Clinical trial results:
A Phase III randomised, double blind, placebo-controlled, parallel group study to assess the efficacy and safety over 48 weeks of orally inhaled Tiotropium bromide (2.5 µg and 5 µg once daily) delivered by the Respimat® inhaler in adolescents (12 to 17 years old) with moderate persistent asthma.

Summary

EudraCT number	2010-021093-11
Trial protocol	LV HU ES SK IT DE NO Outside EU/EEA
Global end of trial date	27 December 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	08 April 2015

Trial information

Trial identification

Sponsor protocol code	205.444

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01257230
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim Pharma GmbH & Co. KG
Sponsor organisation address	Binger Strasse 173, 55216 Ingelheim Rhein, Germany,
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmgH & Co. KG, +1 800243 0127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmgH & Co. KG, +1 800243 0127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000035-PIP02-09
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 June 2013
Global end of trial reached?	Yes
Global end of trial date	27 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a confirmatory phase III trial to evaluate efficacy and safety of a 48-week treatment with two doses (2.5 µg and 5 µg) of tiotropium bromide compared to placebo administered via the Respimat® device in adolescent patients (12 to 17 years old) with moderate persistent asthma.

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. Administration of rescue medication was allowed throughout the trial as medically needed. For the screening and treatment periods, open-label salbutamol/albuterol inhalers (100 µg per puff) were provided by the sponsor for use as rescue medication.

Background therapy:

Patients maintained their ICS background therapy.

Evidence for comparator: -

Actual start date of recruitment	05 January 2011
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	Slovakia: 45
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Hungary: 135
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Latvia: 81
Country: Number of subjects enrolled	Chile: 57
Country: Number of subjects enrolled	Korea, Republic of: 29
Country: Number of subjects enrolled	Mexico: 19
Country: Number of subjects enrolled	Russian Federation: 71
Country: Number of subjects enrolled	Ukraine: 93
Country: Number of subjects enrolled	United States: 67

Worldwide total number of subjects	673
EEA total number of subjects	337

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)	1
Adolescents (12-17 years)	672
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 the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strict inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any specific entry criteria were violated. Thus, out of 673 enrolled, 398 subjects were randomized.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo respimat

Arm description:

Inhalation of placebo solution once daily for 48 weeks, delivered by the Respimat Inhaler.

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

Dosage and administration details:

Patients received placebo (tiotropium-matching placebo solution for inhalation). The patients were to inhale 2 puffs from the Respimat® inhaler (placebo) every evening.

Arm title	Tio R2.5

Arm description:

Inhalation of 2.5µg tiotropium bromide solution (Tio R2.5) once daily for 48 weeks, delivered by the Respimat Inhaler.

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:

Patients received 2.5 µg tiotropium (Tio R2.5). The patients were to inhale 2 puffs (1.25 mcg of tiotropium) per puff from the Respimat® inhaler every evening.

Arm title	Tio R5

Arm description:

Inhalation of 5µg tiotropium bromide solution (Tio R5) once daily for 48 weeks, delivered by the Respimat Inhaler.

One subject was not treated thus was not considered as starter nor non-completer.

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:

Patients received 5 µg tiotropium (Tio R5). The patients were to inhale 2 puffs (2.5 mcg of tiotropium) from the Respimat® inhaler every evening.

Number of subjects in period 1[1]	Placebo respimat	Tio R2.5	Tio R5
Started	138	125	134
Completed	132	115	129
Not completed	6	10	5
Consent withdrawn by subject	-	4	1
Adverse event, non-fatal	2	-	-
Protocol deviation	3	-	1
not specified	1	5	-
Lack of efficacy	-	1	-
Reasons other than stated above	-	-	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication. One patient in the Tio R5 arm has started but was not treated, thus does not feature in this flowchart.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo respimat
Reporting group description:	
Inhalation of placebo solution once daily for 48 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R2.5
Reporting group description:	
Inhalation of 2.5µg tiotropium bromide solution (Tio R2.5) once daily for 48 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R5
Reporting group description:	
Inhalation of 5µg tiotropium bromide solution (Tio R5) once daily for 48 weeks, delivered by the Respimat Inhaler. One subject was not treated thus was not considered as starter nor non-completer.	

Reporting group values	Placebo respimat	Tio R2.5	Tio R5
Number of subjects	138	125	134
Age categorical Units: Subjects			

Age continuous			
Treated set (TS) which included all randomised patients who were dispensed trial medication and received at least one documented dose of trial medication. TS was used in the description.			
Units: years			
arithmetic mean	14.2	14.2	14.5
standard deviation	± 1.7	± 1.8	± 1.6
Gender categorical			
Treated Set (TS)			
Units: Subjects			
Female	50	44	45
Male	88	81	89

Reporting group values	Total		
Number of subjects	397		
Age categorical Units: Subjects			

Age continuous			
Treated set (TS) which included all randomised patients who were dispensed trial medication and received at least one documented dose of trial medication. TS was used in the description.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Treated Set (TS)			
Units: Subjects			
Female	139		
Male	258		

End points

End points reporting groups

Reporting group title	Placebo respimat
Reporting group description:	
Inhalation of placebo solution once daily for 48 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R2.5
Reporting group description:	
Inhalation of 2.5µg tiotropium bromide solution (Tio R2.5) once daily for 48 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R5
Reporting group description:	
Inhalation of 5µg tiotropium bromide solution (Tio R5) once daily for 48 weeks, delivered by the Respimat Inhaler.	

One subject was not treated thus was not considered as starter nor non-completer.

Primary: FEV1 peak0-3 Change From Baseline

End point title	FEV1 peak0-3 Change From Baseline

End point description:

Change from baseline in peak Forced expiratory volume in 1 second within the first 3 hours post dosing (FEV1 peak0-3) measured at week 24.

Note, the measured values presented are actually adjusted means.

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

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24 (from MMRM output).

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	137[1]	120[2]	131[3]	
Units: litre(s)				
least squares mean (standard error)	0.373 (± 0.037)	0.507 (± 0.04)	0.547 (± 0.038)	

Notes:

[1] - Full Analysis Set (FAS)

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based Mixed Model Repeated Measures (MMRM). Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction. Patient was included as a random effect in the model.

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
P-value	= 0.0085 [4]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.134
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.234
Variability estimate	Standard error of the mean
Dispersion value	0.051

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.

Statistical analysis title	Tio R5 vs Placebo

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Comparison groups	Tio R5 v Placebo respimat
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [5]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.174
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.076
upper limit	0.272
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[5] - Stepwise testing of the null hypothesis was used to test the efficacy of Tio R5 and then Tio R2.5, each over placebo.

Secondary: Trough FEV1 Change From Baseline

End point title	Trough FEV1 Change From Baseline

End point description:

Change from baseline in Trough (pre-dose) Forced expiratory volume in 1 second (FEV1) measured at week 24.

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24 (from MMRM output).

End point type	Secondary

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	137[6]	119[7]	131[8]	
Units: litre(s)				
least squares mean (standard error)	0.283 (± 0.04)	0.367 (± 0.044)	0.4 (± 0.041)	

Notes:

[6] - FAS

[7] - FAS

[8] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R2.5 minus placebo.

Comparison groups	Placebo respimat v Tio R2.5
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1307 [9]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.084
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.194
Variability estimate	Standard error of the mean
Dispersion value	0.056

Notes:

[9] - Stepwise testing of the null hypothesis was used to test the efficacy of Tio R5 and then Tio R2.5, each over placebo.

Statistical analysis title	Placebo vs Tio R5

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R5 minus placebo

Comparison groups	Placebo respimat v Tio R5
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 [10]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.117
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.223
Variability estimate	Standard error of the mean
Dispersion value	0.054

Notes:

[10] - Stepwise testing of the null hypothesis was used to test the efficacy of Tio R5 and then Tio R2.5, each over placebo.

Secondary: FVC peak0-3 Change From Baseline

End point title	FVC peak0-3 Change From Baseline

End point description:

Change from baseline in Maximum forced vital capacity (FVC) measured within the first 3 h after administration of trial medication (FVC peak0–3h) after 24 weeks of treatment.

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24 (from MMRM output).

End point type	Secondary

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	137[11]	120[12]	131[13]	
Units: litre(s)				
least squares mean (standard error)	0.331 (± 0.041)	0.419 (± 0.045)	0.403 (± 0.043)	

Notes:

[11] - FAS

[12] - FAS

[13] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

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
P-value	= 0.1231
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.088
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.057

Statistical analysis title	Placebo vs Tio R5

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R5 minus placebo

Comparison groups	Placebo respimat v Tio R5
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.195
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.182
Variability estimate	Standard error of the mean
Dispersion value	0.056

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

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

End point description:

Change from baseline of area under the curve (AUC) from 0 to 3 h for FEV1 (FEV1 AUC 0–3h) after 24 weeks of treatment. The AUC was calculated by using the trapezoidal rule divided by the observation time (3h).

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24.

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	137[14]	119[15]	131[16]	
Units: litre(s)				
least squares mean (standard error)	0.281 (± 0.035)	0.411 (± 0.038)	0.463 (± 0.036)	

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R2.5 minus placebo

Comparison groups	Placebo respimat v Tio R2.5
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0079
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.225
Variability estimate	Standard error of the mean
Dispersion value	0.049

Statistical analysis title	Tio R5 vs Placebo

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R5 minus placebo

Comparison groups	Tio R5 v Placebo respimat
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.181
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.088
upper limit	0.275
Variability estimate	Standard error of the mean
Dispersion value	0.048

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

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

End point description:

Change from baseline of area under the curve (AUC) from 0 to 3 h for FVC (FVC AUC0–3h) after 24 weeks of treatment. The AUC was calculated by using the trapezoidal rule divided by the observation time (3h).

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24 (from MMRM output).

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	137[17]	119[18]	131[19]	
Units: litre(s)				
least squares mean (standard error)	0.24 (± 0.039)	0.33 (± 0.042)	0.311 (± 0.04)	

Notes:

[17] - FAS

[18] - FAS

[19] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R2.5 minus placebo

Comparison groups	Placebo respimat v Tio R2.5
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0945
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.016
upper limit	0.196
Variability estimate	Standard error of the mean
Dispersion value	0.054

Statistical analysis title	Placebo vs Tio R5

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.
Difference calculated as Tio R5 minus placebo

Comparison groups	Placebo respimat v Tio R5
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1755
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.071

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.175
Variability estimate	Standard error of the mean
Dispersion value	0.053

Secondary: Trough FVC Change From Baseline

End point title	Trough FVC Change From Baseline

End point description:

Change from baseline of Trough (pre-dose) forced vital capacity (FVC) measured 10 min before the administration of trial medication after 24 weeks of treatment.

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24 (from MMRM output).

End point type	Secondary

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	137[20]	119[21]	131[22]	
Units: litre(s)				
least squares mean (standard error)	0.281 (± 0.043)	0.345 (± 0.047)	0.316 (± 0.045)	

Notes:

[20] - FAS

[21] - FAS

[22] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R2.5 minus placebo

Comparison groups	Placebo respimat v Tio R2.5

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2921
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.055
upper limit	0.181
Variability estimate	Standard error of the mean
Dispersion value	0.06

Statistical analysis title	Placebo vs Tio R5

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R5 minus placebo

Comparison groups	Placebo respimat v Tio R5
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5495
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.059

Secondary: FEF25-75 Change From Baseline

End point title	FEF25-75 Change From Baseline

End point description:

Change from baseline in mean forced expiratory flow between 25% and 75% of the FVC (FEF25-75%), also known as maximum mid-expiratory flow, at individual time points after 24 weeks of treatment.

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24.

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	137[23]	120[24]	131[25]	
Units: litre(s)/Sec				
least squares mean (standard error)				
10 minutes pre-dose (N1=137, N2=119, N3=131)	0.332 (± 0.072)	0.461 (± 0.079)	0.609 (± 0.074)	
30 minutes post-dose (N1=137, N2=120, N3=131)	0.372 (± 0.066)	0.536 (± 0.072)	0.763 (± 0.068)	
1 hour post-dose (N1=137, N2=120, N3=131)	0.359 (± 0.067)	0.596 (± 0.072)	0.835 (± 0.069)	
2 hours post-dose (N1=137, N2=120, N3=131)	0.403 (± 0.069)	0.615 (± 0.075)	0.857 (± 0.071)	
3 hours post=dose (N1=137, N2=120, N3=131)	0.347 (± 0.068)	0.653 (± 0.074)	0.85 (± 0.07)	

Notes:

[23] - FAS

[24] - FAS

[25] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Use of PRN Rescue Medication During the Day

End point title	Use of PRN Rescue Medication During the Day

End point description:

Change from baseline in the number of puffs of rescue medication (salbutamol/albuterol) used during the day (24 hour period) based on the weekly mean at week 24.

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24 (from MMRM output).

End point type	Secondary

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	135[26]	117[27]	125[28]	
Units: Number of puff(s) of rescue medication				
least squares mean (standard error)	-0.524 (± 0.098)	-0.556 (± 0.104)	-0.48 (± 0.1)	

Notes:

[26] - FAS

[27] - FAS

[28] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5 at week 24

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R2.5 minus placebo

Comparison groups	Placebo respimat v Tio R2.5
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8253
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.312
upper limit	0.249
Variability estimate	Standard error of the mean
Dispersion value	0.143

Statistical analysis title	Placebo vs Tio R5 at week 24

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

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
P-value	= 0.7559
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.044

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.232
upper limit	0.319
Variability estimate	Standard error of the mean
Dispersion value	0.14

Secondary: Use of PRN Rescue Medication During the Daytime

End point title	Use of PRN Rescue Medication During the Daytime

End point description:

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

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24.

End point type	Secondary

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	132[29]	114[30]	122[31]	
Units: Number of puff(s) of rescue medication				
least squares mean (standard error)	-0.206 (± 0.066)	-0.209 (± 0.071)	-0.215 (± 0.068)	

Notes:

[29] - FAS

[30] - FAS

[31] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5 at week 24

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R2.5 minus placebo

Comparison groups	Placebo respimat v Tio R2.5

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.976
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.184
upper limit	0.178
Variability estimate	Standard error of the mean
Dispersion value	0.092

Statistical analysis title	Placebo vs Tio R5 at week 24

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

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	superiority
P-value	= 0.9224
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.186
upper limit	0.168
Variability estimate	Standard error of the mean
Dispersion value	0.09

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

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

End point description:

Change from baseline in the number of puffs of rescue medication (salbutamol/albuterol) used during the night-time based on the weekly mean at week 24.

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24 (from MMRM output).

End point type	Secondary

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	132[32]	110[33]	124[34]	
Units: Number of puff(s) of rescue medication				
least squares mean (standard error)	-0.144 (± 0.059)	-0.122 (± 0.064)	-0.032 (± 0.061)	

Notes:

[32] - FAS

[33] - FAS

[34] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo at week 24

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R2.5 minus placebo

Comparison groups	Tio R2.5 v Placebo respimat
Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7852
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.185
Variability estimate	Standard error of the mean
Dispersion value	0.083

Statistical analysis title	Placebo vs Tio R5 at week 24

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R5 minus placebo

Comparison groups	Placebo respimat v Tio R5

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1649
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.046
upper limit	0.271
Variability estimate	Standard error of the mean
Dispersion value	0.081

Secondary: Control of Asthma as Assessed by ACQ Total Score

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

End point description:

Change from baseline in Asthma Control Questionnaire (ACQ) total score measured at week 24.
The ACQ 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 total score was calculated as the mean of the responses to all 7 questions.

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24.

End point type	Secondary

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	136[35]	120[36]	132[37]	
Units: unit(s) of ACQ scores				
least squares mean (standard error)	1.213 (± 0.062)	1.053 (± 0.067)	1.116 (± 0.064)	

Notes:

[35] - FAS

[36] - FAS

[37] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5 at week 24

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical

effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R2.5 minus placebo

Comparison groups	Placebo respimat v Tio R2.5
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0653
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.087

Statistical analysis title	Placebo vs Tio R5 at week 24

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R5 minus placebo

Comparison groups	Placebo respimat v Tio R5
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2516
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.263
upper limit	0.069
Variability estimate	Standard error of the mean
Dispersion value	0.084

Secondary: Control of Asthma as Assessed by ACQ6

End point title	Control of Asthma as Assessed by ACQ6

End point description:

Change from baseline in AQC6 score at week 24.
The ACQ6 score is calculated as the mean of the responses to the first 6 questions of the ACQ. The ACQ 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.

The measured values presented are actually adjusted means.

In FAS we have 138, 125, 134 patients in each of 3 treatment arms.
Currently reported numbers are numbers of patients with endpoint at week 24.

End point type	Secondary

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	136[38]	120[39]	132[40]	
Units: unit(s) of ACQ6 score				
least squares mean (standard error)	1.173 (± 0.068)	1.026 (± 0.073)	1.119 (± 0.07)	

Notes:

[38] - FAS

[39] - FAS

[40] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5 at week 24

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R2.5 minus placebo

Comparison groups	Placebo respimat v Tio R2.5
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.333
upper limit	0.038
Variability estimate	Standard error of the mean
Dispersion value	0.095

Statistical analysis title	Placebo vs Tio R5 at week 24

Statistical analysis description:

Using a restricted maximum likelihood (REML)-based MMRM. Analyses included the fixed, categorical

effects of treatment, country, week, and treatment-by-week interaction, as well as the covariates of baseline value and baseline-by-week-interaction Patient was included as a random effect in the model.

Difference calculated as Tio R5 minus placebo

Comparison groups	Placebo respimat v Tio R5
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5589
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.235
upper limit	0.127
Variability estimate	Standard error of the mean
Dispersion value	0.092

Secondary: ACQ6 Responders

End point title	ACQ6 Responders

End point description:

Responder rates based on the ACQ6 after 24 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)

The ACQ6 score is calculated as the mean of the responses to the first 6 questions of the ACQ. The ACQ 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.

End point type	Secondary

End point timeframe:

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	138[41]	125[42]	134[43]	
Units: percentage of participants				
number (not applicable)				
responder	69.6	76.8	72.4	
no change	22.5	20	23.1	
worsening	8	3.2	4.5	

Notes:

[41] - FAS

[42] - FAS

[43] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: ACQ Total Score Responders

End point title	ACQ Total Score Responders

End point description:

Responder rates based on the ACQ total score after 24 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).
The ACQ 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.

End point type	Secondary

End point timeframe:

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	138[44]	125[45]	134[46]	
Units: percentage of participants				
number (not applicable)				
responder	66.7	76	74.6	
no change	27.5	21.6	23.1	
worsening	5.8	2.4	2.2	

Notes:

[44] - FAS

[45] - FAS

[46] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Severe Asthma Exacerbation During the 48 Week Treatment Period

End point title	Time to First Severe Asthma Exacerbation During the 48 Week Treatment Period

End point description:

The median time to first severe asthma exacerbation was not calculable, so the number of patients who experienced a severe asthma exacerbation are presented for the measured values. A severe asthma exacerbation was defined as a subgroup of all asthma exacerbations that required treatment with systemic corticosteroid for at least 3 days.

End point type	Secondary

End point timeframe:

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	138[47]	125[48]	134[49]	
Units: participant(s)				
number (not applicable)				
cumulative failure	9	5	2	
cumulative censored	129	120	132	

Notes:

[47] - FAS

[48] - FAS

[49] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5 during 48 weeks treatment
Statistical analysis description:	
Cox's proportional hazard regression model with treatment as an effect.	
Comparison groups	Placebo respimat v Tio R2.5
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4023
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	1.87

Statistical analysis title	Placebo vs Tio R5 during 48 weeks treatment
Statistical analysis description:	
Cox's proportional hazard regression model with treatment as an effect.	
Comparison groups	Placebo respimat v Tio R5
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.062
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	1.08

Secondary: Time to First Asthma Exacerbation During the 48 Week Treatment Period

End point title	Time to First Asthma Exacerbation During the 48 Week Treatment Period

End point description:

The median time to first asthma exacerbation was not calculable, so the number of patients who experienced an asthma exacerbation are presented for the measured values.

End point type	Secondary

End point timeframe:

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	138[50]	125[51]	134[52]	
Units: participants				
number (not applicable)				
cumulative failure	37	34	30	
cumulative censored	101	91	104	

Notes:

[50] - FAS

[51] - FAS

[52] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5 during 48 weeks treatment

Statistical analysis description:

Cox's proportional hazard regression model with treatment as an effect.

Comparison groups	Placebo respimat v Tio R2.5
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.66

Statistical analysis title	Placebo vs Tio R5 during 48 weeks treatment

Statistical analysis description:

Cox's proportional hazard regression model with treatment as an effect.

Comparison groups	Placebo respimat v Tio R5
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4198
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.33

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first drug administration until 30 days after the last drug administration, up to 416 days.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Inhalation of placebo solution once daily for 48 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R2.5
Reporting group description:	
Inhalation of 2.5µg tiotropium bromide solution (Tio R2.5) once daily for 48 weeks, delivered by the Respimat Inhaler.	
Reporting group title	Tio R5
Reporting group description:	
Inhalation of 5µg tiotropium bromide solution (Tio R5) once daily for 48 weeks, delivered by the Respimat Inhaler.	

Serious adverse events	Placebo	Tio R2.5	Tio R5
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 138 (1.45%)	2 / 125 (1.60%)	3 / 134 (2.24%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Teratoma			
subjects affected / exposed	1 / 138 (0.72%)	0 / 125 (0.00%)	0 / 134 (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
Injury, poisoning and procedural complications			
Arterial injury			
subjects affected / exposed	0 / 138 (0.00%)	1 / 125 (0.80%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic rupture			

subjects affected / exposed	0 / 138 (0.00%)	1 / 125 (0.80%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	0 / 138 (0.00%)	1 / 125 (0.80%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	0 / 138 (0.00%)	1 / 125 (0.80%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy to plants			
subjects affected / exposed	0 / 138 (0.00%)	0 / 125 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	0 / 138 (0.00%)	0 / 125 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 138 (0.00%)	0 / 125 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 138 (0.00%)	1 / 125 (0.80%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			
subjects affected / exposed	0 / 138 (0.00%)	1 / 125 (0.80%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haematoma			

subjects affected / exposed	0 / 138 (0.00%)	1 / 125 (0.80%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	0 / 138 (0.00%)	1 / 125 (0.80%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 138 (0.00%)	0 / 125 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	0 / 138 (0.00%)	1 / 125 (0.80%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 138 (0.00%)	1 / 125 (0.80%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 138 (0.72%)	0 / 125 (0.00%)	0 / 134 (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	62 / 138 (44.93%)	55 / 125 (44.00%)	62 / 134 (46.27%)

Investigations			
Peak expiratory flow rate decreased			
subjects affected / exposed	8 / 138 (5.80%)	9 / 125 (7.20%)	6 / 134 (4.48%)
occurrences (all)	21	21	18
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 138 (1.45%)	7 / 125 (5.60%)	9 / 134 (6.72%)
occurrences (all)	8	15	17
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	32 / 138 (23.19%)	27 / 125 (21.60%)	23 / 134 (17.16%)
occurrences (all)	81	57	41
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	17 / 138 (12.32%)	13 / 125 (10.40%)	20 / 134 (14.93%)
occurrences (all)	24	15	27
Respiratory tract infection viral			
subjects affected / exposed	11 / 138 (7.97%)	11 / 125 (8.80%)	10 / 134 (7.46%)
occurrences (all)	14	12	11
Tonsillitis			
subjects affected / exposed	7 / 138 (5.07%)	2 / 125 (1.60%)	1 / 134 (0.75%)
occurrences (all)	7	2	1
Upper respiratory tract infection			
subjects affected / exposed	6 / 138 (4.35%)	2 / 125 (1.60%)	7 / 134 (5.22%)
occurrences (all)	6	2	7
Viral infection			
subjects affected / exposed	6 / 138 (4.35%)	5 / 125 (4.00%)	7 / 134 (5.22%)
occurrences (all)	6	5	10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2011	Global amendment no. 1 (dated 18 Feb 2011) was limited to administrative changes, corrections and clarifications. To follow the project standard and to establish consistency between studies, the definition for treatment-emergent AEs was extended to include all AEs occurring until 30 days (instead of 21 days as stipulated in the original protocol) after the last intake of trial drug.
06 May 2011	Significant changes to the CTP introduced by global amendment no. 2 (dated 06 May 2011) were to allow reversibility testing for inclusion criterion no. 7 to be repeated once within 2 weeks if the patient did not reverse sufficiently during the first test, and correction of the reporting period for both AEs and SAEs to until 30 days after the last intake of trial drug.
06 February 2012	Significant changes to the CTP introduced by global amendment no. 3 (dated 06 Feb 2012) included an increase in the washout period prior to Visit 1 for LABAs given twice daily from 24 h to 72 h (3 days) and for LABAs given once daily from 48 hours to 4 days to avoid their influence on screening spirometry values. Other changes included clarification of (S)AE reporting, and addition of AEs that are defined as 'always serious adverse events'. Completion of question 7 of the ACQ at Visits 4, 6, and 8 was to be performed during programming of the dataset for the CTR and not by data management. The sample size was increased from 81 randomised patients per treatment group to 127 randomised patients per treatment group following an update to the expected SD for the primary endpoint of change from trial baseline in FEV1 peak0–3h from 270 mL to 340 mL (based on the results from previous trials of tiotropium in asthma).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported