Clinical trial results:
A randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (2.5 µg and 5 µg once daily) over 12 weeks as add-on controller therapy on top of usual care in adolescents (12 to 17 years old) with severe persistent asthma.

Summary

EudraCT number	2010-021778-13
Trial protocol	LV HU BG DE IT PT Outside EU/EEA
Global end of trial date	16 October 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	205.456

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim Pharma GmbH & Co. KG
Sponsor organisation address	Binger Strasse 173 , 55216 Ingelheim am Rhein , Germany,
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmbH & Co. KG, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmbH & Co. KG, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 October 2013
Global end of trial reached?	Yes
Global end of trial date	16 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is 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 12 weeks of treatment.

Protection of trial subjects:

The safety of the patients was of paramount importance and was ensured by monitoring the patients closely for AEs.
At-home monitoring of lung function was conducted throughout the entire run-in and treatment periods with the AM3®. The AM3® device was programmed to alert the patient to contact the doctor if significant PEF deterioration occurred or if the patient reported taking high amounts of rescue medication. Patients continued taking their usual maintenance therapy, including ICS and other controller medications and had free access to rescue medication (salbutamol), thus limiting the risk that patients might experience a significant asthmatic adverse event. Moreover, to control acute exacerbations during the trial all patients had access through the investigator to appropriate medications, as medically necessary. To further guarantee the safety of the patients a set of rules leading to withdrawal of patients with severe asthma deterioration was implemented and all procedures and examinations were evaluated for their safety and feasibility in adolescents. Furthermore, an independent Data Safety Monitoring Board was established to monitor safety.

Background therapy:

Patients maintained their background therapy, including ICS in combination with a LABA and/or LTRA and/or sustained release theophylline.

Evidence for comparator: -

Actual start date of recruitment	31 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	Germany: 30
Country: Number of subjects enrolled	Latvia: 57
Country: Number of subjects enrolled	Hungary: 123
Country: Number of subjects enrolled	Bulgaria: 56
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Guatemala: 26

Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Argentina: 67
Country: Number of subjects enrolled	Philippines: 8
Country: Number of subjects enrolled	Ukraine: 88
Country: Number of subjects enrolled	United States: 36
Country: Number of subjects enrolled	South Africa: 24
Worldwide total number of subjects	554
EEA total number of subjects	278

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)	553
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 sites for the management of adolescent patients diagnosed with asthma which ensure the subjects met all inclusion/exclusion criteria. Subjects were not to be randomised to the trial if any entry criteria were violated. Thus, out of 554 enrolled patients, 329 were randomised.

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	Tio R2.5

Arm description:

Inhalation of 2.5mcg tiotropium bromide solution once daily for 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.

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

Dosage and administration details:

2 puffs once daily for a total dose of 2.5 µg that is 1.25 mcg per puff (calculated as free cation, ex mouthpiece, evening dosing) via Respimat inhaler.

Arm title	Tio R5

Arm description:

Inhalation of 5mcg tiotropium bromide solution once daily for 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.

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

Dosage and administration details:

2 puffs once daily for a total dose of 5 µg that is 2.5 mcg per puff (calculated as free cation, ex mouthpiece, evening dosing) via Respimat inhaler.

Arm title	Placebo Respimat

Arm description:

Inhalation of placebo solution once daily for 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.

Arm type	Placebo

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

Dosage and administration details:

Two puffs of a solution via Respimat inhaler once daily in the evening.

Number of subjects in period 1[1]	Tio R2.5	Tio R5	Placebo Respimat
Started	127	130	135
Completed	126	130	132
Not completed	1	0	3
Other reason not defined	1	-	-
Adverse event, non-fatal	-	-	1
Protocol deviation	-	-	2

Notes:

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

Baseline characteristics

Reporting groups	
Reporting group title	Tio R2.5
Reporting group description:	
Inhalation of 2.5mcg tiotropium bromide solution once daily for 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.	
Reporting group title	Tio R5
Reporting group description:	
Inhalation of 5mcg tiotropium bromide solution once daily for 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.	
Reporting group title	Placebo Respimat
Reporting group description:	
Inhalation of placebo solution once daily for 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.	

Reporting group values	Tio R2.5	Tio R5	Placebo Respimat
Number of subjects	127	130	135
Age categorical			
Units: Subjects			
Age continuous			
Treated Set (TS): includes all randomized subjects who were dispensed study medication and were documented to take at least 1 dose of the investigational treatment.			
Units: years			
arithmetic mean	14.4	14.3	14.1
standard deviation	± 1.8	± 1.6	± 1.7
Gender categorical			
Treated Set (TS)			
Units: Subjects			
Female	47	47	56
Male	80	83	79

Reporting group values	Total		
Number of subjects	392		
Age categorical			
Units: Subjects			
Age continuous			
Treated Set (TS): includes all randomized subjects who were dispensed study medication and were documented to take at least 1 dose of the investigational treatment.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Treated Set (TS)			
Units: Subjects			
Female	150		
Male	242		

End points

End points reporting groups

Reporting group title	Tio R2.5
Reporting group description:	
Inhalation of 2.5mcg tiotropium bromide solution once daily for 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.	
Reporting group title	Tio R5
Reporting group description:	
Inhalation of 5mcg tiotropium bromide solution once daily for 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.	
Reporting group title	Placebo Respimat
Reporting group description:	
Inhalation of placebo solution once daily for 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.	

Primary: FEV1 peak0-3h Change From Baseline

End point title	FEV1 peak0-3h Change From Baseline
End point description:	
Change from baseline in peak forced expiratory volume in 1 second within the first 3 hours post dosing (FEV1 peak0-3) measured at week 12. Full Analysis Set (FAS): included all randomized patients who were dispensed study medication and were documented to have taken at least 1 dose of investigational treatment. In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint at week 12 (from MMRM output).	
End point type	Primary
End point timeframe:	
Baseline and 12 weeks	

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126[1]	130[2]	132[3]	
Units: Liter(s)				
least squares mean (standard error)	0.55 (± 0.046)	0.528 (± 0.045)	0.438 (± 0.045)	

Notes:

[1] - Full Analysis Set (FAS)

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week

and baseline*week interactions

The first statistical test is Tio R5 vs Placebo and then Tio R2.5 vs Placebo because it was pre-specified order of hierarchical testing.

Comparison groups	Tio R2.5 v Placebo Respimat
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0457 [5]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.22
Variability estimate	Standard error of the mean
Dispersion value	0.055

Notes:

[4] - Difference calculated as Tio R2.5 minus placebo

[5] - 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:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

The first statistical test is Tio R5 vs Placebo and then Tio R2.5 vs Placebo because it was pre-specified order of hierarchical testing.

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.1039 [7]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.019
upper limit	0.198
Variability estimate	Standard error of the mean
Dispersion value	0.055

Notes:

[6] - Difference calculated as Tio R5 minus placebo

[7] - 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 12.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint at week 12 (from MMRM output).

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126[8]	130[9]	132[10]	
Units: Liters				
least squares mean (standard error)	0.345 (± 0.048)	0.284 (± 0.048)	0.23 (± 0.048)	

Notes:

[8] - FAS

[9] - FAS

[10] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). Model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

The first statistical test is Tio R5 vs Placebo and then Tio R2.5 vs Placebo because it was pre-specified order of hierarchical testing.

Comparison groups	Tio R2.5 v Placebo Respimat
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0509 [12]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.231
Variability estimate	Standard error of the mean
Dispersion value	0.059

Notes:

[11] - Difference calculated as Tio R2.5 minus placebo

[12] - 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:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). Model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

The first statistical test is Tio R5 vs Placebo and then Tio R2.5 vs Placebo because it was pre-specified order of hierarchical testing.

Comparison groups	Tio R5 v Placebo Respimat
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.3605 [14]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.061
upper limit	0.168
Variability estimate	Standard error of the mean
Dispersion value	0.058

Notes:

[13] - Difference calculated as Tio R5 minus placebo

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

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

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

End point description:

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

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint at week 12.

End point type	Secondary

End point timeframe:

Baseline and 10 mins before drug administration and 30 mins, 1 hour (h), 2h, 3h after drug administration at 12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126[15]	130[16]	132[17]	
Units: litre(s)				
least squares mean (standard error)	0.449 (± 0.043)	0.423 (± 0.043)	0.336 (± 0.043)	

Notes:
[15] - FAS
[16] - FAS
[17] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0338
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.217
Variability estimate	Standard error of the mean
Dispersion value	0.053

Statistical analysis title	Placebo vs Tio R5

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0999
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.191

Variability estimate	Standard error of the mean
Dispersion value	0.053

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 AUC0-3h) after 12
weeks of treatment. The AUC was calculated by using the trapezoidal rule divided by the observation time (3h).

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint at week 12.

End point type	Secondary

End point timeframe:

Baseline and 10 mins before drug administration and 30 mins, 1 hour (h), 2h, 3h after drug administration at 12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126[18]	130[19]	132[20]	
Units: litre(s)				
least squares mean (standard error)	0.262 (± 0.047)	0.227 (± 0.046)	0.175 (± 0.045)	

Notes:

[18] - FAS

[19] - FAS

[20] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R2.5 v Placebo Respimat
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1252
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.087

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.198
Variability estimate	Standard error of the mean
Dispersion value	0.057

Statistical analysis title	Tio R5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R5 v Placebo Respimat
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3549
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.058
upper limit	0.163
Variability estimate	Standard error of the mean
Dispersion value	0.056

Secondary: Use of PRN Rescue Medication During the Day change from baseline

End point title	Use of PRN Rescue Medication During the Day change from baseline

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 12.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint at week 12.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124[21]	130[22]	131[23]	
Units: number of puffs of rescue medication				
least squares mean (standard error)	-0.483 (± 0.122)	-0.54 (± 0.12)	-0.482 (± 0.118)	

Notes:

[21] - FAS

[22] - FAS

[23] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R2.5 v Placebo Respimat
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.996
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.301
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.153

Statistical analysis title	Tio R5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R5 v Placebo Respimat
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.703
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.058

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.355
upper limit	0.239
Variability estimate	Standard error of the mean
Dispersion value	0.151

Secondary: Use of PRN Rescue Medication During the Daytime change from baseline

End point title	Use of PRN Rescue Medication During the Daytime change from baseline

End point description:

Change from baseline in the number of puffs of rescue medication (salbutamol/albuterol) used during the daytime based on the weekly mean at week 12.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint at week 12.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124[24]	130[25]	131[26]	
Units: number of puffs of rescue medication				
least squares mean (standard error)	-0.295 (± 0.075)	-0.312 (± 0.073)	-0.262 (± 0.073)	

Notes:

[24] - FAS

[25] - FAS

[26] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R2.5 v Placebo Respimat
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7309
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.032

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.217
upper limit	0.153
Variability estimate	Standard error of the mean
Dispersion value	0.094

Statistical analysis title	Tio R5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R5 v Placebo Respimat
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5954
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.232
upper limit	0.133
Variability estimate	Standard error of the mean
Dispersion value	0.093

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

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

End point description:

Change from baseline in the number of puffs of rescue medication (salbutamol/albuterol) used during the night-time based on the
weekly mean at week 12.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint at week 12.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124[27]	129[28]	131[29]	
Units: number of puffs of rescue medication				
least squares mean (standard error)	-0.092 (± 0.066)	-0.159 (± 0.065)	-0.18 (± 0.064)	

Notes:

[27] - FAS

[28] - FAS

[29] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R2.5 v Placebo Respimat
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2841
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.074
upper limit	0.252
Variability estimate	Standard error of the mean
Dispersion value	0.083

Statistical analysis title	Placebo vs Tio R5

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). The model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.795
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.021

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.182
Variability estimate	Standard error of the mean
Dispersion value	0.082

Secondary: Time to First Severe Asthma Exacerbation During the 12-week treatment period

End point title	Time to First Severe Asthma Exacerbation During the 12-week treatment period

End point description:

Time in days to first severe asthma exacerbation during the 12 week treatment period. 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 an initiation of treatment with systemic corticosteroids for at least 3 days or, in case of ongoing and preexisting systemic corticosteroid therapy, requiring at least doubling of previous daily doses of systemic corticosteroids for at least 3 days.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint during 12 weeks period.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127[30]	130[31]	135[32]	
Units: participant(s)				
cumulative failure	1	2	1	
cumulative censored	126	128	134	

Notes:

[30] - FAS

[31] - FAS

[32] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo

Statistical analysis description:

Cox's proportional regression model with treatment as effect

Comparison groups	Tio R2.5 v Placebo Respimat

Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9671
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	16.95

Statistical analysis title	Tio R5 vs Placebo
Statistical analysis description:	
Cox's proportional regression model with treatment as an effect	
Comparison groups	Tio R5 v Placebo Respimat
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5557
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	22.7

Secondary: Analysis of Time to First Asthma Exacerbation during the 12 week treatment period

End point title	Analysis of Time to First Asthma Exacerbation during the 12 week treatment period

End point description:

Time in days to first asthma exacerbation during the 12 week treatment period. 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.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint during 12 weeks period.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127[33]	130[34]	135[35]	
Units: participant(s)				
cumulative failure	18	15	25	
cumulative censored	109	115	110	

Notes:

[33] - FAS

[34] - FAS

[35] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo
Statistical analysis description: Cox's proportional regression model with treatment as a effect.	
Comparison groups	Tio R2.5 v Placebo Respimat
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3567
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.38

Statistical analysis title	Placebo vs Tio R5
Statistical analysis description: Cox's proportional regression model with treatment as a effect.	
Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1168
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.14

Secondary: Clinically Relevant Abnormalities for Physical Examination, ECG, Vital Signs and Laboratory Tests

End point title	Clinically Relevant Abnormalities for Physical Examination, ECG, Vital Signs and Laboratory Tests

End point description:

Clinically relevant abnormalities for physical examination, ECG, vital signs and laboratory tests. New abnormal findings or worsening
of baseline conditions were reported as adverse events.

End point type	Secondary

End point timeframe:

From first drug administration until 30 days after last drug intake, up to 142 days

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127[36]	130[37]	135[38]	
Units: percentage of subjects with events				
number (not applicable)				
peak expiratory flow rate decrease	9	5	13	
blood glucose decrease	1	0	0	

Notes:

[36] - TS

[37] - TS

[38] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: FVC peak0-3h Change From Baseline

End point title	FVC peak0-3h 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 peak0-3h) after 12 weeks of treatment.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint during 12 weeks period.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126[39]	130[40]	132[41]	
Units: litre(s)				
least squares mean (standard error)	0.37 (± 0.049)	0.342 (± 0.048)	0.279 (± 0.048)	

Notes:

[39] - FAS

[40] - FAS

[41] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). Model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R2.5 v Placebo Respimat
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1264
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.207
Variability estimate	Standard error of the mean
Dispersion value	0.059

Statistical analysis title	Tio R5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). Model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R5 v Placebo Respimat
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2845
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.063

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.053
upper limit	0.179
Variability estimate	Standard error of the mean
Dispersion value	0.059

Secondary: ACQ Total Score Responders

End point title	ACQ Total Score Responders

End point description:

Responder rates based on the ACQ total score after 12 weeks of treatment. Analysis was performed using the following categories and definitions: responder (change from trial baseline ≤-0.5), no change (- 0.5 <change from trial baseline <0.5) and worsening (change from trial baseline ≥0.5) 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.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint at week 12.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127[42]	130[43]	135[44]	
Units: Percentage of participants				
number (not applicable)				
Responder	74.8	73.1	73.3	
No change	22	26.2	23.7	
Worsening	3.1	0.8	3	

Notes:

[42] - FAS

[43] - FAS

[44] - FAS

Statistical analyses

No statistical analyses for this end point

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:

Asthma Control Questionnaire (ACQ) total score measured at week 12. 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.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with

endpoint at week 12.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126[45]	130[46]	132[47]	
Units: unit of ACQ total score				
least squares mean (standard error)	1.292 (± 0.066)	1.27 (± 0.065)	1.234 (± 0.064)	

Notes:

[45] - FAS

[46] - FAS

[47] - FAS

Statistical analyses

Statistical analysis title	Placebo vs Tio R2.5

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). Model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Placebo Respimat v Tio R2.5
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4762
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.102
upper limit	0.219
Variability estimate	Standard error of the mean
Dispersion value	0.082

Statistical analysis title	Tio R5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). Model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R5 v Placebo Respimat

Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6558
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.123
upper limit	0.196
Variability estimate	Standard error of the mean
Dispersion value	0.081

Secondary: Control of Asthma as Assessed by ACQ6 Score.

End point title	Control of Asthma as Assessed by ACQ6 Score.

End point description:

Asthma Control Questionnaire (ACQ) score measured at week 12. 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. ACQ6 score was calculated as the mean of the responses to the first 6 questions of the ACQ.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint at week 12.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	126[48]	130[49]	132[50]	
Units: unit on an ACQ6 scale				
least squares mean (standard error)	1.262 (± 0.071)	1.197 (± 0.07)	1.144 (± 0.069)	

Notes:

[48] - FAS

[49] - FAS

[50] - FAS

Statistical analyses

Statistical analysis title	Tio R2.5 vs Placebo

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). Model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Tio R2.5 v Placebo Respimat

Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1819
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.055
upper limit	0.292
Variability estimate	Standard error of the mean
Dispersion value	0.088

Statistical analysis title	Placebo vs Tio R5

Statistical analysis description:

A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM). Model was adjusted for treatment, country, week, baseline, treatment*week and baseline*week interactions

Comparison groups	Placebo Respimat v Tio R5
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5448
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.119
upper limit	0.226
Variability estimate	Standard error of the mean
Dispersion value	0.088

Secondary: ACQ6 Score Responders

End point title	ACQ6 Score Responders

End point description:

Responder rates based on the ACQ6 score after 12 weeks of treatment. Analysis was performed using the following categories and
definitions: responder (change from trial baseline <= -0.5), no change (-0.5 < change from trial baseline <0.5) and worsening (change from trial baseline >= 0.5). 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. ACQ6 was calculated as the mean of the responses to the first 6 questions of the ACQ.

In FAS we have 127, 130, 135 patients. Currently reported numbers are numbers of patients with endpoint at week 12.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Tio R2.5	Tio R5	Placebo Respimat	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127[51]	130[52]	135[53]	
Units: percentage of participants				
number (not applicable)				
Responder	74	74.6	74.1	
No change	19.7	23.1	23.7	
Worsening	6.3	2.3	2.2	

Notes:

[51] - FAS

[52] - FAS

[53] - FAS

Statistical analyses

No statistical analyses for this end point

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 142 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 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.	
Reporting group title	Tio R2.5
Reporting group description:	
Inhalation of 2.5mcg tiotropium bromide solution once daily for 12 weeks delivered by the Respimat Inhaler, as add on therapy on top of usual care.	
Reporting group title	Tio R5
Reporting group description:	
Inhalation of 5mcg tiotropium bromide solution once daily for 12 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	0 / 135 (0.00%)	1 / 127 (0.79%)	2 / 130 (1.54%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 135 (0.00%)	0 / 127 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 135 (0.00%)	0 / 127 (0.00%)	1 / 130 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis atopic			

subjects affected / exposed	0 / 135 (0.00%)	1 / 127 (0.79%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pyoderma			
subjects affected / exposed	0 / 135 (0.00%)	1 / 127 (0.79%)	0 / 130 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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	23 / 135 (17.04%)	23 / 127 (18.11%)	16 / 130 (12.31%)
Investigations			
Peak expiratory flow rate decreased			
subjects affected / exposed	13 / 135 (9.63%)	9 / 127 (7.09%)	5 / 130 (3.85%)
occurrences (all)	19	17	12
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	14 / 135 (10.37%)	14 / 127 (11.02%)	14 / 130 (10.77%)
occurrences (all)	19	25	16

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2011	This amendment introduced changes to clarify wording and study procedures/data to be collected, to introduce some administrative changes (e.g. information regarding the planned number of participating countries was updated), and to correct minor typographical errors and inconsistencies between the synopsis, study flow charts, the eCRF, and the text of the protocol, or to align procedures in this protocol with the other tiotropium studies and update the information and risk assessment for tiotropium based on newly available data. It was also clarified that patients could return to their pre-study medication during the follow-up period.Entrance criteria were amended as noted in Section 9.3. Of particular note, to take into account that the trial population spanned a wide range from a 12-year-old child to a 17-year old near-adult, showing enormous heterogeneity with regard to stature, body weight, development status, etc, inclusion criterion no. 4 (dose recommendations for ICS) was adjusted to avoid a bias toward the upper age range of patients.
20 February 2012	This amendment introduced changes to clarify wording and study procedures/data to be collected, to introduce some administrative changes, and to correct minor typographical errors and inconsistencies between the synopsis, study flow charts, the eCRF, and the text of the protocol, or to align procedures in this protocol with the other tiotropium studies. The text was also amended to update information on tiotropium based on recently completed trials and/or recently published data. Rather than specify the number of countries involved in the study, the text was revised to describe this as a multinational study. Entrance criteria were amended as noted in Section 9.3. A significant AE was defined, as follows: hepatic injury defined by the following alterations of liver parameters: an elevation of AST and/or ALT >3 fold ULN combined with an elevation of total bilirubin >2 fold ULN measured in the same blood draw sample. Information was provided to clarify recording of asthma exacerbations as AEs at a withdrawal or follow-up visit. There was a change in the sample size calculation, as a result of which the numbers of patients to be randomised was changed from 64 per treatment group to 125. This was required based on an update of the expected standard deviation for the primary endpoint FEV1 peak 0-3h 300 mL to 420 mL. The planned number of centres was increased from 40 to 80-90 following the increase in the planned sample size.
28 February 2013	This amendment introduced changes to clarify wording and study procedures/data to be collected, to introduce some administrative changes (including a change in the Coordinating Investigator), and to correct minor typographical errors and inconsistencies between the synopsis, study flow charts, the eCRF (including the addition of an eCRF to capture data from the Respimat® dose indicator), and the text of the protocol, or to align procedures in this protocol with the other tiotropium studies. The text was also amended to update information on tiotropium based on recently completed trials and/or recently published data. Entrance criteria were amended as noted in Section 9.3. In addition, there was a change in the sample size description, as a result of which the numbers of patients to be randomised was changed from 125 per treatment group to a total of 375 to clarify that recruitment would continue until overall 375 patients had been randomised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported