Clinical trial results:
A Phase II Randomised, Double-blind, Placebo-controlled, Incomplete Crossover Trial With 4-week Treatment Periods to Evaluate Efficacy and Safety of Tiotropium Inhalation Solution (Doses of 1.25 µg, 2.5 µg and 5 µg) Delivered Via Respimat® Inhaler Once Daily in the Evening in Adolescents (12 to 17 Yrs Old) With Moderate Persistent Asthma

Summary

EudraCT number	2009-017745-55
Trial protocol	DE SI LT LV
Global end of trial date	11 April 2011

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	17 May 2015

Trial information

Trial identification

Sponsor protocol code	205.424

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01122680
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim Pharma GmbH & Co. KG
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, +1 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	23 May 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 March 2011
Global end of trial reached?	Yes
Global end of trial date	11 April 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the efficacy and safety of tiotropium 1.25 µg (2 actuations of 0.625 µg), tiotropium 2.5 µg (2 actuations of 1.25 µg) and tiotropium 5 µg (2 actuations of 2.5 µg) once daily in the evening delivered by the Respimat inhaler in adolescents (12 to 17 years) with moderate persistent asthma, compared to placebo and on top of maintenance therapy with an inhaled corticosteroid controller medication. It is a randomised, double-blind, placebo-controlled Phase II trial with incomplete cross-over design. Patients need to be still symptomatic, i. e. not fully controlled with their maintenance treatment.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be randomised to trial treatment. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Salbutamol, short-acting β2-adrenergic agonist (SABA), was provided as rescue medication for use as necessary during the trial.

Background therapy:

Patients maintained their background therapy , including inhaled corticosteroids (ICS).

Evidence for comparator: -

Actual start date of recruitment	17 June 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Lithuania: 43
Country: Number of subjects enrolled	Slovenia: 6
Country: Number of subjects enrolled	United States: 25
Country: Number of subjects enrolled	Latvia: 49
Country: Number of subjects enrolled	Germany: 16
Worldwide total number of subjects	139
EEA total number of subjects	114

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)	0
Adolescents (12-17 years)	139
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In this incomplete crossover design, 105 patients were randomised to one of four sequences (in general terms, ABC, BDA, CAD or DCB). Whilst there were 4 possible treatments, A, B, C and D, each patient would receive a maximum of 3 different treatments. Hence, approximately 75 patients would receive each of A, B, C and D at any time point.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Period 1 (4 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Tio R5/Placebo/Tio R1.25

Arm description:

Patients treated with Tiotropium 5 µg in period I, with a matching Placebo in period II and with Tiotropium 1.25 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium bromide/Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio R5 - 2 puffs once daily for a total dose of 5 µg (evening dosing)
Placebo - 2 puffs once daily (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 µg (evening dosing)

Arm title	Tio R1.25/Tio R5/Tio R2.5

Arm description:

Patients treated with Tiotropium 1.25 µg in period I, with Tiotropium 5 µg in period II and with Tiotropium 2.5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
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:

Tio R1.25 - 2 puffs once daily for a total dose of 1.25 µg (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 µg (evening dosing)

Arm title	Placebo/Tio R2.5/Tio R5

Arm description:

Patients treated with a matching Placebo in period I, with Tiotropium 2.5 µg in period II and with Tiotropium 5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Placebo/Tiotropium bromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Placebo - 2 puffs once daily (evening dosing)
Tio R2.5 - 2 puffs once daily for a total dose of 2.5 µg (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 µg (evening dosing)

Arm title	Tio R2.5/Tio R1.25/Placebo

Arm description:

Patients treated with Tiotropium 2.5 µg in period I, with Tiotropium 1.25 µg in period II and with a matching Placebo in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium bromide/Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio R2.5 - 2 puffs once daily for a total dose of 2.5 µg (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 µg (evening dosing)
Placebo - 2 puffs once daily (evening dosing)

Number of subjects in period 1	Tio R5/Placebo/Tio R1.25	Tio R1.25/Tio R5/Tio R2.5	Placebo/Tio R2.5/Tio R5
Started	29	26	26
Completed	26	25	26
Not completed	3	1	0
Adverse event, non-fatal	1	-	-
Non-compliant	1	-	-
Other	1	1	-

Number of subjects in period 1	Tio R2.5/Tio R1.25/Placebo
Started	24

Completed	24
Not completed	0
Adverse event, non-fatal	-
Non-compliant	-
Other	-

Period 2

Period 2 title	Period 2 (4 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Tio R5/Placebo/Tio R1.25

Arm description:

Patients treated with Tiotropium 5 µg in period I, with a matching Placebo in period II and with Tiotropium 1.25 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium bromide/Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio R5 - 2 puffs once daily for a total dose of 5 µg (evening dosing)
Placebo - 2 puffs once daily (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 µg (evening dosing)

Arm title	Tio R1.25/Tio R5/Tio R2.5

Arm description:

Patients treated with Tiotropium 1.25 µg in period I, with Tiotropium 5 µg in period II and with Tiotropium 2.5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
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:

Tio R1.25 - 2 puffs once daily for a total dose of 1.25 µg (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 µg (evening dosing)
Tio R2.5 - 2 puffs once daily for a total dose of 2.5 µg (evening dosing)

Arm title	Placebo/Tio R2.5/Tio R5

Arm description:

Patients treated with a matching Placebo in period I, with Tiotropium 2.5 µg in period II and with Tiotropium 5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Placebo/Tiotropium bromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Placebo - 2 puffs once daily (evening dosing)
Tio R2.5 - 2 puffs once daily for a total dose of 2.5 µg (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 µg (evening dosing)

Arm title	Tio R2.5/Tio R1.25/Placebo

Arm description:

Patients treated with Tiotropium 2.5 µg in period I, with Tiotropium 1.25 µg in period II and with a matching Placebo in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium bromide/Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio R2.5 - 2 puffs once daily for a total dose of 2.5 µg (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 µg (evening dosing)
Placebo - 2 puffs once daily (evening dosing)

Number of subjects in period 2	Tio R5/Placebo/Tio R1.25	Tio R1.25/Tio R5/Tio R2.5	Placebo/Tio R2.5/Tio R5
Started	26	25	26
Completed	25	25	26
Not completed	1	0	0
Other	1	-	-
Non-compliant	-	-	-

Number of subjects in period 2	Tio R2.5/Tio R1.25/Placebo
Started	24
Completed	23
Not completed	1
Other	-
Non-compliant	1

Period 3

Period 3 title	Period 3 (4 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Tio R5/Placebo/Tio R1.25

Arm description:

Patients treated with Tiotropium 5 µg in period I, with a matching Placebo in period II and with Tiotropium 1.25 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium bromide/Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio R5 - 2 puffs once daily for a total dose of 5 µg (evening dosing)
Placebo - 2 puffs once daily (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 µg (evening dosing)

Arm title	Tio R1.25/Tio R5/Tio R2.5

Arm description:

Patients treated with Tiotropium 1.25 µg in period I, with Tiotropium 5 µg in period II and with Tiotropium 2.5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
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:

Tio R1.25 - 2 puffs once daily for a total dose of 1.25 µg (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 µg (evening dosing)
Tio R2.5 - 2 puffs once daily for a total dose of 2.5 µg (evening dosing)

Arm title	Placebo/Tio R2.5/Tio R5

Arm description:

Patients treated with a matching Placebo in period I, with Tiotropium 2.5 µg in period II and with Tiotropium 5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence

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

Dosage and administration details:

Placebo - 2 puffs once daily (evening dosing)
Tio R2.5 - 2 puffs once daily for a total dose of 2.5 µg (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 µg (evening dosing)

Arm title	Tio R2.5/Tio R1.25/Placebo

Arm description:

Patients treated with Tiotropium 2.5 µg in period I, with Tiotropium 1.25 µg in period II and with a matching Placebo in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium bromide/Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio R2.5 - 2 puffs once daily for a total dose of 2.5 µg (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 µg (evening dosing)
Placebo - 2 puffs once daily (evening dosing)

Number of subjects in period 3	Tio R5/Placebo/Tio R1.25	Tio R1.25/Tio R5/Tio R2.5	Placebo/Tio R2.5/Tio R5
Started	25	25	26
Completed	24	24	26
Not completed	1	1	0
Adverse event, non-fatal	1	-	-
Consent withdrawn	-	1	-

Number of subjects in period 3	Tio R2.5/Tio R1.25/Placebo
Started	23
Completed	23
Not completed	0
Adverse event, non-fatal	-
Consent withdrawn	-

Period 4

Period 4 title	Overall trial (Treatment period)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Placebo once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.

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

Dosage and administration details:

2 puffs once daily (evening dosing)

Arm title	Tio R1.25

Arm description:

Tiotropium 1.25 microgram once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.

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 1.25 µg (evening dosing)

Arm title	Tio R2.5

Arm description:

Tiotropium 2.5 microgram once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.

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 (evening dosing)

Arm title	Tio R5

Arm description:

Tiotropium 5 microgram once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.

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 (evening dosing)

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Since the baseline characteristics are presented for the overall trial and at least one defined period had to be selected as a baseline period, overall trial (treatment period) was used to report the baseline characteristics.

Number of subjects in period 4	Placebo	Tio R1.25	Tio R2.5
Started	75	75	75
Completed	74	72	74
Not completed	1	3	1
Adverse event, non-fatal	-	1	-
Other	1	1	-
Non-compliant	-	1	-
Consent withdrawn	-	-	1

Number of subjects in period 4	Tio R5
Started	80
Completed	77
Not completed	3
Adverse event, non-fatal	1
Other	1
Non-compliant	1
Consent withdrawn	-

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall trial (Treatment period)
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects 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.

Reporting group values	Overall trial (Treatment period)	Total	
Number of subjects	105	105	
Age categorical Units: Subjects			

Age Continuous | Units: years			
arithmetic mean	14		
standard deviation	± 1.5	-	
Gender, Male/Female Units: Number			
Female	38	38	
Male	67	67	
Forced expiratory volume in 1s (FEV1) Units: Litre			
arithmetic mean	2.742		
standard deviation	± 0.697	-	

End points

End points reporting groups

Reporting group title	Tio R5/Placebo/Tio R1.25

Reporting group description:

Patients treated with Tiotropium 5 µg in period I, with a matching Placebo in period II and with Tiotropium 1.25 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Tio R1.25/Tio R5/Tio R2.5

Reporting group description:

Patients treated with Tiotropium 1.25 µg in period I, with Tiotropium 5 µg in period II and with Tiotropium 2.5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Placebo/Tio R2.5/Tio R5

Reporting group description:

Patients treated with a matching Placebo in period I, with Tiotropium 2.5 µg in period II and with Tiotropium 5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Tio R2.5/Tio R1.25/Placebo

Reporting group description:

Patients treated with Tiotropium 2.5 µg in period I, with Tiotropium 1.25 µg in period II and with a matching Placebo in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Tio R5/Placebo/Tio R1.25

Reporting group description:

Patients treated with Tiotropium 5 µg in period I, with a matching Placebo in period II and with Tiotropium 1.25 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Tio R1.25/Tio R5/Tio R2.5

Reporting group description:

Patients treated with Tiotropium 1.25 µg in period I, with Tiotropium 5 µg in period II and with Tiotropium 2.5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Placebo/Tio R2.5/Tio R5

Reporting group description:

Patients treated with a matching Placebo in period I, with Tiotropium 2.5 µg in period II and with Tiotropium 5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Tio R2.5/Tio R1.25/Placebo

Reporting group description:

Patients treated with Tiotropium 2.5 µg in period I, with Tiotropium 1.25 µg in period II and with a matching Placebo in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Tio R5/Placebo/Tio R1.25

Reporting group description:

Patients treated with Tiotropium 5 µg in period I, with a matching Placebo in period II and with Tiotropium 1.25 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Tio R1.25/Tio R5/Tio R2.5

Reporting group description:

Patients treated with Tiotropium 1.25 µg in period I, with Tiotropium 5 µg in period II and with Tiotropium 2.5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Placebo/Tio R2.5/Tio R5

Reporting group description:

Patients treated with a matching Placebo in period I, with Tiotropium 2.5 µg in period II and with Tiotropium 5 µg in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Tio R2.5/Tio R1.25/Placebo

Reporting group description:

Patients treated with Tiotropium 2.5 µg in period I, with Tiotropium 1.25 µg in period II and with a matching Placebo in period III. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off-treatment periods) between treatments.

Reporting group title	Placebo

Reporting group description:

Placebo once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.

Reporting group title	Tio R1.25

Reporting group description:

Tiotropium 1.25 microgram once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.

Reporting group title	Tio R2.5

Reporting group description:

Tiotropium 2.5 microgram once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.

Reporting group title	Tio R5

Reporting group description:

Tiotropium 5 microgram once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.

Primary: Forced Expiratory Volume (FEV1) peak (0-3h) response

End point title	Forced Expiratory Volume (FEV1) peak (0-3h) response

End point description:

The FEV1 peak (0-3h) response is determined at the end of the 4 week treatment period. This is the difference between the maximum FEV1 measured within the first 3 hours post dosing and the FEV1 baseline measurement. Analysis adjusted for treatment, period, patient and baseline using a mixed model. The analysis set used for this analysis was full analysis set (FAS) reduced to patients with non-missing FEV1 data. The FAS is defined as patients randomised, treated, with baseline data and at least one on-treatment efficacy measurement after 4 weeks on treatment within a period.

End point type	Primary

End point timeframe:

Baseline and 4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[1]	73[2]	74[3]	77[4]
Units: Litre				
least squares mean (standard error)	0.489 (± 0.047)	0.556 (± 0.047)	0.546 (± 0.047)	0.602 (± 0.046)

Notes:

[1] - Full Analysis Set (FAS) reduced to patients with non-missing FEV1 data.

[2] - Full Analysis Set (FAS) reduced to patients with non-missing FEV1 data.

[3] - Full Analysis Set (FAS) reduced to patients with non-missing FEV1 data.

[4] - Full Analysis Set (FAS) reduced to patients with non-missing FEV1 data.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Mixed model repeated measures (MMRM) was used. This MMRM model includes treatment, period and baseline as fixed effects, and patient as a random effect. Difference was calculated as Tio R5 minus Placebo.

The actual number of subjects analyzed is 104. As this is an incomplete cross over study and arms are not mutually exclusive, the pre-specified, by the system automatically calculated number that is provided in the statistical analysis below (151) does not reflect the actual number.

Comparison groups	Placebo v Tio R5
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0043 [5]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.036
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.039

Notes:

[5] - First step of closed testing procedure, where the active treatments are compared to placebo. If this statisical test is significant at the 0.05 alpha level then proceed to comparison of the next lower dose to placebo.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Mixed model repeated measures (MMRM) was used. This MMRM model includes treatment, period and baseline as fixed effects, and patient as a random effect. Difference was calculated as Tio R2.5 minus Placebo.

The actual number of subjects analyzed is 104. As this is an incomplete cross over study and arms are not mutually exclusive, the pre-specified, by the system automatically calculated number that is provided in the statistical analysis below (148) does not reflect the actual number.

Comparison groups	Placebo v Tio R2.5

Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1484 [6]
Method	Mixed effect repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.135
Variability estimate	Standard error of the mean
Dispersion value	0.039

Notes:

[6] - Second step of closed testing procedure. If this statisical test significant at the 0.05 alpha level then proceed to comparison of the next lower dose to placebo.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Mixed model repeated measures (MMRM) was used. This MMRM model includes treatment, period and baseline as fixed effects, and patient as a random effect. Difference was calculated as Tio R1.25 minus Placebo.

The actual number of subjects analyzed is 104. As this is an incomplete cross over study and arms are not mutually exclusive, the pre-specified, by the system automatically calculated number that is provided in the statistical analysis below (147) does not reflect the actual number.

Comparison groups	Tio R1.25 v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0664 [7]
Method	Mixed effect repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.138
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[7] - This test is considered as descriptive.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Mixed model repeated measures (MMRM) was used. This MMRM model includes treatment, period and baseline as fixed effects, and patient as a random effect. Difference was calculated as Tio R5 minus Tio R1.25.

The actual number of subjects analyzed is 104. As this is an incomplete cross over study and arms are not mutually exclusive, the pre-specified, by the system automatically calculated number that is provided in the statistical analysis below (150) does not reflect the actual number.

Comparison groups	Tio R1.25 v Tio R5

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	equivalence
Method	Mixed effect repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.124
Variability estimate	Standard error of the mean
Dispersion value	0.039

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Mixed model repeated measures (MMRM) was used. This MMRM model includes treatment, period and baseline as fixed effects, and patient as a random effect. Difference was calculated as Tio R5 minus Tio R2.5.

The actual number of subjects analyzed is 104. As this is an incomplete cross over study and arms are not mutually exclusive, the pre-specified, by the system automatically calculated number that is provided in the statistical analysis below (151) does not reflect the actual number.

Comparison groups	Tio R2.5 v Tio R5
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	equivalence
Method	Mixed effect repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.126
Variability estimate	Standard error of the mean
Dispersion value	0.036

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Mixed model repeated measures (MMRM) was used. This MMRM model includes treatment, period and baseline as fixed effects, and patient as a random effect. Difference was calculated as Tio R2.5 minus Tio R1.25.

The actual number of subjects analyzed is 104. As this is an incomplete cross over study and arms are not mutually exclusive, the pre-specified, by the system automatically calculated number that is provided in the statistical analysis below (147) does not reflect the actual number.

Comparison groups	Tio R2.5 v Tio R1.25

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	equivalence
Method	Mixed effect repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.088
upper limit	0.069
Variability estimate	Standard error of the mean
Dispersion value	0.04

Secondary: Trough FEV1 response

End point title	Trough FEV1 response

End point description:

The trough FEV1 is defined as the pre-dose FEV1 measured just prior to the last administration of randomised treatment. Response was defined as the change from baseline at the end of the 4-week treatment period. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[8]	73[9]	74[10]	77[11]
Units: Litre				
least squares mean (standard error)	0.292 (± 0.045)	0.384 (± 0.045)	0.353 (± 0.045)	0.442 (± 0.045)

Notes:

[8] - FAS with non-missing FEV1 data.

[9] - FAS with non-missing FEV1 data.

[10] - FAS with non-missing FEV1 data.

[11] - FAS with non-missing FEV1 data.

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 Area under the curve from 0 to 3 h (AUC0-3h) response

End point title	FEV1 Area under the curve from 0 to 3 h (AUC0-3h) response

End point description:

FEV1 (AUC0-3h) will be calculated as the area under the curve from 0 to 3 hours using the trapezoidal rule divided by the observation time (3 hours) to report in litres. Response was defined as the change from baseline at the end of the 4-week treatment period. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[12]	73[13]	74[14]	77[15]
Units: Litre				
least squares mean (standard error)	0.363 (± 0.045)	0.455 (± 0.045)	0.434 (± 0.045)	0.497 (± 0.045)

Notes:

[12] - FAS with non-missing FEV1 data.

[13] - FAS with non-missing FEV1 data.

[14] - FAS with non-missing FEV1 data.

[15] - FAS with non-missing FEV1 data.

Statistical analyses

No statistical analyses for this end point

Secondary: FEV1 individual measurements response at each time-point

End point title	FEV1 individual measurements response at each time-point

End point description:

Individual FEV1 measurements at each time-point ("personal best"). Response was defined as the change from baseline at the end of the 4-week treatment period. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks (10 min pre-dose, 30 min, 1,2,3 hours (hr) post-dose)

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[16]	73[17]	74[18]	77[19]
Units: Litre				
least squares mean (standard error)				
Timepoint -0:10 hr response	0.292 (± 0.045)	0.384 (± 0.045)	0.353 (± 0.045)	0.442 (± 0.045)
Timepoint 0:30 hr response	0.337 (± 0.047)	0.456 (± 0.047)	0.407 (± 0.047)	0.486 (± 0.047)
Timepoint 1:00 hr response	0.353 (± 0.048)	0.456 (± 0.048)	0.416 (± 0.048)	0.505 (± 0.047)
Timepoint 2:00 hr response	0.394 (± 0.047)	0.467 (± 0.048)	0.453 (± 0.047)	0.501 (± 0.047)
Timepoint 3:00 hr response	0.396 (± 0.048)	0.467 (± 0.048)	0.489 (± 0.048)	0.497 (± 0.047)

Notes:

[16] - FAS with non-missing FEV1 data.

[17] - FAS with non-missing FEV1 data.

[18] - FAS with non-missing FEV1 data.

[19] - FAS with non-missing FEV1 data.

Statistical analyses

No statistical analyses for this end point

Secondary: Forced Vital Capacity (FVC) peak (0-3h) response

End point title	Forced Vital Capacity (FVC) peak (0-3h) response

End point description:

The FVC peak (0-3h) response is determined at the end of the 4 week treatment period. This is the difference between the maximum FVC measured within the first 3 hours post dosing and the FVC baseline measurement. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[20]	73[21]	74[22]	77[23]
Units: Litre				
least squares mean (standard error)	0.546 (± 0.049)	0.554 (± 0.049)	0.554 (± 0.048)	0.548 (± 0.048)

Notes:

[20] - FAS with non-missing FVC data.

[21] - FAS with non-missing FVC data.

[22] - FAS with non-missing FVC data.

[23] - FAS with non-missing FVC data.

Statistical analyses

No statistical analyses for this end point

Secondary: FVC Trough response

End point title	FVC Trough response

End point description:

The trough FVC response is defined as the pre-dose FVC measured just prior to the last administration of randomised treatment. Response was defined as the change from baseline at the end of the 4-week treatment period. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[24]	73[25]	74[26]	77[27]
Units: Litre				
least squares mean (standard error)	0.357 (± 0.047)	0.375 (± 0.047)	0.381 (± 0.047)	0.4 (± 0.047)

Notes:

[24] - FAS with non-missing FVC data.

[25] - FAS with non-missing FVC data.

[26] - FAS with non-missing FVC data.

[27] - FAS with non-missing FVC data.

Statistical analyses

No statistical analyses for this end point

Secondary: FVC Area under the curve from 0 to 3 h (AUC0-3h) response

End point title	FVC Area under the curve from 0 to 3 h (AUC0-3h) response

End point description:

FVC (AUC0-3h) will be calculated as the area under the curve from 0 to 3 hours using the trapezoidal rule divided by the observation time (3 hours) to report in litres. Response was defined as the change from baseline at the end of the 4-week treatment period. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[28]	73[29]	74[30]	77[31]
Units: Litre				
least squares mean (standard error)	0.413 (± 0.046)	0.441 (± 0.046)	0.417 (± 0.045)	0.429 (± 0.045)

Notes:

[28] - FAS with non-missing FVC data.

[29] - FAS with non-missing FVC data.

[30] - FAS with non-missing FVC data.

[31] - FAS with non-missing FVC data.

Statistical analyses

No statistical analyses for this end point

Secondary: FVC individual measurements at each time-point

End point title	FVC individual measurements at each time-point

End point description:

Individual FVC measurements at each time-point ("personal best"). Response was defined as the change from baseline at the end of the 4-week treatment period. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks (10 min pre-dose, 30 min, 1,2,3 hours post-dose)

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[32]	73[33]	74[34]	77[35]
Units: Litre				
least squares mean (standard error)				
Timepoint -0:10 hr response	0.357 (± 0.047)	0.375 (± 0.047)	0.381 (± 0.047)	0.4 (± 0.047)
Timepoint 0:30 hr response	0.397 (± 0.049)	0.434 (± 0.049)	0.394 (± 0.049)	0.409 (± 0.049)
Timepoint 1:00 hr response	0.417 (± 0.049)	0.443 (± 0.05)	0.387 (± 0.049)	0.448 (± 0.049)
Timepoint 2:00 hr response	0.429 (± 0.048)	0.438 (± 0.048)	0.444 (± 0.048)	0.423 (± 0.048)
Timepoint 3:00 hr response	0.43 (± 0.048)	0.461 (± 0.048)	0.454 (± 0.048)	0.456 (± 0.048)

Notes:

[32] - FAS with non-missing FVC data.

[33] - FAS with non-missing FVC data.

[34] - FAS with non-missing FVC data.

[35] - FAS with non-missing FVC data.

Statistical analyses

No statistical analyses for this end point

Secondary: Forced expiratory flow (FEF) 25-75% individual measurements response at each time point

End point title	Forced expiratory flow (FEF) 25-75% individual measurements response at each time point

End point description:

FEF 25-75% is the mean forced expiratory flow between 25% and 75% of the FVC determined at the end of the 4-week treatment period. This is often referred to as the maximum midexpiratory flow. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks (10 min pre-dose, 30 min, 1,2,3 hours post-dose)

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49[36]	47[37]	47[38]	50[39]
Units: Litre				
least squares mean (standard error)				
Timepoint -0:10 hr response	0.242 (± 0.081)	0.533 (± 0.082)	0.38 (± 0.082)	0.566 (± 0.08)
Timepoint 0:30 hr response	0.268 (± 0.083)	0.643 (± 0.084)	0.513 (± 0.084)	0.647 (± 0.082)

Timepoint 1:00 hr response	0.321 (± 0.087)	0.655 (± 0.087)	0.569 (± 0.087)	0.641 (± 0.086)
Timepoint 2:00 hr response	0.357 (± 0.088)	0.678 (± 0.089)	0.607 (± 0.089)	0.622 (± 0.087)
Timepoint 3:00 hr response	0.329 (± 0.083)	0.662 (± 0.084)	0.616 (± 0.084)	0.62 (± 0.083)

Notes:

[36] - FAS with non-missing FEF data

[37] - FAS with non-missing FEF data

[38] - FAS with non-missing FEF data

[39] - FAS with non-missing FEF data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean morning peak expiratory flow (PEF) response

End point title	Mean morning peak expiratory flow (PEF) response

End point description:

Mean morning PEF assessed by patients at home. Response was defined as the change from baseline based on the weekly mean of the last week of treatment for each treatment period. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73[40]	75[41]	73[42]	79[43]
Units: Litre/min				
least squares mean (standard error)	7.267 (± 6.152)	18.613 (± 6.118)	23.185 (± 6.146)	20.491 (± 6.031)

Notes:

[40] - FAS with non-missing morning PEF data

[41] - FAS with non-missing morning PEF data

[42] - FAS with non-missing morning PEF data

[43] - FAS with non-missing morning PEF data

Statistical analyses

No statistical analyses for this end point

Secondary: Mean evening PEF response

End point title	Mean evening PEF response

End point description:

Mean evening PEF assessed by patients at home. Response was defined as the change from baseline based on the weekly mean of the last week of treatment for each treatment period. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73[44]	74[45]	75[46]	79[47]
Units: Litre/min				
least squares mean (standard error)	-0.552 (± 6.098)	5.985 (± 6.089)	18.971 (± 6.043)	16.565 (± 5.97)

Notes:

[44] - FAS with non-missing evening PEF data

[45] - FAS with non-missing evening PEF data

[46] - FAS with non-missing evening PEF data

[47] - FAS with non-missing evening PEF data

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the number of puffs of rescue medication per day

End point title	Change from baseline in the number of puffs of rescue medication per day

End point description:

Mean number of inhalations (puffs) of unscheduled rescue salbutamol therapy during whole day. Response was defined as change from baseline based on the weekly mean of the last week of treatment for each treatment periodAnalysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73[48]	73[49]	73[50]	79[51]
Units: Puffs/day				
least squares mean (standard error)	-0.412 (± 0.155)	-0.635 (± 0.156)	-0.521 (± 0.154)	-0.528 (± 0.151)

Notes:

[48] - FAS with non-missing data for rescue medication

[49] - FAS with non-missing data for rescue medication

[50] - FAS with non-missing data for rescue medication

[51] - FAS with non-missing data for rescue medication

Statistical analyses

No statistical analyses for this end point

Secondary: Control of asthma as assessed by Asthma control questionnaire (ACQ)

End point title	Control of asthma as assessed by Asthma control questionnaire

	(ACQ)

End point description:

ACQ is a questionnaire consisting of a seven point Likert scale ranging from 0 to 6, whereby 0 represents good control and 6 represents poor control of asthma. The scale describes the frequency and severity of asthma symptoms. This endpoint was determined at the end of each 4-week treatment period. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74[52]	73[53]	74[54]	77[55]
Units: Units on a scale				
least squares mean (standard error)	1.371 (± 0.078)	1.189 (± 0.079)	1.366 (± 0.078)	1.287 (± 0.078)

Notes:

[52] - FAS with non-missing ACQ data

[53] - FAS with non-missing ACQ data

[54] - FAS with non-missing ACQ data

[55] - FAS with non-missing ACQ data

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean number of nighttime awakenings

End point title	Change from baseline in mean number of nighttime awakenings

End point description:

Mean number of nighttime awakenings due to asthma symptoms as assessed by patients eDiary incorporated in the AM3® device. Response was defined as change from baseline based on the weekly mean of the last week of treatment for each treatment period. Analysis adjusted for treatment, period, patient and baseline using a mixed model.

End point type	Secondary

End point timeframe:

Baseline and 4 weeks

End point values	Placebo	Tio R1.25	Tio R2.5	Tio R5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73[56]	75[57]	73[58]	79[59]
Units: Night awakenings per week				
least squares mean (standard error)	-0.086 (± 0.03)	-0.027 (± 0.03)	-0.074 (± 0.03)	-0.066 (± 0.029)

Notes:

[56] - FAS with non-missing data for nighttime awakenings

[57] - FAS with non-missing data for nighttime awakenings

[58] - FAS with non-missing data for nighttime awakenings
[59] - FAS with non-missing data for nighttime awakenings

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 4 weeks + 30 days if in last period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.	
Reporting group title	Tio R1.25
Reporting group description: Tiotropium 1.25 microgram once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.	
Reporting group title	Tio R2.5
Reporting group description: Tiotropium 2.5 microgram once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.	
Reporting group title	Tio R5
Reporting group description: Tiotropium 5 microgram once daily (QD) in the evening delivered by the Respimat® inhaler, on top on maintenance therapy with an inhaled corticosteroid controller medication.	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Although non-serious adverse events were reported, the 5% threshold wasn't reached on a preferred term level.

Serious adverse events	Placebo	Tio R1.25	Tio R2.5
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 75 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Presyncope			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
H1N1 influenza			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 75 (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
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 75 (0.00%)	1 / 75 (1.33%)	0 / 75 (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

Serious adverse events	Tio R5		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 80 (1.25%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Presyncope			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
H1N1 influenza			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia mycoplasmal			

subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	Tio R1.25	Tio R2.5
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 75 (0.00%)	0 / 75 (0.00%)	0 / 75 (0.00%)

Non-serious adverse events	Tio R5		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 80 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2010	Flowcharts, inclusion criterion 4, instructions for use of the AM3® device and instructions for 24 h lung function testing was revised for consistency, practicality, and clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported