value	0.123

Notes:

[5] - All treatment comparisons were exploratory, no formal hypothesis testing was performed.

Primary: FEV1 peak (0-3h) Change From Baseline

End point title	FEV1 peak (0-3h) Change From Baseline[6]

End point description:

Change from baseline in peak Forced expiratory volume in 1 second within the first 3 hours post dosing

(FEV1 peak (0-3h)) measured at week 12. Full analysis set (FAS) represents the analysed population. No imputation for missing data was employed.

End point type	Primary

End point timeframe:

10 minutes before drug administration and 30 minutes, 1 hour (h), 2h and 3h after drug administration at baseline and week 12

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal hypothesis testing was performed.

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[7]	7[8]	2[9]	
Units: Litres				
arithmetic mean (standard deviation)	0.158 (± 0.026)	0.13 (± 0.125)	0.145 (± 0.078)	

Notes:

[7] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[8] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[9] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly mean Overnight asthma symptom score response

End point title	Weekly mean Overnight asthma symptom score response

End point description:

Change from baseline in weekly mean overnight asthma symptom score response as assessed by PACD in the last wk of 12 wk treatment period. Overnight score is score from the following question in PACD, "How much did your child cough last night after your child was put to bed for night until he/she awoke this morning?".This endpoint was determined only for patients with 2 or more nights with symptoms per week during baseline period. In this case, the baseline period is 7 days used to derive baseline value. Patient has a night with symptoms if question was answered with scores 1, 2, 3, 4 or 5 or patient received β-Agonist at least one time since he/she went to bed. Week was defined as 7 days. Scores range from 0 (best) to 4 (worst), value of 5 indicates severity of symptoms is unknown. Measured values presented are adjusted means. FAS represents analysed population. Missing data in a wk was imputed by available data from patient during that wk, but no imputation for wks with no data.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31[10]	31[11]	28[12]	
Units: units on a scale				
arithmetic mean (standard error)	-0.671 (± 0.11)	-0.588 (± 0.111)	-0.655 (± 0.116)	

Notes:

[10] - FAS including patients with available endpoint data at week 12

[11] - FAS including patients with available endpoint data at week 12

[12] - FAS including patients with available endpoint data at week 12

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of covariance (ANCOVA) was used. This ANCOVA model included the fixed, categorical effect of treatment as well as continuous fixed covariate of baseline.
Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.5995
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.229
upper limit	0.394
Variability estimate	Standard error of the mean
Dispersion value	0.157

Notes:

[13] - All treatment comparisons were exploratory, no formal hypothesis testing was performed.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of covariance (ANCOVA) was used. This ANCOVA model included the fixed, categorical effect of treatment as well as continuous fixed covariate of baseline.
Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.9251
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.303
upper limit	0.333
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[14] - All treatment comparisons were exploratory, no formal hypothesis testing was performed.

Secondary: Weekly Percentage of days without asthma symptoms

End point title	Weekly Percentage of days without asthma symptoms

End point description:

Weekly Percentage of days without asthma symptoms at wk 12. A day without asthma symptoms was defined as a day during which the patient experienced no asthma symptoms, did not use rescue medication (salbutamol/albuterol) and had no asthma exacerbation/worsening requiring systemic corticosteroids, or unscheduled visits to a doctor's office, emergency department, or hospital. A week was defined as 7 days.

The measured values presented are adjusted means.

FAS represents analysed population. Missing data in a wk was imputed by available data from patient during that wk, but no imputation for wks with no data.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34[15]	36[16]	30[17]	
Units: percentage of days				
arithmetic mean (standard error)	53.151 (± 7.405)	55.401 (± 7.181)	50.654 (± 7.873)	

Notes:

[15] - FAS, including patients with available endpoint data at week 12

[16] - FAS, including patients with available endpoint data at week 12

[17] - FAS, including patients with available endpoint data at week 12

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of covariance (ANCOVA) was used. This ANCOVA model included the fixed, categorical effect of treatment as well as continuous fixed covariate of baseline.
Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.8279
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.243
upper limit	22.743

Variability estimate	Standard error of the mean
Dispersion value	10.324

Notes:

[18] - All treatment comparisons were exploratory, no formal hypothesis testing was performed.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of covariance (ANCOVA) was used. This ANCOVA model included the fixed, categorical effect of treatment as well as continuous fixed covariate of baseline.
Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.8181
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.497
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.987
upper limit	18.994
Variability estimate	Standard error of the mean
Dispersion value	10.826

Notes:

[19] - All treatment comparisons were exploratory, no formal hypothesis testing was performed.

Secondary: Weekly percentage of days with use of salbutamol (albuterol) rescue medication

End point title	Weekly percentage of days with use of salbutamol (albuterol) rescue medication

End point description:

Weekly percentage of days with use of salbutamol (albuterol) rescue medication at wk 12. A week was defined as 7 days.

FAS represents analysed population. Missing data in a wk was imputed by available data from patient during that wk, but no imputation for wks with no data.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34[20]	36[21]	30[22]	
Units: percentage of days				
arithmetic mean (standard deviation)	24.94 (± 36.8)	24.23 (± 36.86)	24.88 (± 38.45)	

Notes:

[20] - FAS, including patients with available endpoint data at week 12

[21] - FAS, including patients with available endpoint data at week 12

[22] - FAS, including patients with available endpoint data at week 12

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly mean nighttime awakenings due to asthma symptoms

End point title	Weekly mean nighttime awakenings due to asthma symptoms

End point description:

Change from baseline in the weekly mean nighttime awakenings due to asthma symptoms as assessed by the PACD, in the last wk of the 12 wk treatment period.
The weekly mean was calculated as the average of the weekly scores for the question "Did your child wake up during the night due to his/her asthma?" The question was answered on a 5-point verbal rating scale, with scores ranging from 1 (did not wake up) to 5 (was awake all night). A week was defined as 7 days.
The measured values presented are adjusted means.
FAS represents analysed population. Missing data in a wk was imputed by available data from patient during that wk, but no imputation for wks with no data.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34[23]	36[24]	31[25]	
Units: units on a scale				
arithmetic mean (standard error)	-0.318 (± 0.08)	-0.257 (± 0.078)	-0.392 (± 0.084)	

Notes:

[23] - FAS, including patients with available endpoint data at week 12

[24] - FAS, including patients with available endpoint data at week 12

[25] - FAS, including patients with available endpoint data at week 12

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of covariance (ANCOVA) was used. This ANCOVA model included the fixed, categorical effect of treatment as well as continuous fixed covariate of baseline.
Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	= 0.5869
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.161
upper limit	0.283
Variability estimate	Standard error of the mean
Dispersion value	0.112

Notes:

[26] - All treatment comparisons were exploratory, no formal hypothesis testing was performed.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis of covariance (ANCOVA) was used. This ANCOVA model included the fixed, categorical effect of treatment as well as continuous fixed covariate of baseline.
Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	= 0.523
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.305
upper limit	0.156
Variability estimate	Standard error of the mean
Dispersion value	0.116

Notes:

[27] - All treatment comparisons were exploratory, no formal hypothesis testing was performed.

Secondary: Trough FEV1 Change From Baseline

End point title	Trough FEV1 Change From Baseline

End point description:

Change from baseline in Trough (pre-dose) Forced expiratory volume in 1 second (FEV1) measured at week 12.
FAS represents the analysed population. No imputation for missing data was employed.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[28]	7[29]	2[30]	
Units: Litres				
arithmetic mean (standard deviation)	0.06 (± 0.032)	0.017 (± 0.108)	0.085 (± 0.163)	

Notes:

[28] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[29] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[30] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 AUC (0-3h) Change From Baseline

End point title	FEV1 AUC (0-3h) Change From Baseline

End point description:

Change from baseline of area under the curve (AUC) from 0 to 3 h for FEV1 (FEV1 AUC 0–3h) after 12 weeks of treatment. The AUC was calculated by using the trapezoidal rule divided by the observation time (3h).

FAS represents the analysed population. No imputation for missing data was employed.

End point type	Secondary

End point timeframe:

10 minutes before drug administration and 30 minutes, 1 hour (h), 2h and 3h after drug administration at baseline and week 12

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[31]	7[32]	2[33]	
Units: Litres				
arithmetic mean (standard deviation)	0.104 (± 0.043)	0.072 (± 0.114)	0.077 (± 0.116)	

Notes:

[31] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[32] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[33] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

Statistical analyses

No statistical analyses for this end point

Secondary: FVC peak (0-3h) Change From Baseline

End point title	FVC peak (0-3h) Change From Baseline

End point description:

Change from baseline in maximum forced vital capacity (FVC) measured within the first 3 hours after administration of trial medication (FVC peak (0–3h)) after 12 weeks of treatment. FAS represents the analysed population. No imputation for missing data was employed.

End point type	Secondary

End point timeframe:

10 minutes before drug administration and 30 minutes, 1 hour (h), 2h and 3h after drug administration at baseline and week 12

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[34]	7[35]	2[36]	
Units: Litres				
arithmetic mean (standard deviation)	0.21 (± 0.054)	0.136 (± 0.143)	0.06 (± 0.085)	

Notes:

[34] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[35] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[36] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

Statistical analyses

No statistical analyses for this end point

Secondary: Trough FVC Change From Baseline

End point title	Trough FVC Change From Baseline

End point description:

Change from baseline of trough (pre-dose) forced vital capacity (FVC) measured 10 min before the administration of trial medication after 12 weeks of treatment. FAS represents the analysed population. No imputation for missing data was employed.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[37]	7[38]	2[39]	
Units: Litres				
arithmetic mean (standard deviation)	0.155 (± 0.06)	-0.027 (± 0.133)	-0.05 (± 0.226)	

Notes:

[37] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[38] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[39] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

Statistical analyses

No statistical analyses for this end point

Secondary: FVC AUC (0-3h) Change From Baseline

End point title	FVC AUC (0-3h) Change From Baseline

End point description:

Change from baseline of area under the curve (AUC) from 0 to 3 h for FVC (FVC AUC0–3h) after 12 weeks of treatment. The AUC was calculated by using the trapezoidal rule divided by the observation time (3h).
FAS represents the analysed population. No imputation for missing data was employed.

End point type	Secondary

End point timeframe:

10 minutes before drug administration and 30 minutes, 1 hour (h), 2h and 3h after drug administration at baseline and week 12

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[40]	7[41]	2[42]	
Units: Litres				
arithmetic mean (standard deviation)	0.164 (± 0.037)	0.035 (± 0.105)	0.003 (± 0.13)	

Notes:

[40] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[41] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[42] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

Statistical analyses

No statistical analyses for this end point

Secondary: Individual FEV1 measurements

End point title	Individual FEV1 measurements

End point description:

Change from baseline in individual FEV1 measurements at each timepoint after 12 weeks.
FAS represents the analysed population. No imputation for missing data was employed.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[43]	7[44]	2[45]	
Units: Litres				
arithmetic mean (standard deviation)				
Time: 0 hours	0.06 (± 0.03)	0.02 (± 0.11)	0.09 (± 0.16)	
Time: 30 minutes	0.11 (± 0.09)	0.03 (± 0.13)	0.12 (± 0.11)	
Time: 1 hour	0.11 (± 0.08)	0.1 (± 0.13)	0.12 (± 0.04)	
Time: 2 hours	0.12 (± 0.05)	0.09 (± 0.13)	0.04 (± 0.16)	
Time: 3 hours	0.1 (± 0.05)	0.06 (± 0.13)	0.05 (± 0.11)	

Notes:

[43] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[44] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[45] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

Statistical analyses

No statistical analyses for this end point

Secondary: Individual FVC measurements

End point title	Individual FVC measurements

End point description:

Change from baseline in individual FVC measurements at each timepoint after 12 weeks.
FAS represents the analysed population. No imputation for missing data was employed.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4[46]	7[47]	2[48]	
Units: Litres				
arithmetic mean (standard deviation)				
Time: 0 hours	0.16 (± 0.06)	-0.03 (± 0.13)	-0.05 (± 0.23)	
Time: 30 minutes	0.13 (± 0.07)	0.04 (± 0.15)	0.06 (± 0.08)	
Time: 1 hour	0.18 (± 0.04)	0.06 (± 0.14)	0.05 (± 0.1)	
Time: 2 hours	0.16 (± 0.04)	0.02 (± 0.1)	-0.03 (± 0.16)	
Time: 3 hours	0.19 (± 0.07)	0.04 (± 0.13)	-0.03 (± 0.13)	

Notes:

[46] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[47] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

[48] - FAS including only 5 years old capable of providing technical acceptable pulmonary function tests

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first drug intake until 30 days after the last drug intake, up to 119 days.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Placebo Respimat
Reporting group description:	
Inhalation of placebo solution once daily for 12 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R2.5
Reporting group description:	
Inhalation of 2.5µg tiotropium bromide solution once daily for 12 weeks, delivered by the Respimat Inhaler	
Reporting group title	Tio R5
Reporting group description:	
Inhalation of 5µg tiotropium bromide solution once daily for 12 weeks, delivered by the Respimat Inhaler	

Serious adverse events	Placebo Respimat	Tio R2.5	Tio R5
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 34 (8.82%)	0 / 36 (0.00%)	0 / 31 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 31 (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
Bronchopneumonia			

subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 34 (2.94%)	0 / 36 (0.00%)	0 / 31 (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

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

Non-serious adverse events	Placebo Respimat	Tio R2.5	Tio R5
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 34 (70.59%)	19 / 36 (52.78%)	16 / 31 (51.61%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	1 / 31 (3.23%)
occurrences (all)	0	3	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 34 (17.65%)	3 / 36 (8.33%)	3 / 31 (9.68%)
occurrences (all)	11	3	5
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	2 / 34 (5.88%)	0 / 36 (0.00%)	1 / 31 (3.23%)
occurrences (all)	3	0	4
Mouth ulceration			
subjects affected / exposed	2 / 34 (5.88%)	0 / 36 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	3 / 34 (8.82%)	3 / 36 (8.33%)	1 / 31 (3.23%)
occurrences (all)	3	4	1
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	9 / 34 (26.47%)	5 / 36 (13.89%)	2 / 31 (6.45%)
occurrences (all)	12	6	3
Cough			
subjects affected / exposed	3 / 34 (8.82%)	4 / 36 (11.11%)	2 / 31 (6.45%)
occurrences (all)	4	4	2
Nasal congestion			
subjects affected / exposed	1 / 34 (2.94%)	3 / 36 (8.33%)	1 / 31 (3.23%)
occurrences (all)	1	3	1
Rhinitis allergic			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	3 / 34 (8.82%)	0 / 36 (0.00%)	3 / 31 (9.68%)
occurrences (all)	6	0	3
Wheezing			
subjects affected / exposed	0 / 34 (0.00%)	2 / 36 (5.56%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	1 / 31 (3.23%)
occurrences (all)	3	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 34 (11.76%)	1 / 36 (2.78%)	2 / 31 (6.45%)
occurrences (all)	6	1	2
Ear infection			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
Gastroenteritis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 36 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
Nasopharyngitis			
subjects affected / exposed	5 / 34 (14.71%)	7 / 36 (19.44%)	2 / 31 (6.45%)
occurrences (all)	8	9	5

Pharyngitis			
subjects affected / exposed	2 / 34 (5.88%)	0 / 36 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Pneumonia			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	0 / 31 (0.00%)
occurrences (all)	2	1	0
Respiratory tract infection viral			
subjects affected / exposed	4 / 34 (11.76%)	3 / 36 (8.33%)	3 / 31 (9.68%)
occurrences (all)	4	3	3
Rhinitis			
subjects affected / exposed	3 / 34 (8.82%)	2 / 36 (5.56%)	3 / 31 (9.68%)
occurrences (all)	3	2	8
Sinusitis			
subjects affected / exposed	2 / 34 (5.88%)	1 / 36 (2.78%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 34 (2.94%)	3 / 36 (8.33%)	5 / 31 (16.13%)
occurrences (all)	1	5	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2012	Impulse oscillometry (IOS) was added as an efficacy assessment for children aged 2-5 years (at Visit 1) who were able to perform technically acceptable IOS measurements and were not participating in the PFT or Rint measurements. The assessment was included as an alternative option to collect pulmonary function data in pre-schoolers for sites that did not have Rint equipment but experience in IOS and IOS equipment available. Furthermore, the information on prohibited and allowed medications during the trial was detailed and it was explicitly stated that randomised patients who withdrew prematurely were not replaced.
07 May 2013	When the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) agreed to the Paediatric Investigation Plan (PIP) for tiotropium in January 2013, they also requested the sponsor to recruit 30 patients aged 1 to 2 years. The inclusion of these patients was ensured by an adjustable screening cap per age group that was implemented in IVRS/IWRS. Furthermore, the amount of blood that was allowed to be collected for laboratory testing was amended to follow the respective guideline of the European Commission. To reduce the burden of daily completion of the PACD and additional diary card when the screening period was prolonged due to illness, this protocol amendment also implemented the option to temporarily interrupt filling of both forms.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported