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 delivered via Respimat® inhaler once daily in the evening in children 6 to 11 years old with moderate persistent asthma.

Summary

EudraCT number	2010-022458-18
Trial protocol	DE LV LT HU
Global end of trial date	25 September 2012

Results information

Result version number	v1 (current)
This version publication date	23 June 2016
First version publication date	17 April 2015

Trial information

Trial identification

Sponsor protocol code	205.425

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01383499
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 , +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG , +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 October 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 September 2012
Global end of trial reached?	Yes
Global end of trial date	25 September 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of 3 doses of tiotripium solution for inhalation in comparison to placebo delivered by the Respimat® inhaler on top of usual care in children (6 to 11 years old) with moderate persistent asthma. In addition, pharmacokinetic profiling in this age group was evaluated.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required. Rescue medication, open-label salbutamol 100 micrograms per puff was administered as needed.

Background therapy:

Patients maintained their inhaled corticosteroids (ICS) background therapy.

Evidence for comparator: -

Actual start date of recruitment	23 August 2011
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	Germany: 14
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	Latvia: 58
Country: Number of subjects enrolled	Lithuania: 31
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Ukraine: 17
Worldwide total number of subjects	171
EEA total number of subjects	137

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)	171
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects had to meet all inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated. Therefore, out of 171 enrolled patients, only 101 were randomised.

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, Monitor, Data analyst, Carer, Assessor

Arms

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

Arm description:

Patients treated with Tiotropium 5 mcg in Period 1, with Placebo in Period 2 and with Tiotropium 1.25 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium 5 micrograms /Placebo/ Tiotropium 1.25 micrograms
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 micrograms (evening dosing)
Placebo - 2 puffs once daily (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 micrograms (evening dosing)

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

Arm description:

Patients treated with Tiotropium 1.25 mcg in Period 1, with Tiotropium 5 mcg in Period 2 and with Tiotropium 2.5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium 1.25 micrograms/Tiotropium 5 micrograms/Tiotropium 2.5 micrograms
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 micrograms (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 micrograms (evening dosing)
Tio R2.5 - 2 puffs once daily for a total dose of 2.5 micrograms (evening dosing)

Arm title	Placebo/Tio R2.5/Tio R5

Arm description:

Patients treated with Placebo in Period 1, with Tiotropium 2.5 mcg in Period 2 and with Tiotropium 5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 2.5 micrograms/ Tiotropium 5 micrograms
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 micrograms (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 micrograms (evening dosing)

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

Arm description:

Patients treated with Tiotropium 2.5 mcg in Period 1, with Tiotropium 1.25 mcg in Period 2 and with Placebo in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium 2.5 micrograms / Tiotropium 1.25 micrograms/ /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 micrograms (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 micrograms (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	27	24	25
Completed	26	24	25
Not completed	1	0	0
Consent withdrawn by subject	1	-	-

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

Started	25
Completed	25
Not completed	0
Consent withdrawn by subject	-

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, Monitor, Data analyst, Carer, Assessor

Arms

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

Arm description:

Patients treated with Tiotropium 5 mcg in Period 1, with Placebo in Period 2 and with Tiotropium 1.25 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium 5 micrograms /Placebo/ Tiotropium 1.25 micrograms
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 micrograms (evening dosing)
Placebo - 2 puffs once daily (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 micrograms (evening dosing)

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

Arm description:

Patients treated with Tiotropium 1.25 mcg in Period 1, with Tiotropium 5 mcg in Period 2 and with Tiotropium 2.5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium 1.25 micrograms / Tiotropium 5 micrograms / Tiotropium 2.5 micrograms
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 micrograms (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 micrograms (evening dosing)
Tio R2.5 - 2 puffs once daily for a total dose of 2.5 micrograms (evening dosing)

Arm title	Placebo/Tio R2.5/Tio R5

Arm description:

Patients treated with Placebo in Period 1, with Tiotropium 2.5 mcg in Period 2 and with Tiotropium 5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 2.5 micrograms /Tiotropium 5 micrograms
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 micrograms (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 micrograms (evening dosing)

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

Arm description:

Patients treated with Tiotropium 2.5 mcg in Period 1, with Tiotropium 1.25 mcg in Period 2 and with Placebo in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium 2.5 micrograms / Tiotropium 1.25 micrograms /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 micrograms (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 micrograms (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	24	25
Completed	26	24	25

Number of subjects in period 2	Tio R2.5/Tio R1.25/Placebo
Started	25

Completed	25

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, Monitor, Data analyst, Carer, Assessor

Arms

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

Arm description:

Patients treated with Tiotropium 5 mcg in Period 1, with Placebo in Period 2 and with Tiotropium 1.25 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium 5 micrograms /Placebo/ Tiotropium 1.25 micrograms
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 micrograms (evening dosing)
Placebo - 2 puffs once daily (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 micrograms (evening dosing)

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

Arm description:

Patients treated with Tiotropium 1.25 mcg in Period 1, with Tiotropium 5 mcg in Period 2 and with Tiotropium 2.5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium 1.25 micrograms / Tiotropium 5 micrograms / Tiotropium 2.5 micrograms
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 micrograms (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 micrograms (evening dosing)
Tio R2.5 - 2 puffs once daily for a total dose of 2.5 micrograms (evening dosing)

Arm title	Placebo/Tio R2.5/Tio R5

Arm description:

Patients treated with Placebo in Period 1, with Tiotropium 2.5 mcg in Period 2 and with Tiotropium 5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 2.5 micrograms /Tiotropium 5 micrograms
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 micrograms (evening dosing)
Tio R5 - 2 puffs once daily for a total dose of 5 micrograms (evening dosing)

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

Arm description:

Patients treated with Tiotropium 2.5 mcg in Period 1, with Tiotropium 1.25 mcg in Period 2 and with Placebo in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of maintenance therapy with an inhaled corticosteroid controller medication. No washouts (off treatment periods) between treatments.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium 2.5 micrograms / Tiotropium 1.25 micrograms/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 micrograms (evening dosing)
Tio R1.25 - 2 puffs once daily for a total dose of 1.25 micrograms (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	26	24	25
Completed	26	24	25

Number of subjects in period 3	Tio R2.5/Tio R1.25/Placebo
Started	25

Completed	25

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, Monitor, Data analyst, Carer, Assessor

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 of maintenance therapy with an inhaled corticosteroid controller medication. One patient was randomised to placebo arm but not treated.

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:

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

Arm title	Tio R1.25

Arm description:

Tiotropium 1.25 microgram once daily (QD) in the evening delivered by the Respimat® inhaler, on top of maintenance therapy with an inhaled corticosteroid controller medication. One patient was randomised to Tio R1.25 arm, but was not treated.

Arm type	Experimental
Investigational medicinal product name	Tiotropium 1.25 micrograms
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

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

Arm title	Tio R2.5

Arm description:

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

Arm type	Experimental

Investigational medicinal product name	Tiotropium 2.5 micrograms
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

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

Arm title	Tio R5

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Tiotropium 5 micrograms
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

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

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	76	75	74
Completed	76	75	74
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

Number of subjects in period 4	Tio R5
Started	76
Completed	75
Not completed	1
Consent withdrawn by subject	1

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	101	101	
Age categorical Units: Subjects			

Age Continuous | Units: years			
arithmetic mean	8.8		
standard deviation	± 1.7	-	
Gender, Male/Female Units: participants			
Female	32	32	
Male	69	69	
Study Specific Characteristic |			
Forced expiratory volume in 1s (FEV1)			
Units: Litre			
arithmetic mean	1.64		
standard deviation	± 0.386	-	

End points reporting groups

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

Reporting group description:

Patients treated with Tiotropium 5 mcg in Period 1, with Placebo in Period 2 and with Tiotropium 1.25 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 mcg in Period 1, with Tiotropium 5 mcg in Period 2 and with Tiotropium 2.5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 Placebo in Period 1, with Tiotropium 2.5 mcg in Period 2 and with Tiotropium 5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 mcg in Period 1, with Tiotropium 1.25 mcg in Period 2 and with Placebo in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 mcg in Period 1, with Placebo in Period 2 and with Tiotropium 1.25 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 mcg in Period 1, with Tiotropium 5 mcg in Period 2 and with Tiotropium 2.5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 Placebo in Period 1, with Tiotropium 2.5 mcg in Period 2 and with Tiotropium 5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 mcg in Period 1, with Tiotropium 1.25 mcg in Period 2 and with Placebo in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 mcg in Period 1, with Placebo in Period 2 and with Tiotropium 1.25 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 mcg in Period 1, with Tiotropium 5 mcg in Period 2 and with Tiotropium 2.5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 Placebo in Period 1, with Tiotropium 2.5 mcg in Period 2 and with Tiotropium 5 mcg in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 mcg in Period 1, with Tiotropium 1.25 mcg in Period 2 and with Placebo in Period 3. All products were administered once daily (QD) in the evening, delivered by the Respimat® inhaler, on top of 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 of maintenance therapy with an inhaled corticosteroid controller medication. One patient was randomised to placebo arm but not treated.

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 of maintenance therapy with an inhaled corticosteroid controller medication. One patient was randomised to Tio R1.25 arm, but was not treated.

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 of 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 of 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.

FAS= Full analysis set which 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	76[1]	75[2]	74[3]	75[4]
Units: Litre				
least squares mean (standard error)	0.185 (± 0.025)	0.261 (± 0.026)	0.29 (± 0.026)	0.272 (± 0.026)

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

[4] - FAS

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 common baseline as fixed effects, and patient as random effect. Difference was calculated as Tio R5 minus Placebo.

The actual number of subjects analyzed is 75. As this is a cross over study and arms are not mutually exclusive, the pre-specified, 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	= 0.0002 [5]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	0.132
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[5] - First step of closed testing procedure, where the active treatments are compared to placebo. If this statistical 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 was used (MMRM). This MMRM model includes treatment, period and common baseline as fixed effects, and patient as random effect. Difference was calculated as Tio R2.5 minus Placebo.

The actual number of subjects analyzed is 74. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis below (150) does not reflect the actual number.

Comparison groups	Placebo v Tio R2.5

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.059
upper limit	0.149
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[6] - Second step of closed testing procedure. If this statistical 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 3

Statistical analysis description:

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

The actual number of subjects analyzed is 75. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis below (151) does not reflect the actual number.

Comparison groups	Placebo v Tio R1.25
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.023

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Mixed model repeated measures was used (MMRM). This MMRM model includes treatment, period and common baseline as fixed effects, and patient as random effect. Difference was calculated as Tio R5 minus Tio R1.25. The actual number of subjects analyzed is 74. As this is a cross over study and arms are not mutually exclusive, the pre-specified, 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[7]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.057
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[7] - This statistical analysis was evaluated only descriptively

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Mixed model repeated measures was used. This MMRM model includes treatment, period and common baseline as fixed effects, and patient as random effect. Difference was calculated as Tio R5 minus Tio R2.5 The actual number of subjects analyzed is 73.

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis below (149) does not reflect the actual number.

Comparison groups	Tio R5 v Tio R2.5
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	equivalence[8]
Method	Mixed model repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	-0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.063
upper limit	0.028
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[8] - This statistical analysis was evaluated only descriptively.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Mixed model repeated measures was used. This MMRM model includes treatment, period and common baseline as fixed effects, and patient as random effect. Difference was calculated as Tio R2.5 minus Tio R1.25. The actual number of subjects analyzed is 73.

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis below (149) does not reflect the actual number.

Comparison groups	Tio R1.25 v Tio R2.5

Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	equivalence[9]
Method	Mixed models repeated measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.016
upper limit	0.074
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[9] - This statistical analysis was evaluated only descriptively.

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. 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	76[10]	75[11]	74[12]	75[13]
Units: Litre				
least squares mean (standard error)	0.085 (± 0.026)	0.16 (± 0.026)	0.19 (± 0.026)	0.183 (± 0.026)

Notes:

[10] - FAS

[11] - FAS

[12] - FAS

[13] - FAS

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	76[14]	75[15]	74[16]	75[17]
Units: Litre				
least squares mean (standard error)	0.202 (± 0.029)	0.208 (± 0.029)	0.253 (± 0.029)	0.239 (± 0.029)

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

[17] - FAS

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. 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	76[18]	75[19]	74[20]	75[21]
Units: Litre				
least squares mean (standard error)	0.06 (± 0.03)	0.109 (± 0.03)	0.107 (± 0.03)	0.113 (± 0.03)

Notes:

[18] - FAS

[19] - FAS

[20] - FAS

[21] - FAS

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. 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	76[22]	75[23]	74[24]	75[25]
Units: Litre				
least squares mean (standard error)	0.11 (± 0.025)	0.178 (± 0.025)	0.208 (± 0.025)	0.201 (± 0.025)

Notes:

[22] - FAS

[23] - FAS

[24] - FAS

[25] - FAS

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. 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	76[26]	75[27]	74[28]	75[29]
Units: Litre				
least squares mean (standard error)	0.087 (± 0.027)	0.097 (± 0.027)	0.134 (± 0.027)	0.11 (± 0.027)

Notes:

[26] - FAS

[27] - FAS

[28] - FAS

[29] - FAS

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. 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	76[30]	75[31]	73[32]	75[33]
Units: Litre/min				
least squares mean (standard error)	-0.928 (± 5.103)	14.474 (± 5.127)	12.045 (± 5.177)	15.439 (± 5.127)

Notes:

[30] - FAS

[31] - FAS

[32] - FAS- Only patients with baseline and week 4 values were analysed

[33] - FAS

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. 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	76[34]	75[35]	73[36]	75[37]
Units: Litre/min				
least squares mean (standard error)	-0.568 (± 5.081)	9.91 (± 5.103)	6.991 (± 5.15)	15.91 (± 5.103)

Notes:

[34] - FAS

[35] - FAS

[36] - FAS- Only patients with baseline and week 4 values were analysed

[37] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Number of Puffs of Rescue Medication Per Period (24 h, daytime and night-time use)

End point title	Change From Baseline in the Number of Puffs of Rescue Medication Per Period (24 h, daytime and night-time use)

End point description:

Mean number of inhalations (puffs) of unscheduled rescue salbutamol therapy during whole day (24 h, daytime and night-time use). 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	76[38]	75[39]	73[40]	75[41]
Units: Puffs				
least squares mean (standard error)				
24 h	-0.664 (± 0.105)	-0.691 (± 0.105)	-0.314 (± 0.106)	-0.55 (± 0.105)
Daytime	-0.338 (± 0.061)	-0.348 (± 0.062)	-0.13 (± 0.062)	-0.258 (± 0.062)
Night-time	-0.354 (± 0.06)	-0.355 (± 0.06)	-0.18 (± 0.06)	-0.272 (± 0.06)

Notes:

[38] - FAS

[39] - FAS

[40] - FAS- Only patients with baseline and week 4 values were analysed

[41] - FAS

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 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. 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	76[42]	75[43]	74[44]	75[45]
Units: Score				
least squares mean (standard error)	0.966 (± 0.066)	0.909 (± 0.066)	0.846 (± 0.066)	0.879 (± 0.066)

Notes:

[42] - FAS

[43] - FAS

[44] - FAS

[45] - FAS

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. Analysis adjusted for treatment, period, patient and baseline using a mixed model. The scores for this question used the following scale where: 1='Did not wake up', 2='Woke up once', 3='Woke up 2-5 times', 4='Woke up more than 5 times' and 5='Was awake all night'.

End point type	Secondary

End point timeframe:

Baseline and last week of treatment (week 4)

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	76[46]	75[47]	73[48]	75[49]
Units: scores on a scale				
least squares mean (standard error)	-0.135 (± 0.034)	-0.104 (± 0.034)	-0.08 (± 0.034)	-0.099 (± 0.034)

Notes:

[46] - FAS

[47] - FAS

[48] - FAS- Only patients with baseline and week 4 values were analysed

[49] - FAS

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	15.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily (QD) in the evening delivered by the Respimat® inhaler, on top of 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 of 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 of 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 of maintenance therapy with an inhaled corticosteroid controller medication.	

Serious adverse events	Placebo	Tio R1.25	Tio R2.5
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 76 (0.00%)	0 / 75 (0.00%)	0 / 74 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Tio R5		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 76 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	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 / 76 (0.00%)	0 / 75 (0.00%)	0 / 74 (0.00%)

Non-serious adverse events	Tio R5		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 76 (0.00%)		

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.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 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. In addition, there was a change in the sample size calculation, as a result of which the numbers of patients to be randomised was changed from 92 to 104. This was required based on unblinded information of completed trials with tiotropium in asthma that necessitated an update of the expected standard deviation for the primary endpoint FEV 1 peak 0-3h 0.228L to 0.280L and the expected drop-out rate from 30% to 8%. For pharmacokinetic analyses, the '2/3rd rule' (used for the presentation of descriptive statistics) was ignored during this trial. Instead, it was decided to display descriptive statistics for concentrations and PK parameters if at least three individual values were available.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported