Clinical trial results:
A randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution (2.5 mcg and 5 mcg) delivered via Respimat inhaler once daily in the evening over 12 weeks as add-on controller therapy on top of usual care in children (6 to 11 years old) with severe persistent asthma.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-001777-43
Trial protocol	LV LT DE BE CZ HU PL SK RO BG
Global end of trial date	18 May 2015

Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

Trial information

Trial identification

Sponsor protocol code	205.446

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01634152
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	173 Binger Strasse, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim , +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	10 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2015
Global end of trial reached?	Yes
Global end of trial date	18 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall purpose of the trial is to evaluate efficacy and safety of tiotropium inhalation solution (2.5 mcg and 5 mcg) delivered via Respimat inhaler once daily in the evening over 12 weeks, compared to placebo, as add-on controller therapy on top of usual care in children (6 to 11 years old) with severe persistent asthma. The primary objective of the trial is to demonstrate superiority of tiotropium (5 mcg and possibly 2.5 mcg once daily in the evening) over placebo with regard to the primary pulmonary function endpoint after 12 weeks of treatment. Secondary objectives are to evaluate efficacy of tiotropium with regard to other efficacy endpoints, and to evaluate the safety of tiotropium, compared to placebo, as add on controller therapy on top of usual care in this patient population.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 60
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Brazil: 28
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Czech Republic: 25
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Guatemala: 60
Country: Number of subjects enrolled	Hungary: 65
Country: Number of subjects enrolled	Latvia: 62
Country: Number of subjects enrolled	Lithuania: 34
Country: Number of subjects enrolled	Poland: 36

Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Russian Federation: 67
Country: Number of subjects enrolled	Slovakia: 10
Country: Number of subjects enrolled	Ukraine: 106
Country: Number of subjects enrolled	United States: 45
Worldwide total number of subjects	635
EEA total number of subjects	262

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	635
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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Respimat

Arm description:

Inhalation of placebo solution (2 puffs) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.

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 evening. Dose not applicable.

Arm title	Tio R2.5

Arm description:

Inhalation of 2.5mcg tiotropium (Tio R2.5) solution (2 puffs of 1.25mcg) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care. One patient was randomised to the Tio R2.5 arm, however this patient was not treated. Consequently, number of subject that started is 137 but only 136 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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 actuations once daily in the evening, for a total dose of 2.5 mcg.

Arm title	Tio R5

Arm description:

Inhalation of 5mcg tiotropium (Tio R5) solution (2 puffs of 2.5mcg) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.

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 actuations once daily in the evening, for a total dose of 5 mcg.

Number of subjects in period 1[1]	Placebo Respimat	Tio R2.5	Tio R5
Started	134	136	130
Completed	130	136	126
Not completed	4	0	4
Other reason not defined above	1	-	1
Adverse event, non-fatal	2	-	2
Consent withdrawn not due to AE	1	-	1

Notes:

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

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Respimat
Reporting group description:	
Inhalation of placebo solution (2 puffs) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.	
Reporting group title	Tio R2.5
Reporting group description:	
Inhalation of 2.5mcg tiotropium (Tio R2.5) solution (2 puffs of 1.25mcg) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care. One patient was randomised to the Tio R2.5 arm, however this patient was not treated. Consequently, number of subject that started is 137 but only 136 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.	
Reporting group title	Tio R5
Reporting group description:	
Inhalation of 5mcg tiotropium (Tio R5) solution (2 puffs of 2.5mcg) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.	

Reporting group values	Placebo Respimat	Tio R2.5	Tio R5
Number of subjects	134	136	130
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	9.1	8.8	9.2
standard deviation	± 1.6	± 1.7	± 1.6
Gender, Male/Female Units: Participants			
Female	41	40	40
Male	93	96	90

Reporting group values	Total		
Number of subjects	400		
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	121		
Male	279		

End points

End points reporting groups

Reporting group title	Placebo Respimat

Reporting group description:

Inhalation of placebo solution (2 puffs) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.

Reporting group title	Tio R2.5

Reporting group description:

Inhalation of 2.5mcg tiotropium (Tio R2.5) solution (2 puffs of 1.25mcg) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care. One patient was randomised to the Tio R2.5 arm, however this patient was not treated. Consequently, number of subject that started is 137 but only 136 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

Reporting group title	Tio R5

Reporting group description:

Inhalation of 5mcg tiotropium (Tio R5) solution (2 puffs of 2.5mcg) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.

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

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

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. Measured values presented are actually adjusted means.Full analysis set (FAS) was the same as the treated set which included all randomised patients who were dispensed and received at least one documented dose of trial medication. Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	130[1]	135[2]	128[3]	
Units: Litres				
arithmetic mean (standard error)	0.252 (± 0.025)	0.287 (± 0.025)	0.391 (± 0.026)	

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:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous

fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Tio R2.5 v Placebo Respimat
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.2724
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.099
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

[4] - Stepwise testing of the null hypothesis was used to test the efficacy of Tio R5 and then Tio R2.5, each over placebo. The analysis was performed in a stepwise manner, firstly for this endpoint, then Trough FEV1. Each step was only considered confirmatory if all previous steps were successful.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.075
upper limit	0.203
Variability estimate	Standard error of the mean
Dispersion value	0.033

Notes:

[5] - Stepwise testing of the null hypothesis was used to test the efficacy of Tio R5 and then Tio R2.5, each over placebo. The analysis was performed in a stepwise manner, firstly for this endpoint, then Trough FEV1. Each step was only considered confirmatory if all previous steps were successful.

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. Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	130[6]	135[7]	128[8]	
Units: Litres				
arithmetic mean (standard error)	0.136 (± 0.027)	0.154 (± 0.026)	0.223 (± 0.027)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.5898
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.048
upper limit	0.085
Variability estimate	Standard error of the mean
Dispersion value	0.034

Notes:

[9] - Stepwise testing of the null hypothesis was used to test the efficacy of Tio R5 and then Tio R2.5, each over placebo. The analysis for this endpoint was performed in a stepwise manner after the analysis of the primary endpoint was performed. Each step was only considered confirmatory if all previous steps were successful.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5

Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0117
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.154
Variability estimate	Standard error of the mean
Dispersion value	0.034

Notes:

[10] - Stepwise testing of the null hypothesis was used to test the efficacy of Tio R5 and then Tio R2.5, each over placebo. The analysis for this endpoint was performed in a stepwise manner after the analysis of the primary endpoint was performed. Each step was only considered confirmatory if all previous steps were successful.

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. The measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	130[11]	135[12]	128[13]	
Units: Litres				
arithmetic mean (standard error)	0.244 (± 0.028)	0.201 (± 0.027)	0.275 (± 0.028)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.2277
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.113
upper limit	0.027
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.3998
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.101
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

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

Secondary: Trough FVC Change From Baseline

End point title	Trough FVC Change From Baseline

End point description:

Change from baseline in Trough (pre-dose) FVC measured at week 12. Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	130[16]	135[17]	128[18]	
Units: Litres				
arithmetic mean (standard error)	0.141 (± 0.029)	0.094 (± 0.029)	0.15 (± 0.03)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo..

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.203
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.121
upper limit	0.026
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5

Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.8194
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.066
upper limit	0.083
Variability estimate	Standard error of the mean
Dispersion value	0.038

Notes:

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

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 hours 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). Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

End point type	Secondary

End point timeframe:

Baseline and 10 mins before drug administration and 30 mins, 1 hour (h), 2h, 3h after drug administration at 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	130[21]	135[22]	128[23]	
Units: Litres				
arithmetic mean (standard error)	0.175 (± 0.023)	0.206 (± 0.022)	0.301 (± 0.023)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.2907
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.088
Variability estimate	Standard error of the mean
Dispersion value	0.029

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.126
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.068
upper limit	0.184
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

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

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 hours for FVC (Forced vital capacity) (FVC AUC (0-3h)) after 12 weeks of treatment. The AUC was calculated by using the trapezoidal rule divided by the observation time (3h). Measured values presented are actually adjusted means. Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

End point type	Secondary

End point timeframe:

Baseline and 10 mins before drug administration and 30 mins, 1 hour (h), 2h, 3h after drug administration at 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	130[26]	135[27]	128[28]	
Units: Litres				
arithmetic mean (standard error)	0.145 (± 0.025)	0.105 (± 0.024)	0.182 (± 0.025)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	= 0.2008
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.103
upper limit	0.022
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Tio R5 v Placebo Respimat

Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.2545
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

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

Secondary: FEV1 change from baseline at each individual timepoint

End point title	FEV1 change from baseline at each individual timepoint

End point description:

Forced expiratory volume in one second (FEV1) change from baseline at each individual timepoint. The measured values presented are actually adjusted means.Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

End point type	Secondary

End point timeframe:

Baseline and 10 mins before drug administration and 30 mins, 1 hour (h), 2h, 3h after drug administration at 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	130[31]	135[32]	128[33]	
Units: Litres				
arithmetic mean (standard error)				
10 minutes pre-dose	0.136 (± 0.027)	0.154 (± 0.026)	0.223 (± 0.027)	
30 minutes post-dose	0.166 (± 0.024)	0.202 (± 0.023)	0.285 (± 0.024)	
1 hour post-dose	0.177 (± 0.025)	0.203 (± 0.024)	0.3 (± 0.025)	
2 hours post-dose	0.191 (± 0.025)	0.216 (± 0.025)	0.324 (± 0.026)	
3 hours post-dose	0.168 (± 0.026)	0.215 (± 0.026)	0.308 (± 0.026)	

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: FVC change from baseline at each individual timepoint

End point title	FVC change from baseline at each individual timepoint

End point description:

FVC change from baseline at each individual timepoint. The measured values presented are actually adjusted means.Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

End point type	Secondary

End point timeframe:

Baseline and 10 mins before drug administration and 30 mins, 1 hour (h), 2h, 3h after drug administration at 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	130[34]	135[35]	128[36]	
Units: Litres				
arithmetic mean (standard error)				
10 minutes pre-dose	0.141 (± 0.029)	0.094 (± 0.029)	0.15 (± 0.03)	
30 minutes post-dose	0.13 (± 0.026)	0.096 (± 0.026)	0.164 (± 0.027)	
1 hour post-dose	0.146 (± 0.027)	0.097 (± 0.026)	0.181 (± 0.027)	
2 hours post-dose	0.159 (± 0.028)	0.113 (± 0.027)	0.199 (± 0.028)	
3 hours post-dose	0.132 (± 0.028)	0.11 (± 0.028)	0.176 (± 0.029)	

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Control of Asthma as Assessed by ACQ-IA Total Score

End point title	Control of Asthma as Assessed by ACQ-IA Total Score

End point description:

Change from baseline in Interviewer-Administered Asthma Control Questionnaire (ACQ-IA) total score measured at week 12. The ACQ-IA is a scale containing 7 questions. Each question has a 7 point scale which ranges from 0 to 6. A score of 0 corresponds to no impairment and a score of 6 corresponds to maximum impairment. ACQ-IA total score is calculated as the mean of the responses to all 7 questions. The measured values presented are actually adjusted means.Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	130[37]	136[38]	126[39]	
Units: Units on a scale				
arithmetic mean (standard error)	1.026 (± 0.06)	1.046 (± 0.059)	0.948 (± 0.061)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	= 0.798
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.133
upper limit	0.173
Variability estimate	Standard error of the mean
Dispersion value	0.078

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	= 0.3166
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.233
upper limit	0.076
Variability estimate	Standard error of the mean
Dispersion value	0.079

Notes:

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

Secondary: ACQ-IA Total Score Responders

End point title	ACQ-IA Total Score Responders

End point description:

Responder categories based on the ACQ-IA total score after 12 weeks of treatment. Analysis was performed using the following categories and definitions: responder (change from trial baseline ≤-0.5), no change (-0.5 <change from trial baseline <0.5) and worsening (change from trial baseline ≥0.5) No statistical testing was performed for ACQ-IA total score responders. The ACQ-IA is a scale containing 7 questions, each question has a 7-point scale which ranges from 0 to 6; a score of 0 corresponds to no impairment and a score of 6 corresponds to maximum impairment.
Missing data for patients not withdrawn from the study were either categorised as no change or based on available data, withdrawn patients were imputed based upon discontinuation reason.

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	134[42]	136[43]	130[44]	
Units: Percentage of participants				
number (not applicable)				
Responder	76.9	79.4	80.8	
No change	20.9	18.4	16.2	
Worsening	2.2	2.2	3.1	

Notes:

[42] - FAS

[43] - FAS

[44] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Use of PRN Rescue Medication per Day

End point title	Use of PRN Rescue Medication per Day

End point description:

Change from baseline in the number of puffs of rescue medication (salbutamol/albuterol) used per day (24 hour period) based on the weekly mean at week 12. The measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	128[45]	136[46]	127[47]	
Units: Number of puffs of rescue medication				
arithmetic mean (standard error)	-0.57 (± 0.096)	-0.553 (± 0.094)	-0.66 (± 0.097)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other[48]
P-value	= 0.8916
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.227
upper limit	0.261
Variability estimate	Standard error of the mean
Dispersion value	0.124

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	= 0.4789
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.336
upper limit	0.158
Variability estimate	Standard error of the mean
Dispersion value	0.126

Notes:

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

Secondary: Use of PRN Rescue Medication During the Daytime

End point title	Use of PRN Rescue Medication During the Daytime

End point description:

Change from baseline in the number of puffs of rescue medication (salbutamol/albuterol) used during the daytime based on the weekly mean at week 12. Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	127[50]	136[51]	126[52]	
Units: Number of puffs of rescue medication				
arithmetic mean (standard error)	-0.279 (± 0.057)	-0.294 (± 0.055)	-0.365 (± 0.057)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.8361
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.129
Variability estimate	Standard error of the mean
Dispersion value	0.074

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other[54]
P-value	= 0.2461
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.233
upper limit	0.06

Variability estimate	Standard error of the mean
Dispersion value	0.075

Notes:

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

Secondary: Use of PRN Rescue Medication During the Night-time

End point title	Use of PRN Rescue Medication During the Night-time

End point description:

Change from baseline in the number of puffs of rescue medication (salbutamol/albuterol) used during the night-time based on the weekly mean at week 12. Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	128[55]	136[56]	126[57]	
Units: Number of puffs of rescue medication				
arithmetic mean (standard error)	-0.285 (± 0.051)	-0.25 (± 0.05)	-0.31 (± 0.052)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other[58]
P-value	= 0.6029
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.035

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.096
upper limit	0.165
Variability estimate	Standard error of the mean
Dispersion value	0.067

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	= 0.7034
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.158
upper limit	0.107
Variability estimate	Standard error of the mean
Dispersion value	0.067

Notes:

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

Secondary: Peak expiratory flow (PEF) a.m. change from baseline

End point title	Peak expiratory flow (PEF) a.m. change from baseline

End point description:

Change from baseline in the morning (a.m.) peak expiratory flow based on the weekly mean at week 12. Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	128[60]	136[61]	126[62]	
Units: L/min				
arithmetic mean (standard error)	8.343 (± 3.613)	13.119 (± 3.5)	13.086 (± 3.63)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	= 0.3083
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4.776
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.419
upper limit	13.97
Variability estimate	Standard error of the mean
Dispersion value	4.686

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[64]
P-value	= 0.3179
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4.743

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.571
upper limit	14.057
Variability estimate	Standard error of the mean
Dispersion value	4.747

Notes:

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

Secondary: Peak expiratory flow (PEF) p.m. change from baseline

End point title	Peak expiratory flow (PEF) p.m. change from baseline

End point description:

Change from baseline in the evening (p.m.) peak expiratory flow based on the weekly mean at week 12. Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	127[65]	136[66]	126[67]	
Units: L/min				
arithmetic mean (standard error)	7.892 (± 3.717)	8.459 (± 3.599)	3.785 (± 3.731)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	other[68]
P-value	= 0.9061
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.567

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.866
upper limit	10.001
Variability estimate	Standard error of the mean
Dispersion value	4.807

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	= 0.399
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.107
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.658
upper limit	5.444
Variability estimate	Standard error of the mean
Dispersion value	4.867

Notes:

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

Secondary: Peak expiratory flow (PEF) variability change from baseline

End point title	Peak expiratory flow (PEF) variability change from baseline

End point description:

Change from baseline in the peak expiratory flow variability based on the weekly mean at week 12.
Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	127[70]	136[71]	125[72]	
Units: Percentage of PEF				
arithmetic mean (standard error)	0.15 (± 0.777)	-0.8 (± 0.749)	-0.352 (± 0.78)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	other[73]
P-value	= 0.3542
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.959
upper limit	1.06
Variability estimate	Standard error of the mean
Dispersion value	1.025

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	other[74]
P-value	= 0.6298
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.502

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.545
upper limit	1.541
Variability estimate	Standard error of the mean
Dispersion value	1.042

Notes:

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

Secondary: FEV1 a.m. change from baseline

End point title	FEV1 a.m. change from baseline

End point description:

Change from baseline in morning (a.m.) FEV1 based on the weekly mean at week 12. Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	128[75]	136[76]	126[77]	
Units: Litres				
arithmetic mean (standard error)	0.174 (± 0.03)	0.142 (± 0.029)	0.125 (± 0.03)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other[78]
P-value	= 0.4066
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.032

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.107
upper limit	0.043
Variability estimate	Standard error of the mean
Dispersion value	0.038

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[79]
P-value	= 0.2032
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.125
upper limit	0.027
Variability estimate	Standard error of the mean
Dispersion value	0.039

Notes:

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

Secondary: FEV1 p.m. change from baseline

End point title	FEV1 p.m. change from baseline

End point description:

Change from baseline in evening (p.m.) FEV1 based on the weekly mean at week 12. Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	127[80]	136[81]	126[82]	
Units: Litres				
arithmetic mean (standard error)	0.155 (± 0.031)	0.104 (± 0.03)	0.094 (± 0.032)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	other[83]
P-value	= 0.2064
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.131
upper limit	0.028
Variability estimate	Standard error of the mean
Dispersion value	0.041

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other[84]
P-value	= 0.141
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.061

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.142
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.041

Notes:

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

Secondary: Change from baseline in nighttime awakenings

End point title	Change from baseline in nighttime awakenings

End point description:

Change from baseline in nighttime awakenings based on the weekly mean at week 12. Nighttime awakenings was assessed by the question "Did you wake up during the night due to your asthma?" from the e-diary. Scores range from 1 (did not wake up) to 5 (was awake all night). Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	128[85]	136[86]	126[87]	
Units: Units on a scale				
arithmetic mean (standard error)	-0.165 (± 0.032)	-0.166 (± 0.031)	-0.159 (± 0.033)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other[88]
P-value	= 0.9869
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.083
upper limit	0.082
Variability estimate	Standard error of the mean
Dispersion value	0.042

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[89]
P-value	= 0.873
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.077
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.043

Notes:

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

Secondary: Change from baseline in morning asthma symptoms

End point title	Change from baseline in morning asthma symptoms

End point description:

Change from baseline in morning asthma symptoms based on the weekly mean at week 12. Morning asthma symptoms was assessed by the question "how were your asthma symptoms this morning?" from the e-diary. Scores range from 1 (no asthma symptoms) to 5 (very severe asthma symptoms).
Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	128[90]	136[91]	126[92]	
Units: Units on a scale				
arithmetic mean (standard error)	-0.207 (± 0.038)	-0.213 (± 0.037)	-0.221 (± 0.038)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other[93]
P-value	= 0.9043
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.103
upper limit	0.091
Variability estimate	Standard error of the mean
Dispersion value	0.049

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	other[94]
P-value	= 0.7708
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.112
upper limit	0.083
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

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

Secondary: Change from baseline in daytime asthma symptoms

End point title	Change from baseline in daytime asthma symptoms

End point description:

Change from baseline in daytime asthma symptoms based on the weekly mean at week 12. Daytime asthma symptoms was assessed by the question "how were your asthma symptoms during the day?" from the e-diary. Scores range from 1 (no asthma symptoms) to 5 (very severe asthma symptoms). Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	127[95]	136[96]	126[97]	
Units: Units on a scale				
arithmetic mean (standard error)	-0.226 (± 0.04)	-0.262 (± 0.039)	-0.239 (± 0.041)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	other[98]
P-value	= 0.4864
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.139
upper limit	0.066
Variability estimate	Standard error of the mean
Dispersion value	0.052

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other[99]
P-value	= 0.7991
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.117
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.053

Notes:

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

Secondary: Change from baseline in daytime activity limitations

End point title	Change from baseline in daytime activity limitations

End point description:

Change from baseline in daytime activity limitations based on the weekly mean at week 12. Daytime activity limitations was assessed by the question "how limited were you in your activities today because of your asthma?" from the e-diary. Scores range from 1 (not limited) to 5 (totally limited). Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	127[100]	136[101]	126[102]	
Units: Units on a scale				
arithmetic mean (standard error)	-0.21 (± 0.039)	-0.203 (± 0.038)	-0.222 (± 0.039)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	other[103]
P-value	= 0.8884
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.092
upper limit	0.106
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

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

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other[104]
P-value	= 0.8115
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.112
upper limit	0.088
Variability estimate	Standard error of the mean
Dispersion value	0.051

Notes:

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

Secondary: Change from baseline in daytime experiences of shortness of breath

End point title	Change from baseline in daytime experiences of shortness of breath

End point description:

Change from baseline in daytime experiences of shortness of breath based on the weekly mean at week 12. Daytime experiences of shortness of breath was assessed by the question "how much shortness of breath did you experience during the day" from the e-diary. Scores range from 1 (none) to 5 (a very great deal). Measured values presented are actually adjusted means. Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	127[105]	136[106]	126[107]	
Units: Units on a scale				
arithmetic mean (standard error)	-0.204 (± 0.039)	-0.187 (± 0.038)	-0.287 (± 0.04)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5

Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	other[108]
P-value	= 0.7498
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.084
upper limit	0.117
Variability estimate	Standard error of the mean
Dispersion value	0.051

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other[109]
P-value	= 0.1108
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.185
upper limit	0.019
Variability estimate	Standard error of the mean
Dispersion value	0.052

Notes:

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

Secondary: Change from baseline in daytime experiences of wheeze or cough

End point title	Change from baseline in daytime experiences of wheeze or cough

End point description:

Change from baseline in daytime experiences of wheeze or cough based on the weekly mean at week 12. Daytime experiences of wheeze or cough was assessed by the question "did you experience wheeze or cough during the day?" from the e-diary. Scores range from 1 (not at all) to 5 (all the time).
Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	127[110]	136[111]	126[112]	
Units: Units on a scale				
arithmetic mean (standard error)	-0.249 (± 0.045)	-0.263 (± 0.044)	-0.32 (± 0.046)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	other[113]
P-value	= 0.8055
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.131
upper limit	0.102
Variability estimate	Standard error of the mean
Dispersion value	0.059

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5

Number of subjects included in analysis	253
Analysis specification	Pre-specified
Analysis type	other[114]
P-value	= 0.236
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.189
upper limit	0.047
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

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

Secondary: Change from baseline in asthma symptom-free days

End point title	Change from baseline in asthma symptom-free days

End point description:

Change from baseline in asthma symptom-free days based on the weekly mean at week 12. A day was considered as an asthma symptom-free day if there were no symptoms reported via the e-Diary and no use of rescue medication reported via the eDiary during that day. Measured values presented are actually adjusted means.
Missing data at a visit was imputed by the available data from the patient at that visit. Completely missing data were handled by the statistical model.

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	128[115]	136[116]	127[117]	
Units: Days				
arithmetic mean (standard error)	0.147 (± 0.031)	0.13 (± 0.03)	0.172 (± 0.031)	

Notes:

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

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

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

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	other[118]
P-value	= 0.6748
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.097
upper limit	0.063
Variability estimate	Standard error of the mean
Dispersion value	0.041

Notes:

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

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Repeated measures restricted maximum likelihood model was used. The model included the fixed, categorical effects of treatment, country, visit and treatment-by-visit interaction, as well the continuous fixed covariates of baseline and baseline-by-visit interaction. Patient was included as random effect. Difference calculated as Tio R5 minus placebo.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	other[119]
P-value	= 0.5497
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.056
upper limit	0.105
Variability estimate	Standard error of the mean
Dispersion value	0.041

Notes:

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug intake until 30 days after last drug intake, up to 164 days

Adverse event reporting additional description:

The final study visit was postponed if the status of the patient could affect the primary endpoint, for example, in cases of asthma exacerbations, therefore patients could remain on treatment for longer than the planned 12 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo Respimat

Reporting group description:

Inhalation of placebo solution (2 puffs) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.

Reporting group title	Tio R2.5

Reporting group description:

Inhalation of 2.5mcg tiotropium solution (2 puffs of 1.25mcg) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.

Reporting group title	Tio R5

Reporting group description:

Inhalation of 5mcg tiotropium solution (2 puffs of 2.5mcg) once daily for 12 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.

Serious adverse events	Placebo Respimat	Tio R2.5	Tio R5
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 134 (1.49%)	2 / 136 (1.47%)	4 / 130 (3.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 134 (0.00%)	1 / 136 (0.74%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 134 (0.75%)	1 / 136 (0.74%)	3 / 130 (2.31%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Asthmatic crisis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 136 (0.00%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 134 (0.00%)	0 / 136 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo Respimat	Tio R2.5	Tio R5
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 134 (36.57%)	36 / 136 (26.47%)	35 / 130 (26.92%)
Investigations			
Peak expiratory flow rate decreased			
subjects affected / exposed	20 / 134 (14.93%)	15 / 136 (11.03%)	15 / 130 (11.54%)
occurrences (all)	32	23	29
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	29 / 134 (21.64%)	20 / 136 (14.71%)	22 / 130 (16.92%)
occurrences (all)	47	29	29
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 134 (8.21%)	6 / 136 (4.41%)	6 / 130 (4.62%)
occurrences (all)	12	6	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2013	This amendment introduced changes to clarify wording and trial procedures, to replace the name and contact information of the former CI with the name and contact information of the new CI, and to correct minor typographical errors and inconsistencies and update the information and risk assessment for tiotropium based on newly available data. Some clarification in regard to inclusion and exclusion criteria was introduced. The amendment also clarified the process to administer information to the patient and collect assent from the patient in case the patient him/herself was not able to read or sign him/herself.
12 February 2015	The second protocol amendment introduced changes to update the affiliation and contact information of the CI, to correct minor typographical errors and inconsistencies, and to include updated information on tiotropium based on newly available data. The CTP was also updated with definitions and procedures used by the sponsor for AEs, SAEs, AESI, and reporting of such events. To be in line with other clinical trials of the same development program, the endpoint 'FEF25-75 response determined at the end of the 12-week treatment period' was amended to 'individual FEF25-75 response at each time point and visit during the 12-week treatment period'. The following further endpoints were added for the same reason: FEV1 peak0-3h expressed as percentage of patient's predicted FEV1 after 12 weeks of treatment, trough FEV1 expressed as percentage of patient's predicted FEV1 after 12 weeks of treatment, time to first symptomatic asthma exacerbation during the 12-week treatment period, ACQ-IA6 and ACQ-IA6 responder. The description of the safety analyses was amended to remove frequency tables with the number and percentage of patients with marked changes in vital signs recorded in conjunction with spirometry at any time during the trial and at each time point separately by treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported