Clinical trial results:
A randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution (2.5 g and 5 g) delivered via Respimat® inhaler once daily in the evening over 48 weeks in children (6 to 11 years old) with moderate persistent asthma

Summary

EudraCT number	2011-001758-26
Trial protocol	LV LT PT DE BG SE HU GB
Global end of trial date	08 December 2015

Results information

Result version number	v1 (current)
This version publication date	19 June 2016
First version publication date	19 June 2016

Trial information

Trial identification

Sponsor protocol code	205.445

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01634139
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?	
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	05 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 June 2015
Global end of trial reached?	Yes
Global end of trial date	08 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall purpose of the trial was to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (2.5 µg and 5 µg once daily in the evening) over 48 weeks, compared to placebo, in children (6 to 11 years old) with moderate persistent asthma. The primary objective of the trial was to demonstrate superiority of tiotropium (5 µg and possibly 2.5 µg once daily in the evening) over placebo with regard to the primary pulmonary function endpoint after 24 weeks of treatment. Secondary objectives were to evaluate efficacy of tiotropium with regard to other efficacy endpoints after 24 and 48 week of treatment, and to evaluate the long-term safety of tiotropium of a 48 week treatment, 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	03 August 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	Bulgaria: 31
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Guatemala: 81
Country: Number of subjects enrolled	Hungary: 52
Country: Number of subjects enrolled	Korea, Republic of: 27
Country: Number of subjects enrolled	Latvia: 94
Country: Number of subjects enrolled	Lithuania: 13
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Portugal: 24
Country: Number of subjects enrolled	Romania: 12
Country: Number of subjects enrolled	Russian Federation: 74
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Ukraine: 123
Country: Number of subjects enrolled	United Kingdom: 6

Country: Number of subjects enrolled	United States: 47
Worldwide total number of subjects	615
EEA total number of subjects	258

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)	614
Adolescents (12-17 years)	1
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 48 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.

One patient was randomised to the Placebo arm, however this patient was not treated. Consequently, number of subject that started is 132 but only 131 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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 48 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 136 but only 135 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 48 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	131	135	135
Completed	122	130	130
Not completed	9	5	5
Consent withdrawn not due to AE	4	3	2
Non compliant with protocol	1	-	-
Other reason not defined above	4	-	3
Lost to follow-up	-	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one 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 48 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.

One patient was randomised to the Placebo arm, however this patient was not treated. Consequently, number of subject that started is 132 but only 131 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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 48 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 136 but only 135 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 48 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	131	135	135
Age categorical Units: Subjects			

Age Continuous			
Treated set (TS) which included all randomised patients who were dispensed study medication and were documented to have taken at least 1 dose of investigational treatment.			
Units: Years			
arithmetic mean	9	9	8.9
standard deviation	± 1.6	± 1.6	± 1.7
Gender, Male/Female Units: Participants			
Female	46	38	53
Male	85	97	82

Reporting group values	Total		
Number of subjects	401		
Age categorical Units: Subjects			

Age Continuous			
Treated set (TS) which included all randomised patients who were dispensed study medication and were documented to have taken at least 1 dose of investigational treatment.			
Units: Years			
arithmetic mean			
standard deviation	-		

Gender, Male/Female Units: Participants			
Female	137		
Male	264		

End points

End points reporting groups

Reporting group title	Placebo Respimat

Reporting group description:

Inhalation of placebo solution (2 puffs) once daily for 48 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.

One patient was randomised to the Placebo arm, however this patient was not treated. Consequently, number of subject that started is 132 but only 131 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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 48 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 136 but only 135 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 48 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 (FEV) in 1 second within the first 3 hours (h) post dosing (FEV1 peak(0-3h)) measured at week 24.
Measured values presented are actually adjusted means.
The number of participants analysed displays the number of participants with available data at the timepoint of interest.
Full Analysis Set (FAS) was equal to treated set which included all randomised patients who received at least 1 documented dose of study
medication. Missing data at a visit was imputed by 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 24 Weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126[1]	131[2]	134[3]	
Units: Litres (L)				
arithmetic mean (standard error)	0.225 (± 0.027)	0.395 (± 0.026)	0.389 (± 0.026)	

Notes:

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

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

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

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	257
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.108
upper limit	0.231
Variability estimate	Standard error of the mean
Dispersion value	0.031

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.
[5] - The actual number of subjects analyzed is 266, the automatically calculated number that is provided in the statistical analysis (257) reflects only patients with value at week 24, rather than all patients that were included in the analysis.

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	260
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001 [7]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.164
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.103

upper limit	0.255
Variability estimate	Standard error of the mean
Dispersion value	0.031

Notes:

[6] - 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.

[7] - The actual number of subjects analyzed is 266, the automatically calculated number that is provided in the statistical analysis (260) reflects only patients with value at week 24, rather than all patients that were included in the analysis.

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 (FEV) in 1 second (FEV1) measured at week 24 and 48.

Measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[8]	135[9]	135[10]	
Units: Litres (L)				
arithmetic mean (standard error)				
Week 24 (N=126, 131, 134)	0.156 (± 0.031)	0.272 (± 0.03)	0.274 (± 0.03)	
Week 48 (N=124, 130, 130)	0.266 (± 0.032)	0.337 (± 0.03)	0.365 (± 0.031)	

Notes:

[8] - FAS

[9] - FAS

[10] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified

Analysis type	superiority[11]
P-value	= 0.0012
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.186
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[11] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.048
upper limit	0.188
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[12] - 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 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority

P-value	= 0.0477
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.142
Variability estimate	Standard error of the mean
Dispersion value	0.036

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0059
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.036

Secondary: FEV1 Peak (0-3h) at Week 48 Change From Baseline

End point title	FEV1 Peak (0-3h) at Week 48 Change From Baseline

End point description:

Change from baseline in peak forced expiratory volume (FEV) in 1 second within the first 3 hours (h) post dosing (FEV1 peak(0-3h)) measured at week 48.

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 48 Weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124[13]	130[14]	130[15]	
Units: Litres (L)				
arithmetic mean (standard error)	0.351 (± 0.027)	0.474 (± 0.026)	0.477 (± 0.026)	

Notes:

[13] - FAS including patients with available endpoint data at week 48

[14] - FAS including patients with available endpoint data at week 48

[15] - FAS including patients with available endpoint data at week 48

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	254
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	< 0.0001 [17]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.062
upper limit	0.185
Variability estimate	Standard error of the mean
Dispersion value	0.031

Notes:

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

[17] - The actual number of subjects analyzed is 266, the automatically calculated number that is provided in the statistical analysis (254) reflects only patients with value at week 48, rather than all patients that were included in the analysis.

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[18]
P-value	< 0.0001 [19]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.127

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.065
upper limit	0.188
Variability estimate	Standard error of the mean
Dispersion value	0.031

Notes:

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

[19] - The actual number of subjects analyzed is 266, the automatically calculated number that is provided in the statistical analysis (254) reflects only patients with value at week 48, rather than all patients that were included in the analysis.

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 24 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 week 24.

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126[20]	131[21]	134[22]	
Units: Litres (L)				
arithmetic mean (standard error)	0.152 (± 0.026)	0.306 (± 0.025)	0.309 (± 0.025)	

Notes:

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

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

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

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	257
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	< 0.0001 [24]
Method	Mixed models analysis

Parameter estimate	Mean difference (net)
Point estimate	0.154
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.095
upper limit	0.212
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

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

[24] - The actual number of subjects analyzed is 266, the automatically calculated number that is provided in the statistical analysis (257) reflects only patients with value at week 24, rather than all patients that were included in the analysis.

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	260
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	< 0.0001 [26]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.157
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.098
upper limit	0.215
Variability estimate	Standard error of the mean
Dispersion value	0.03

Notes:

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

[26] - The actual number of subjects analyzed is 266, the automatically calculated number that is provided in the statistical analysis (260) reflects only patients with value at week 24, rather than all patients that were included in the analysis.

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 24 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

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126[27]	131[28]	134[29]	
Units: Litres (L)				
arithmetic mean (standard error)	0.13 (± 0.03)	0.235 (± 0.029)	0.207 (± 0.029)	

Notes:

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

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

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

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	257
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.0023 [31]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.172
Variability estimate	Standard error of the mean
Dispersion value	0.034

Notes:

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

[31] - The actual number of subjects analyzed is 266, the automatically calculated number that is provided in the statistical analysis (257) reflects only patients with value at week 24, rather than all patients that were included in the analysis.

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	260
Analysis specification	Pre-specified

Analysis type	other[32]
P-value	= 0.0255 [33]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.143
Variability estimate	Standard error of the mean
Dispersion value	0.034

Notes:

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

[33] - The actual number of subjects analyzed is 266, the automatically calculated number that is provided in the statistical analysis (260) reflects only patients with value at week 24, rather than all patients that were included in the analysis.

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 24 and 48.

Measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[34]	135[35]	135[36]	
Units: Litres (L)				
arithmetic mean (standard error)				
Week 24 (N=126, 131, 134)	0.154 (± 0.035)	0.246 (± 0.034)	0.206 (± 0.034)	
Week 48 (N=124, 130, 130)	0.28 (± 0.035)	0.341 (± 0.034)	0.333 (± 0.034)	

Notes:

[34] - FAS

[35] - FAS

[36] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.0228
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	0.171
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

[37] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[38]
P-value	= 0.198
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.131
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.1256
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.141
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	= 0.188
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.133
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

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

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 24 and 48 Weeks of treatment.

Measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[41]	135[42]	135[43]	
Units: Litres (L)				
arithmetic mean (standard error)				
Week 24 (N=124, 130, 134)	0.215 (± 0.033)	0.325 (± 0.032)	0.307 (± 0.032)	
Week 48 (N=124, 130, 130)	0.361 (± 0.033)	0.43 (± 0.032)	0.413 (± 0.032)	

Notes:

[41] - FAS

[42] - FAS

[43] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[44]
P-value	= 0.0036
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.036
upper limit	0.184
Variability estimate	Standard error of the mean
Dispersion value	0.038

Notes:

[44] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0.0152
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.165
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	= 0.0687
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.143
Variability estimate	Standard error of the mean
Dispersion value	0.038

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0.1666
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.022
upper limit	0.126
Variability estimate	Standard error of the mean
Dispersion value	0.038

Notes:

[47] - 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:

FEV1 change from baseline to week 24 at each individual timepoint.

The measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 24 weeks

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[48]	135[49]	135[50]	
Units: Litres (L)				
arithmetic mean (standard error)				
10 minutes pre-dose (Week 24) (N=126, 131, 134)	0.156 (± 0.031)	0.272 (± 0.03)	0.274 (± 0.03)	
30 minutes post-dose (Week 24) (N=126, 131, 134)	0.156 (± 0.027)	0.295 (± 0.026)	0.307 (± 0.027)	
1 hour post-dose (Week 24) (N=126, 131, 134)	0.165 (± 0.028)	0.313 (± 0.027)	0.312 (± 0.027)	
2 hours post-dose (Week 24) (N=126, 131, 134)	0.144 (± 0.028)	0.307 (± 0.027)	0.312 (± 0.027)	
3 hours post-dose (Week 24) (N=126, 131, 134)	0.147 (± 0.027)	0.325 (± 0.026)	0.322 (± 0.026)	

Notes:
[48] - FAS
[49] - FAS
[50] - FAS

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 at 10 minutes pre-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	= 0.0012
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.186
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:
[51] - 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 at 10 minutes pre-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[52]
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.048
upper limit	0.188
Variability estimate	Standard error of the mean

Dispersion value	0.036

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 30 minutes post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.076
upper limit	0.201
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 30 minutes post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[54]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.088
upper limit	0.213
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

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

Statistical analysis title	Statistical Analysis 5

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 1 hour post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.148
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.084
upper limit	0.211
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

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

Statistical analysis title	Statistical Analysis 6

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 1 hour post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.084
upper limit	0.21
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

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

Statistical analysis title	Statistical Analysis 7

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 2 hours post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.101
upper limit	0.226
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

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

Statistical analysis title	Statistical Analysis 8

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 2 hours post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[58]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.168
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.106
upper limit	0.231
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

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

Statistical analysis title	Statistical Analysis 9

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 3 hours post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266

Analysis specification	Pre-specified
Analysis type	other[59]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.178
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.116
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

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

Statistical analysis title	Statistical Analysis 10

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 3 hours post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[60]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.176
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.114
upper limit	0.238
Variability estimate	Standard error of the mean
Dispersion value	0.032

Notes:

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

Secondary: FVC change from baseline to week 24 at each individual timepoint

End point title	FVC change from baseline to week 24 at each individual timepoint

End point description:

FVC change from baseline to week 24 at each individual timepoint.

The measured values presented are actually adjusted means

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[61]	135[62]	135[63]	
Units: Litres (L)				
arithmetic mean (standard error)				
10 minues pre-dose (Week 24) (N=124, 131, 134)	0.154 (± 0.035)	0.246 (± 0.034)	0.206 (± 0.034)	
30 minutes post-dose (Week 24) (N=124, 131, 13	0.144 (± 0.032)	0.222 (± 0.031)	0.211 (± 0.031)	
1 hour post-dose (Week 24) (N=124, 131, 134)	0.142 (± 0.032)	0.252 (± 0.031)	0.202 (± 0.031)	
2 hours post-dose (Week 24) (N=124, 131, 134)	0.117 (± 0.033)	0.23 (± 0.031)	0.21 (± 0.032)	
3 hours post-dose (Week 24) (N=124, 131, 134)	0.118 (± 0.033)	0.233 (± 0.032)	0.21 (± 0.032)	

Notes:

[61] - FAS

[62] - FAS

[63] - FAS

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 at 10 minues pre-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[64]
P-value	= 0.0228
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	0.171
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

[64] - 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 at 10 minutes pre-dose Week 24

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[65]
P-value	= 0.198
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.027
upper limit	0.131
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 30 minutes post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[66]
P-value	= 0.0344
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 30 minutes post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[67]
P-value	= 0.0696
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.139
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

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

Statistical analysis title	Statistical Analysis 5

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 1 hour post-dose (week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[68]
P-value	= 0.0032
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.182
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

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

Statistical analysis title	Statistical Analysis 6

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 1 hour post-dose (week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	= 0.1044
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.132
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

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

Statistical analysis title	Statistical Analysis 7

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 2 hours post-dose (week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[70]
P-value	= 0.0027
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.186
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

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

Statistical analysis title	Statistical Analysis 8

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 2 hours post-dose (week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266

Analysis specification	Pre-specified
Analysis type	other[71]
P-value	= 0.013
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.166
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

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

Statistical analysis title	Statistical Analysis 9

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 3 hours post-dose (week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[72]
P-value	= 0.0025
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.041
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.038

Notes:

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

Statistical analysis title	Statistical Analysis 10

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 3 hours post-dose (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[73]
P-value	= 0.0156
Method	Mixed models analysis

Parameter estimate	Mean difference (net)
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.166
Variability estimate	Standard error of the mean
Dispersion value	0.038

Notes:

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

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 rescue medication (salbutamol/albuterol) used per day (24 hour period) based on the weekly mean at weeks 24 and 48.

The measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[74]	135[75]	135[76]	
Units: Number of puffs of rescue medication				
arithmetic mean (standard error)				
Week 24 (N=122, 130, 133)	-0.437 (± 0.079)	-0.603 (± 0.077)	0.646 (± 0.077)	
Week 48 (N=120, 123, 127)	-0.484 (± 0.079)	0.638 (± 0.078)	0.685 (± 0.078)	

Notes:

[74] - FAS

[75] - FAS

[76] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[77]
P-value	= 0.1349
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.165
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.382
upper limit	0.051
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

[77] - 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 (week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[78]
P-value	= 0.0588
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.425
upper limit	0.008
Variability estimate	Standard error of the mean
Dispersion value	0.11

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified

Analysis type	other[79]
P-value	= 0.1675
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.154
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.372
upper limit	0.065
Variability estimate	Standard error of the mean
Dispersion value	0.111

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[80]
P-value	= 0.0709
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.201
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.419
upper limit	0.017
Variability estimate	Standard error of the mean
Dispersion value	0.111

Notes:

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

Secondary: Use of PRN Rescue Medication during daytime

End point title	Use of PRN Rescue Medication during daytime

End point description:

Change from baseline in the number of puffs of rescue medication (salbutamol/albuterol) used during daytime based on the weekly mean at weeks 24 and 48.

Measured values presented are actually adjusted means

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[81]	135[82]	135[83]	
Units: Number of puffs of rescue medication				
arithmetic mean (standard error)				
Week 24 (N=121, 130, 133)	-0.234 (± 0.055)	-0.35 (± 0.053)	-0.375 (± 0.053)	
Week 48 (N=119, 123, 125)	-0.247 (± 0.055)	-0.372 (± 0.053)	-0.378 (± 0.053)	

Notes:

[81] - FAS

[82] - FAS

[83] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[84]
P-value	= 0.0749
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.245
upper limit	0.012
Variability estimate	Standard error of the mean
Dispersion value	0.065

Notes:

[84] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[85]
P-value	= 0.0305
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.141
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.269
upper limit	-0.013
Variability estimate	Standard error of the mean
Dispersion value	0.065

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[86]
P-value	= 0.0581
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.255
upper limit	0.004
Variability estimate	Standard error of the mean
Dispersion value	0.066

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[87]
P-value	= 0.0464

Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.002
Variability estimate	Standard error of the mean
Dispersion value	0.066

Notes:

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

Secondary: Use of PRN Rescue Medication during nighttime

End point title	Use of PRN Rescue Medication during nighttime

End point description:

Change from baseline in the number of puffs of rescue medication (salbutamol/albuterol) used during nighttime based on the weekly mean at weeks 24 and 48.

Measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[88]	135[89]	135[90]	
Units: Number of puffs of rescue medication				
arithmetic mean (standard error)				
Week 24 (N=122, 130, 130)	-0.178 (± 0.051)	-0.274 (± 0.05)	-0.304 (± 0.05)	
Week 48 (N=119, 122, 125)	-0.198 (± 0.052)	-0.298 (± 0.05)	-0.301 (± 0.05)	

Notes:

[88] - FAS

[89] - FAS

[90] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[91]
P-value	= 0.1182
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.217
upper limit	0.025
Variability estimate	Standard error of the mean
Dispersion value	0.062

Notes:

[91] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[92]
P-value	= 0.0404
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.126
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.246
upper limit	-0.006
Variability estimate	Standard error of the mean
Dispersion value	0.061

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266

Analysis specification	Pre-specified
Analysis type	other[93]
P-value	= 0.1105
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.221
upper limit	0.023
Variability estimate	Standard error of the mean
Dispersion value	0.062

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[94]
P-value	= 0.0983
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.224
upper limit	0.019
Variability estimate	Standard error of the mean
Dispersion value	0.062

Notes:

[94] - 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 weeks 24 and 48.

Measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[95]	135[96]	135[97]	
Units: Litres per min (L/min)				
arithmetic mean (standard error)				
Week 24 (N=122, 130, 130)	14.153 (± 4.556)	22.66 (± 4.406)	21.646 (± 4.434)	
Week 48 (N=119, 122, 125)	20.824 (± 4.581)	26.362 (± 4.44)	29.598 (± 4.466)	

Notes:

[95] - FAS

[96] - FAS

[97] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[98]
P-value	= 0.1146
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	8.507
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.063
upper limit	19.077
Variability estimate	Standard error of the mean
Dispersion value	5.387

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[99]
P-value	= 0.1628
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	7.493
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.034
upper limit	18.02
Variability estimate	Standard error of the mean
Dispersion value	5.365

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[100]
P-value	= 0.3085
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	5.538
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.127
upper limit	16.203
Variability estimate	Standard error of the mean
Dispersion value	5.435

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[101]

P-value	= 0.1053
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	8.774
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.847
upper limit	19.394
Variability estimate	Standard error of the mean
Dispersion value	5.413

Notes:

[101] - 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 weeks 24 and 48.

Measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[102]	135[103]	135[104]	
Units: Litres per min (L/min)				
arithmetic mean (standard error)				
Week 24 (N= 121, 130, 133)	3.179 (± 4.597)	15.539 (± 4.444)	17.325 (± 4.464)	
Week 48 (N=119, 123, 125)	17.1 (± 4.622)	15.219 (± 4.475)	21.276 (± 4.504)	

Notes:

[102] - FAS

[103] - FAS

[104] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[105]
P-value	= 0.0236
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	12.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.663
upper limit	23.056
Variability estimate	Standard error of the mean
Dispersion value	5.451

Notes:

[105] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[106]
P-value	= 0.0093
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	14.146
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.497
upper limit	24.794
Variability estimate	Standard error of the mean
Dispersion value	5.427

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266

Analysis specification	Pre-specified
Analysis type	other[107]
P-value	= 0.7322
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.882
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.667
upper limit	8.904
Variability estimate	Standard error of the mean
Dispersion value	5.497

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[108]
P-value	= 0.4463
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4.176
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.578
upper limit	14.929
Variability estimate	Standard error of the mean
Dispersion value	5.481

Notes:

[108] - 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 24 and 48.

Measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N’s for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[109]	135[110]	135[111]	
Units: Percentage of PEF				
arithmetic mean (standard error)				
Week 24 (N=121, 129, 128)	-1.204 (± 0.826)	-0.942 (± 0.798)	-1.038 (± 0.803)	
Week 48 (N=117, 120, 121)	-0.32 (± 0.835)	-0.048 (± 0.814)	-0.899 (± 0.818)	

Notes:

[109] - FAS

[110] - FAS

[111] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[112]
P-value	= 0.8008
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.262
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.775
upper limit	2.299
Variability estimate	Standard error of the mean
Dispersion value	1.039

Notes:

[112] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[113]
P-value	= 0.8731
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.875
upper limit	2.208
Variability estimate	Standard error of the mean
Dispersion value	1.041

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[114]
P-value	= 0.7975
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.272
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.803
upper limit	2.346
Variability estimate	Standard error of the mean
Dispersion value	1.058

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[115]

P-value	= 0.5845
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.579
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.656
upper limit	1.498
Variability estimate	Standard error of the mean
Dispersion value	1.059

Notes:

[115] - 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 24 and 48.

Measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[116]	135[117]	135[118]	
Units: Litres (L)				
arithmetic mean (standard error)				
Week 24 (N=121, 129, 128)	0.167 (± 0.042)	0.142 (± 0.041)	0.092 (± 0.041)	
Week 48 (N=119, 123, 125)	0.202 (± 0.042)	0.208 (± 0.041)	0.159 (± 0.041)	

Notes:

[116] - FAS

[117] - FAS

[118] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[119]
P-value	= 0.6166
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.122
upper limit	0.073
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[119] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[120]
P-value	= 0.1267
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.173
upper limit	0.021
Variability estimate	Standard error of the mean
Dispersion value	0.049

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified

Analysis type	other[121]
P-value	= 0.9
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.092
upper limit	0.105
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[122]
P-value	= 0.3897
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.141
upper limit	0.055
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

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

Secondary: ACQ−IA total score

End point title	ACQ−IA total score

End point description:

Interviewer Administered Asthma Control Questionnaire (ACQ-IA) total score change after 24 and 48 weeks of treatment.
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.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

End point type	Secondary

End point timeframe:

Week 24 and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[123]	135[124]	135[125]	
Units: Units on a Scale				
arithmetic mean (standard error)				
Week 24 (N=126, 131, 134)	1.017 (± 0.062)	0.897 (± 0.06)	0.835 (± 0.06)	
Week 48 (N=124, 130, 130)	0.817 (± 0.062)	0.752 (± 0.06)	0.723 (± 0.061)	

Notes:

[123] - FAS

[124] - FAS

[125] - FAS

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 (Week 24)

Comparison groups	Tio R2.5 v Placebo Respimat
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[126]
P-value	= 0.0975
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.262
upper limit	0.022
Variability estimate	Standard error of the mean
Dispersion value	0.072

Notes:

[126] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[127]
P-value	= 0.0116
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.182
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.323
upper limit	-0.041
Variability estimate	Standard error of the mean
Dispersion value	0.072

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[128]
P-value	= 0.3732
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.208
upper limit	0.078
Variability estimate	Standard error of the mean
Dispersion value	0.073

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266

Analysis specification	Pre-specified
Analysis type	other[129]
P-value	= 0.1985
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.236
upper limit	0.049
Variability estimate	Standard error of the mean
Dispersion value	0.073

Notes:

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

Secondary: ACQ−IA responder analysis

End point title	ACQ−IA responder analysis

End point description:

Responder categories based on the ACQ-IA total score after 24 and 48 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:

Weeks 24 and 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[130]	135[131]	135[132]	
Units: Patients				
number (not applicable)				
Responders at Week 24	97	108	118	
No Change at Week 24	34	27	16	
Worsening at Week 24	0	0	1	
Responder at Week 48	114	118	117	
No Change at Week 48	16	14	17	
Worsening at Week 48	1	3	1	

Notes:

[130] - FAS

[131] - FAS

[132] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: PAQLQ(S) total score

End point title	PAQLQ(S) total score

End point description:

Standardised Paediatric Asthma Quality of Life Questionnaire (PAQLQ(S)) total score at weeks 24 and 48.
The PAQLQ(S) is 23 questions on a 7-point scale, ranging from 1 (worst control) to 7 (best control). Total Score is calculated as mean of all 23 questions.

The measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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:

Week 24 and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[133]	135[134]	135[135]	
Units: Units on a Scale				
arithmetic mean (standard error)				
Week 24 (N= 126, 131, 134)	5.966 (± 0.065)	6.142 (± 0.063)	6.093 (± 0.062)	
Week 48 (N=124, 130, 130)	6.309 (± 0.065)	6.288 (± 0.063)	6.327 (± 0.063)	

Notes:

[133] - FAS

[134] - FAS

[135] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[136]
P-value	= 0.0144
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.176

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.035
upper limit	0.316
Variability estimate	Standard error of the mean
Dispersion value	0.072

Notes:

[136] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[137]
P-value	= 0.0747
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.127
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.267
Variability estimate	Standard error of the mean
Dispersion value	0.071

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[138]
P-value	= 0.7654
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.163

upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.072

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[139]
P-value	= 0.8082
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.124
upper limit	0.158
Variability estimate	Standard error of the mean
Dispersion value	0.072

Notes:

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

Secondary: PAQLQ(S) symptom domain score

End point title	PAQLQ(S) symptom domain score

End point description:

PAQLQ(S) symptom domain score at weeks 24 and 48.
The PAQLQ(S) is 23 questions on a 7-point scale, ranging from 1 (worst control) to 7 (best control). The individual domain score was calculated as the mean of the items in the domain.

The measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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:

Week 24 and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[140]	135[141]	135[142]	
Units: Units on a Scale				
arithmetic mean (standard error)				
Week 24 (N=126, 131, 134)	5.84 (± 0.076)	6.015 (± 0.074)	5.967 (± 0.073)	
Week 48 (N=124, 130, 130)	6.195 (± 0.076)	6.177 (± 0.074)	6.199 (± 0.074)	

Notes:

[140] - FAS

[141] - FAS

[142] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[143]
P-value	= 0.0392
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.175
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.341
Variability estimate	Standard error of the mean
Dispersion value	0.085

Notes:

[143] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[144]
P-value	= 0.1351
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Point estimate	0.126
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.039
upper limit	0.292
Variability estimate	Standard error of the mean
Dispersion value	0.084

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[145]
P-value	= 0.8291
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.185
upper limit	0.149
Variability estimate	Standard error of the mean
Dispersion value	0.085

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[146]
P-value	= 0.9655
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided

lower limit	-0.163
upper limit	0.171
Variability estimate	Standard error of the mean
Dispersion value	0.085

Notes:

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

Secondary: PAQLQ(S) activity limitation domain score

End point title	PAQLQ(S) activity limitation domain score

End point description:

PAQLQ(S) activity limitation domain score at weeks 24 and 48. The PAQLQ(S) is 23 questions on a 7-point scale, ranging from 1 (worst control) to 7 (best control). The individual domain score is calculated as the mean of the items in this domain.

The measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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:

Week 24 and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[147]	135[148]	135[149]	
Units: Units on a Scale				
arithmetic mean (standard error)				
Week 24 (N= 126, 131, 134)	5.898 (± 0.069)	6.089 (± 0.067)	6.023 (± 0.067)	
Week 48 (N=124, 130, 130)	6.249 (± 0.07)	6.284 (± 0.068)	6.319 (± 0.067)	

Notes:

[147] - FAS

[148] - FAS

[149] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[150]

P-value	= 0.0139
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.191
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.343
Variability estimate	Standard error of the mean
Dispersion value	0.077

Notes:

[150] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[151]
P-value	= 0.1043
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.276
Variability estimate	Standard error of the mean
Dispersion value	0.077

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[152]
P-value	= 0.6547
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.035

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.118
upper limit	0.187
Variability estimate	Standard error of the mean
Dispersion value	0.078

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[153]
P-value	= 0.3648
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.082
upper limit	0.222
Variability estimate	Standard error of the mean
Dispersion value	0.077

Notes:

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

Secondary: PAQLQ(S) emotional function domain score

End point title	PAQLQ(S) emotional function domain score

End point description:

PAQLQ(S) emotional function domain score at weeks 24 and 48. The PAQLQ(S) is 23 questions on a 7-point scale, ranging from 1 (worst control) to 7 (best control). The individual domain score is calculated as the mean of the items in this domain.

The measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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:

Week 24 Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[154]	135[155]	135[156]	
Units: Units on a Scale				
arithmetic mean (standard error)				
Week 24 (N=126, 131, 134)	6.157 (± 0.067)	6.323 (± 0.065)	6.298 (± 0.064)	
Week 48 (N=124, 130, 130)	6.481 (± 0.067)	6.42 (± 0.065)	6.491 (± 0.065)	

Notes:

[154] - FAS

[155] - FAS

[156] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[157]
P-value	= 0.0256
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.312
Variability estimate	Standard error of the mean
Dispersion value	0.074

Notes:

[157] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified

Analysis type	other[158]
P-value	= 0.0561
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.141
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.286
Variability estimate	Standard error of the mean
Dispersion value	0.074

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[159]
P-value	= 0.4127
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.208
upper limit	0.085
Variability estimate	Standard error of the mean
Dispersion value	0.075

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[160]
P-value	= 0.8922
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.136
upper limit	0.156
Variability estimate	Standard error of the mean
Dispersion value	0.074

Notes:

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

Secondary: Responders in PAQLQ(S) at weeks 24 and 48

End point title	Responders in PAQLQ(S) at weeks 24 and 48

End point description:

Responders in PAQLQ(S) at weeks 24 and 48. 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 PAQLQ(S) total score responders.
The PAQLQ(S) is 23 questions on a 7-point scale, ranging from 1 (worst control) to 7 (best control).

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:

Weeks 24 and 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[161]	135[162]	135[163]	
Units: Patients				
number (not applicable)				
Responders at Week 24	67	82	73	
No Change at Week 24	58	47	56	
Worsening at Week 24	6	6	6	
Responders at Week 48	89	96	92	
No Change at Week 48	39	33	42	
Worsening at Week 48	3	6	1	

Notes:

[161] - FAS

[162] - FAS

[163] - FAS

Statistical analyses

No statistical analyses for this end point

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 24 and 48.

The measured values presented are actually adjusted means.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[164]	135[165]	135[166]	
Units: Litres				
arithmetic mean (standard error)				
Week 24 (N=122, 130, 130)	0.191 (± 0.041)	0.209 (± 0.039)	0.126 (± 0.039)	
Week 48 (N=119, 122, 125)	0.236 (± 0.041)	0.259 (± 0.04)	0.221 (± 0.04)	

Notes:

[164] - FAS

[165] - FAS

[166] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[167]
P-value	= 0.6932
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.075
upper limit	0.113
Variability estimate	Standard error of the mean
Dispersion value	0.048

Notes:

[167] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[168]
P-value	= 0.1741
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.158
upper limit	0.029
Variability estimate	Standard error of the mean
Dispersion value	0.048

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[169]
P-value	= 0.625
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.071
upper limit	0.118
Variability estimate	Standard error of the mean
Dispersion value	0.048

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[170]
P-value	= 0.7597
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.109
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.048

Notes:

[170] - 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 weeks 24 and 48.

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.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[171]	135[172]	135[173]	
Units: Units on a scale				
arithmetic mean (standard error)				
Week 24 (N=122, 130, 130)	-0.07 (± 0.03)	-0.079 (± 0.029)	-0.144 (± 0.029)	

Week 48 (N=119, 122, 125)	-0.101 (± 0.03)	-0.131 (± 0.029)	-0.127 (± 0.029)	

Notes:

[171] - FAS

[172] - FAS

[173] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[174]
P-value	= 0.7931
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.061
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[174] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[175]
P-value	= 0.0369
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.145
upper limit	-0.005
Variability estimate	Standard error of the mean

Dispersion value	0.036

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[176]
P-value	= 0.4086
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.101
upper limit	0.041
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[177]
P-value	= 0.4714
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.097
upper limit	0.045
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[177] - 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 weeks 24 and 48.

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.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[178]	135[179]	135[180]	
Units: Units on a scale				
arithmetic mean (standard error)				
Week 24 (N=122, 130, 130)	-0.138 (± 0.039)	-0.138 (± 0.038)	-0.22 (± 0.038)	
Week 48 (N=119, 122, 125)	-0.177 (± 0.039)	-0.23 (± 0.038)	-0.221 (± 0.038)	

Notes:

[178] - FAS

[179] - FAS

[180] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[181]
P-value	= 0.988
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.001
Confidence interval	
level	95 %

sides	2-sided
lower limit	-0.091
upper limit	0.092
Variability estimate	Standard error of the mean
Dispersion value	0.047

Notes:

[181] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[182]
P-value	= 0.0794
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.173
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[183]
P-value	= 0.2623
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.145
upper limit	0.04
Variability estimate	Standard error of the mean

Dispersion value	0.047

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[184]
P-value	= 0.3552
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.136
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.047

Notes:

[184] - 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 weeks 24 and 48.

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.

The number of participants analysed displays the number of participants included in the statistical model whereas the N’s for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[185]	135[186]	135[187]	
Units: Units on a scale				
arithmetic mean (standard error)				
Week 24 (N=121, 130, 133)	-0.204 (± 0.041)	-0.243 (± 0.04)	-0.263 (± 0.04)	
Week 48 (N=119, 123, 125)	-0.261 (± 0.042)	-0.272 (± 0.041)	-0.312 (± 0.041)	

Notes:

[185] - FAS

[186] - FAS

[187] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[188]
P-value	= 0.4359
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.135
upper limit	0.058
Variability estimate	Standard error of the mean
Dispersion value	0.049

Notes:

[188] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[189]
P-value	= 0.2293
Method	Mixed models analysis
Parameter estimate	Mean difference (net)

Point estimate	-0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.155
upper limit	0.037
Variability estimate	Standard error of the mean
Dispersion value	0.049

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[190]
P-value	= 0.8372
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.108
upper limit	0.088
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[191]
P-value	= 0.3022
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.051
Confidence interval	
level	95 %
sides	2-sided

lower limit	-0.148
upper limit	0.046
Variability estimate	Standard error of the mean
Dispersion value	0.049

Notes:

[191] - 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 weeks 24 and 48.

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.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[192]	135[193]	135[194]	
Units: Units on a scale				
arithmetic mean (standard error)				
Week 24 (N=121, 130, 133)	-0.181 (± 0.039)	-0.212 (± 0.038)	-0.24 (± 0.038)	
Week 48 (N=119, 123, 125)	-0.227 (± 0.039)	-0.238 (± 0.038)	-0.259 (± 0.038)	

Notes:

[192] - FAS

[193] - FAS

[194] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[195]

P-value	= 0.5004
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.122
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

[195] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[196]
P-value	= 0.1982
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.149
upper limit	0.031
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[197]
P-value	= 0.8019
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.012

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.103
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.047

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[198]
P-value	= 0.4872
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.123
upper limit	0.059
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

[198] - 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 weeks 24 and 48.

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.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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:

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[199]	135[200]	135[201]	
Units: Units on a scale				
arithmetic mean (standard error)				
Week 24 (N=121, 130, 133)	-0.134 (± 0.039)	-0.178 (± 0.038)	-0.24 (± 0.038)	
Week 48 (N=119, 123, 125)	-0.219 (± 0.039)	-0.231 (± 0.038)	-0.253 (± 0.038)	

Notes:

[199] - FAS

[200] - FAS

[201] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[202]
P-value	= 0.3498
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.135
upper limit	0.048
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

[202] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266

Analysis specification	Pre-specified
Analysis type	other[203]
P-value	= 0.0222
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.196
upper limit	-0.015
Variability estimate	Standard error of the mean
Dispersion value	0.046

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[204]
P-value	= 0.799
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.104
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.047

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[205]
P-value	= 0.4586
Method	Mixed models analysis

Parameter estimate	Median difference (net)
Point estimate	-0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.126
upper limit	0.057
Variability estimate	Standard error of the mean
Dispersion value	0.047

Notes:

[205] - 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 weeks 24 and 48.

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.

The number of participants analysed displays the number of participants included in the statistical model whereas the N's for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[206]	135[207]	135[208]	
Units: Units on a scale				
arithmetic mean (standard error)				
Week 24 (N=121, 130, 133)	-0.261 (± 0.046)	-0.307 (± 0.045)	-0.355 (± 0.045)	
Week 48 (N=119, 123, 125)	-0.34 (± 0.047)	-0.337 (± 0.045)	-0.393 (± 0.046)	

Notes:

[206] - FAS

[207] - FAS

[208] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[209]
P-value	= 0.4221
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.156
upper limit	0.065
Variability estimate	Standard error of the mean
Dispersion value	0.056

Notes:

[209] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[210]
P-value	= 0.0959
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.204
upper limit	0.017
Variability estimate	Standard error of the mean
Dispersion value	0.056

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[211]
P-value	= 0.9627
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.109
upper limit	0.114
Variability estimate	Standard error of the mean
Dispersion value	0.057

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[212]
P-value	= 0.3457
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	-0.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.165
upper limit	0.058
Variability estimate	Standard error of the mean
Dispersion value	0.057

Notes:

[212] - 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 weeks 24 and 48.

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.

The number of participants analysed displays the number of participants included in the statistical model whereas the N’s for each timepoint display the number of participants with available data at that timepoint.

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 Week 24, Baseline and Week 48

End point values	Placebo Respimat	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	131[213]	135[214]	135[215]	
Units: Days				
arithmetic mean (standard error)				
Week 24 (N=122, 130, 133)	0.135 (± 0.036)	0.176 (± 0.034)	0.172 (± 0.035)	
Week 48 (N=120, 123, 127)	0.151 (± 0.036)	0.17 (± 0.035)	0.18 (± 0.035)	

Notes:

[213] - FAS

[214] - FAS

[215] - FAS

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 (Week 24)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[216]
P-value	= 0.3375
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.043
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.043

Notes:

[216] - 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 (Week 24)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[217]
P-value	= 0.388
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.047
upper limit	0.121
Variability estimate	Standard error of the mean
Dispersion value	0.043

Notes:

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

Statistical analysis title	Statistical Analysis 3

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other[218]
P-value	= 0.6541
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.066
upper limit	0.104
Variability estimate	Standard error of the mean
Dispersion value	0.043

Notes:

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

Statistical analysis title	Statistical Analysis 4

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 (Week 48)

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	266

Analysis specification	Pre-specified
Analysis type	other[219]
P-value	= 0.5089
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.056
upper limit	0.133
Variability estimate	Standard error of the mean
Dispersion value	0.043

Notes:

[219] - 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 day 407.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Inhalation of placebo solution (2 puffs) once daily for 48 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 48 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 (Tio R5) solution (2 puffs of 2.5mcg) once daily for 48 weeks delivered by the Respimat inhaler, as add on therapy on top of usual care.	

Serious adverse events	Placebo	Tio R2.5	Tio R5
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 131 (4.58%)	3 / 135 (2.22%)	1 / 135 (0.74%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	1 / 131 (0.76%)	0 / 135 (0.00%)	0 / 135 (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
Fall			
subjects affected / exposed	1 / 131 (0.76%)	0 / 135 (0.00%)	0 / 135 (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
Skull fracture			
subjects affected / exposed	1 / 131 (0.76%)	0 / 135 (0.00%)	0 / 135 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 131 (1.53%)	2 / 135 (1.48%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranasal sinus haematoma			
subjects affected / exposed	1 / 131 (0.76%)	0 / 135 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 131 (0.76%)	0 / 135 (0.00%)	0 / 135 (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
Gastrointestinal disorders			
Ileus paralytic			
subjects affected / exposed	0 / 131 (0.00%)	0 / 135 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 135 (0.00%)	0 / 135 (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
Appendicitis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 135 (0.74%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal abscess			
subjects affected / exposed	1 / 131 (0.76%)	0 / 135 (0.00%)	0 / 135 (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	Tio R2.5	Tio R5
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 131 (60.31%)	76 / 135 (56.30%)	71 / 135 (52.59%)
Investigations			
Peak expiratory flow rate decreased			
subjects affected / exposed	27 / 131 (20.61%)	31 / 135 (22.96%)	29 / 135 (21.48%)
occurrences (all)	63	73	89
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	57 / 131 (43.51%)	49 / 135 (36.30%)	46 / 135 (34.07%)
occurrences (all)	132	122	131
Rhinitis allergic			
subjects affected / exposed	8 / 131 (6.11%)	4 / 135 (2.96%)	6 / 135 (4.44%)
occurrences (all)	11	4	9
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 131 (9.92%)	15 / 135 (11.11%)	12 / 135 (8.89%)
occurrences (all)	18	21	14
Respiratory tract infection			
subjects affected / exposed	16 / 131 (12.21%)	11 / 135 (8.15%)	13 / 135 (9.63%)
occurrences (all)	29	18	26
Respiratory tract infection viral			
subjects affected / exposed	8 / 131 (6.11%)	8 / 135 (5.93%)	8 / 135 (5.93%)
occurrences (all)	10	11	14
Rhinitis			
subjects affected / exposed	7 / 131 (5.34%)	5 / 135 (3.70%)	2 / 135 (1.48%)
occurrences (all)	7	5	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 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, to correct minor typographical errors and inconsistencies, and to 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.
01 April 2015	With the second amendment, the CTP was 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 48-week treatment period' was amended to 'individual FEF25-75 response at each time point and visit during the 48-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 24 and 48 weeks of treatment, trough FEV1 expressed as percentage of patient's predicted FEV1 after 24 and 48 weeks of treatment, time to first symptomatic asthma exacerbation during the 48-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. Furthermore, the amendment introduced changes to include updated information on tiotropium based on newly available data and to correct minor typographical errors and inconsistencies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported