Clinical trial results:
A randomised, double-blind, 5 treatment arms, 4-period, incomplete cross-over study to determine the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (FDC) (2.5 / 5 µg; and 5 / 5 µg) (delivered by the Respimat® Inhaler) compared with tiotropium (5 µg), olodaterol (5 µg) and placebo (delivered by the Respimat® Inhaler) on lung hyperinflation and exercise endurance time during constant work rate cycle ergometry in patients with Chronic Obstructive Pulmonary Disease (COPD) [MORACTO™ 2]

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2011-004660-30
Trial protocol	NL DE SE AT
Global end of trial date	26 November 2013

Results information

Result version number	v2 (current)
This version publication date	23 July 2016
First version publication date	01 August 2015
Version creation reason	• Correction of full data set Data correction due to a system error in EudraCT

Trial information

Trial identification

Sponsor protocol code	1237.14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01533935
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2013
Global end of trial reached?	Yes
Global end of trial date	26 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are:
1) To compare the effects of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 / 5 µg ; 5 / 5 µg) with tiotropium (5 µg), olodaterol (5 µg) and placebo on lung hyperinflation at rest and during constant work rate exercise in patients with COPD. Lung hyperinflation will be assessed by measurement of inspiratory capacity (IC).
2) To compare the effects of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 / 5 µg ; 5 / 5 µg) with tiotropium (5 µg), olodaterol (5 µg) and placebo on constant work rate exercise tolerance after 6 weeks of treatment in patients with COPD. Exercise tolerance will be assessed by measurement of symptom-limited endurance time at rest and during constant work rate cycle ergometry.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Administration of rescue medication was allowed at any point during the study as medically needed. Open-label salbutamol/albuterol MDI (100 µg per puff) was provided as rescue medication by Boehringer Ingelheim (BI).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 32
Country: Number of subjects enrolled	Argentina: 27
Country: Number of subjects enrolled	Russian Federation: 37
Country: Number of subjects enrolled	United States: 80
Country: Number of subjects enrolled	Netherlands: 56
Country: Number of subjects enrolled	Sweden: 20

Country: Number of subjects enrolled	Austria: 27
Country: Number of subjects enrolled	Germany: 95
Worldwide total number of subjects	374
EEA total number of subjects	198

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)	0
Adults (18-64 years)	222
From 65 to 84 years	152
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all inclusion/exclusion criteria.Subjects were not randomised to trial treatment if any one of the specific entry criteria were violated. Of the enrolled 374 pts, 291 patients entered study.

Period 1

Period 1 title	Overall trial (treatment period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Placebo QD

Arm description:

Placebo inhalation solution delivered once daily (QD) via RESPIMAT inhaler

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 inhalation solution, delivered once daily via the RESPIMAT Inhaler

Arm title	Olodaterol 5 µg QD

Arm description:

Olodaterol fixed dose 5 µg (Olo 5) inhalation solution delivered once daily via RESPIMAT inhaler

Arm type	Active comparator
Investigational medicinal product name	Olodaterol 5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Olodaterol 5 µg inhalation solution, delivered once daily via the RESPIMAT Inhaler

Arm title	Tiotropium 5 µg QD

Arm description:

Tiotropium fixed dose 5 µg (Tio 5) inhalation solution delivered once daily via RESPIMAT inhaler

Arm type	Active comparator
Investigational medicinal product name	Tiotropium 5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 5 µg inhalation solution, delivered once daily via the RESPIMAT Inhaler

Arm title	Tiotropium + Olodaterol 2.5/5 QD

Arm description:

Tio+Olo Fixed Dose Combination (FDC) 2.5/5 µg (Tio+Olo 2.5/5) inhalation solution delivered once daily via RESPIMAT inhaler

Arm type	Experimental
Investigational medicinal product name	Tiotropium 2.5 µg / Olodaterol 5 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio+Olo fixed dose combination (FDC) 2.5/5 µg inhalation solution, delivered once daily via the RESPIMAT Inhaler

Arm title	Tiotropium + Olodaterol 5/5 QD

Arm description:

Tio+Olo FDC 5/5 µg (Tio+Olo 5/5) inhalation solution delivered once daily via RESPIMAT inhaler

Arm type	Experimental
Investigational medicinal product name	Tiotropium 5 µg / Olodaterol 5 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio+Olo FDC 5/5 µg FDC inhalation solution, delivered once daily via the RESPIMAT Inhaler

Number of subjects in period 1	Placebo QD	Olodaterol 5 µg QD	Tiotropium 5 µg QD
Started	216	219	218
Completed	210	210	210
Not completed	6	9	8
Other reason not defined above	1	-	-
Consent withdrawn by subject	2	2	4
Adverse event, non-fatal	3	7	4
Protocol deviation	-	-	-

Number of subjects in period 1	Tiotropium + Olodaterol 2.5/5 QD	Tiotropium + Olodaterol 5/5 QD
Started	219	224
Completed	215	218
Not completed	4	6
Other reason not defined above	-	-

Consent withdrawn by subject	2	2
Adverse event, non-fatal	2	2
Protocol deviation	-	2

Period 2

Period 2 title	Overall trial by sequence
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+Olo 2.5/5 / Tio+Olo 5/5 / Tio / Olo

Arm description:

Patients received a total of four treatments, and each treatment period is separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were
• Fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg.
• Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg.
• Tiotropium fixed dose 5 µg.
• Olodaterol fixed dose 5 µg.

Arm type	treatment sequence
Investigational medicinal product name	Tiotropium 2.5 µg / Olodaterol 5 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium+Olodaterol (2.5/5 µg) FDC inhalation solution was delivered once daily via respimat inhaler in Period 1.

Investigational medicinal product name	Tiotropium 5 µg / Olodaterol 5 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium+Olodaterol (5/5 µg) FDC inhalation solution was delivered once daily via respimat inhaler in period 2.

Investigational medicinal product name	Tiotropium 5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium fixed dose 5 µg (Tio 5) inhalation solution delivered once daily via respimat inhaler in period 3.

Investigational medicinal product name	Olodaterol 5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Olodaterol fixed dose 5 µg (Olo 5) inhalation solution delivered once daily via respimat inhaler in period 4.

Arm title	Tio+Olo 5/5 / Tio / Olo / placebo

Arm description:

Patients received a total of four treatments, and each treatment period is separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were
• Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg.
• Tiotropium fixed dose 5 µg.
• Olodaterol fixed dose 5 µg.
• Oral inhalation of placebo.

Arm type	treatment sequence
Investigational medicinal product name	Tiotropium 5 µg / Olodaterol 5 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio+Olo FDC 5/5 µg (Tio+Olo 5/5) inhalation solution was delivered once daily via respimat inhaler in period 1.

Investigational medicinal product name	Tiotropium 5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium fixed dose 5 µg (Tio 5) inhalation solution delivered once daily via respimat inhaler in period 2.

Investigational medicinal product name	Olodaterol 5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Olodaterol fixed dose 5 µg (Olo 5) inhalation solution delivered once daily via respimat inhaler in period 3.

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 inhalation solution delivered once daily (QD) via respimat inhaler in period 4.

Arm title	Tio / Olo / placebo / Tio+Olo 2.5/5

Arm description:

Patients received a total of four treatments, and each treatment period is separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were
• Tiotropium fixed dose 5 µg.

• Olodaterol fixed dose 5 µg.
• Oral inhalation of placebo.
• Fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg.
One patient received Tio+Olo 5/5 instead of Tio+Olo 2.5/5 by mistake.

Arm type	treatment sequence
Investigational medicinal product name	Tiotropium 5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium fixed dose 5 µg (Tio 5) inhalation solution delivered once daily via respimat inhaler in period 1.

Investigational medicinal product name	Olodaterol 5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Olodaterol fixed dose 5 µg (Olo 5) inhalation solution delivered once daily via respimat inhaler in period 2.

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 inhalation solution delivered once daily (QD) via respimat inhaler in period 3.

Investigational medicinal product name	Tiotropium 2.5 µg / Olodaterol 5 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio+Olo Fixed Dose Combination (FDC) 2.5/5 µg (Tio+Olo 2.5/5) inhalation solution delivered oncedaily via respimat inhaler in period 4.

Arm title	Olo / placebo / Tio+Olo 2.5/5 / Tio+Olo 5/5

Arm description:

Patients received a total of four treatments, and each treatment period is separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were
• Olodaterol fixed dose 5 µg.
• Oral inhalation of placebo.
• Fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg.
• Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg.

Arm type	treatment sequence
Investigational medicinal product name	Olodaterol 5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Olodaterol fixed dose 5 µg (Olo 5) inhalation solution delivered once daily via respimat inhaler in period 1.

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 inhalation solution delivered once daily (QD) via respimat inhaler in period 2.

Investigational medicinal product name	Tiotropium 2.5 µg / Olodaterol 5 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio+Olo Fixed Dose Combination (FDC) 2.5/5 µg (Tio+Olo 2.5/5) inhalation solution delivered once daily via respimat inhaler in period 3.

Investigational medicinal product name	Tiotropium 5 µg / Olodaterol 5 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio+Olo FDC 5/5 µg (Tio+Olo 5/5) inhalation solution delivered once daily via respimat inhaler in period 4.

Arm title	placebo / Tio+Olo 2.5/5 / Tio+Olo 5/5 / Tio

Arm description:

Patients received a total of four treatments, and each treatment period is separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were
• Oral inhalation of placebo.
• Fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg.
• Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg.
• Tiotropium fixed dose 5 µg.

Arm type	treatment sequence
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 inhalation solution delivered once daily (QD) via respimat inhaler in period 1.

Investigational medicinal product name	Tiotropium 2.5 µg / Olodaterol 5 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio+Olo Fixed Dose Combination (FDC) 2.5/5 µg (Tio+Olo 2.5/5) inhalation solution delivered oncedaily via respimat inhaler in period 2.

Investigational medicinal product name	Tiotropium 5 µg / Olodaterol 5 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio+Olo FDC 5/5 µg (Tio+Olo 5/5) inhalation solution delivered once daily via respimat inhaler in period 3.

Investigational medicinal product name	Tiotropium 5 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Tio+Olo FDC 5/5 µg (Tio+Olo 5/5) inhalation solution delivered once daily via respimat inhaler in period 4.

Number of subjects in period 2	Tio+Olo 2.5/5 / Tio+Olo 5/5 / Tio / Olo	Tio+Olo 5/5 / Tio / Olo / placebo	Tio / Olo / placebo / Tio+Olo 2.5/5
Started	58	58	58
Received Placebo	0 [1]	47	52
Received Olo 5	52	52	55
Received Tio 5	54	54	58
Received Tio+Olo 2.5/5	58	0 [2]	49 [3]
Received Tio+Olo 5/5	56	58	1 [4]
Completed	52	45	50
Not completed	6	13	8
Other reason not defined above	1	-	1
Consent withdrawn by subject	-	4	5
Adverse event, non-fatal	5	7	1
Lost to follow-up	-	-	1
Protocol deviation	-	2	-

Number of subjects in period 2	Olo / placebo / Tio+Olo 2.5/5 / Tio+Olo 5/5	placebo / Tio+Olo 2.5/5 / Tio+Olo 5/5 / Tio
Started	59	58
Received Placebo	57	58
Received Olo 5	59	0 [5]
Received Tio 5	0 [6]	52
Received Tio+Olo 2.5/5	56	56
Received Tio+Olo 5/5	54	55
Completed	52	50
Not completed	7	8
Other reason not defined above	-	1
Consent withdrawn by subject	2	4
Adverse event, non-fatal	5	3
Lost to follow-up	-	-

Protocol deviation	-	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, 5 treatment sequence and 4-period incomplete block cross-over trial. In each treatment sequence the subject received only 4 treatments. Thus, the subject completed all 4 treatment arms and this milestone represent the number of subjects who did not received 5th treatment, ie., the placebo.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, 5 treatment sequence and 4-period incomplete block cross-over trial. In each treatment sequence the subject received only 4 treatment.Thus, the subject completed all treatment arms and this milestone represent the number of subjects who did not received 5th treatment, ie., the Tio+Olo 2.5/5.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, 5 treatment sequence and 4-period incomplete block cross-over trial. In each treatment sequence the subject received only 4 treatments. One subject received Tio+Olo 5/5 instead of Tio+Olo 2.5/5 by mistake, thus this milestone represent the number of subjects who received the Tio+Olo 2.5/5.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, 5 treatment sequence and 4-period incomplete block cross-over trial. In each treatment sequence the subject received only 4 treatments. One patient received Tio+Olo 5/5 instead of Tio+Olo 2.5/5 by mistake, thus this milestone represent the number of subjects who received 5th treatment, ie., the Tio+Olo 5/5 instead of Tio+Olo 2.5/5 by mistake.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, 5 treatment sequence and 4-period incomplete block cross-over trial. In each treatment sequence the subject received only 4 treatments. Thus, the subject completed all 4 treatment arms and this milestone represent the number of subjects who did not received 5th treatment, ie., the Olo 5.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This was a randomised, 5 treatment sequence and 4-period incomplete block cross-over trial. In each treatment sequence the subject received only 4 treatment. Thus, the subject completed all 4 treatment arms and this milestone represent the number of subjects who did not received 5th treatment, ie., the Tio 5.

Baseline characteristics

Reporting groups[1]	
Reporting group title	Overall trial (treatment period)

Reporting group description:

A randomised, double-blind, placebo controlled, 5 treatment, 4-period, incomplete, crossover study. Each treatment period was separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were:
• Oral inhalation of placebo
• Tiotropium fixed dose 5 µg
• Olodaterol fixed dose 5 µg
• Fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg
• Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg
Treatment sequence is not considered as a factor which may affect the treatment effect due to sufficient washout period added between treatment cycles. As a result, we only display baseline characteristics as a whole population, but not by treatment sequence.

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 dose of the trial medication.

Reporting group values	Overall trial (treatment period)	Total	
Number of subjects	291	291	
Age categorical Units: Subjects			

Age continuous			
Treated Set (TS) : This patient set included all patients of the Randomised Set (RS : patients who signed the informed consent form and were also randomised, regardless of whether the patient was treated with study medication or not) who were dispensed study medication and were documented to have taken at least 1 dose of study medication.			
Units: years			
arithmetic mean	61.2		
standard deviation	± 7.9	-	
Gender categorical Units: Subjects			
Female	87	87	
Male	204	204	

End points

End points reporting groups

Reporting group title	Placebo QD
Reporting group description:	
Placebo inhalation solution delivered once daily (QD) via RESPIMAT inhaler	
Reporting group title	Olodaterol 5 µg QD
Reporting group description:	
Olodaterol fixed dose 5 µg (Olo 5) inhalation solution delivered once daily via RESPIMAT inhaler	
Reporting group title	Tiotropium 5 µg QD
Reporting group description:	
Tiotropium fixed dose 5 µg (Tio 5) inhalation solution delivered once daily via RESPIMAT inhaler	
Reporting group title	Tiotropium + Olodaterol 2.5/5 QD
Reporting group description:	
Tio+Olo Fixed Dose Combination (FDC) 2.5/5 µg (Tio+Olo 2.5/5) inhalation solution delivered once daily via RESPIMAT inhaler	
Reporting group title	Tiotropium + Olodaterol 5/5 QD
Reporting group description:	
Tio+Olo FDC 5/5 µg (Tio+Olo 5/5) inhalation solution delivered once daily via RESPIMAT inhaler	
Reporting group title	Tio+Olo 2.5/5 / Tio+Olo 5/5 / Tio / Olo
Reporting group description:	
Patients received a total of four treatments, and each treatment period is separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were • Fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg. • Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg. • Tiotropium fixed dose 5 µg. • Olodaterol fixed dose 5 µg.	
Reporting group title	Tio+Olo 5/5 / Tio / Olo / placebo
Reporting group description:	
Patients received a total of four treatments, and each treatment period is separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were • Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg. • Tiotropium fixed dose 5 µg. • Olodaterol fixed dose 5 µg. • Oral inhalation of placebo.	
Reporting group title	Tio / Olo / placebo / Tio+Olo 2.5/5
Reporting group description:	
Patients received a total of four treatments, and each treatment period is separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were • Tiotropium fixed dose 5 µg. • Olodaterol fixed dose 5 µg. • Oral inhalation of placebo. • Fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg. One patient received Tio+Olo 5/5 instead of Tio+Olo 2.5/5 by mistake.	
Reporting group title	Olo / placebo / Tio+Olo 2.5/5 / Tio+Olo 5/5
Reporting group description:	
Patients received a total of four treatments, and each treatment period is separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were • Olodaterol fixed dose 5 µg. • Oral inhalation of placebo. • Fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg. • Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg.	
Reporting group title	placebo / Tio+Olo 2.5/5 / Tio+Olo 5/5 / Tio

Reporting group description:

Patients received a total of four treatments, and each treatment period is separated by a washout period of 21 days. The treatments administered, by oral inhalation delivered once daily in the morning, via the respimat inhaler, were
• Oral inhalation of placebo.
• Fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg.
• Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg.
• Tiotropium fixed dose 5 µg.

Primary: Inspiratory Capacity at Rest Before Constant Work Rate Cycle Ergometry to Symptom Limitation at 75% Work Capacity

End point title	Inspiratory Capacity at Rest Before Constant Work Rate Cycle Ergometry to Symptom Limitation at 75% Work Capacity

End point description:

Inspiratory capacity (IC) at rest before constant work rate cycle ergometry to symptom limitation at 75% maximal work capacity (Wcap). Wcap was defined as the maximum work rate achieved for at least 30 seconds during the incremental cycle ergometry performed at Visit 1.
The presented means are adjusted means from the MMRM (Mixed Effects Model Repeated Measures) model.
Full analysis set (FAS): This patient set included all patients in the Treated Set (TS) who had the study baseline and at least 1 evaluable post-dose measurement for 1 of the primary endpoints. Assignment to the FAS was done after implementation of any data handling rules, which set measurements to missing.

End point type	Primary

End point timeframe:

6 weeks

End point values	Placebo QD	Olodaterol 5 µg QD	Tiotropium 5 µg QD	Tiotropium + Olodaterol 2.5/5 QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	202[1]	208[2]	208[3]	212[4]
Units: litre(s)				
least squares mean (standard error)	2.502 (± 0.026)	2.687 (± 0.025)	2.679 (± 0.025)	2.776 (± 0.025)

Notes:

[1] - Full analysis Set (FAS)

[2] - FAS

[3] - FAS

[4] - FAS

End point values	Tiotropium + Olodaterol 5/5 QD			
Subject group type	Reporting group			
Number of subjects analysed	218[5]			
Units: litre(s)				
least squares mean (standard error)	2.767 (± 0.025)			

Notes:

[5] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5/5 QD vs Placebo QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 5/5 µg QD minus Placebo QD.

Comparison groups	Placebo QD v Tiotropium + Olodaterol 5/5 QD
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.265
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.215
upper limit	0.315
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[6] - The actual number of subjects analyzed is 218. 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 (420) does not reflect the actual number.

Statistical analysis title	Tio+Olo 5/5 QD vs Olo 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 5/5 µg QD minus Olo 5 QD

Comparison groups	Olodaterol 5 µg QD v Tiotropium + Olodaterol 5/5 QD
Number of subjects included in analysis	426
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0015
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.031
upper limit	0.129
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[7] - The actual number of subjects analyzed is 218. 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 (426) does not reflect the actual number.

Statistical analysis title	Tio+Olo 5/5 QD vs Tio 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 5/5 µg QD minus Tio 5 µg QD

Comparison groups	Tiotropium 5 µg QD v Tiotropium + Olodaterol 5/5 QD
Number of subjects included in analysis	426
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.0005
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.088
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.137
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[8] - The actual number of subjects analyzed is 218. 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 (426) does not reflect the actual number.

Statistical analysis title	Tio+Olo 2.5/5 QD vs placebo QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 2.5/5 µg QD minus Placebo µg QD

Comparison groups	Placebo QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.274
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.224
upper limit	0.324

Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[9] - The actual number of subjects analyzed is 212. 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 (414) does not reflect the actual number.

Statistical analysis title	Tio+Olo 2.5/5 QD vs Olo 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 2.5/5 µg QD minus Olo 5 µg QD

Comparison groups	Olodaterol 5 µg QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.0004
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.138
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[10] - The actual number of subjects analyzed is 212. 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 (420) does not reflect the actual number.

Statistical analysis title	Tio+Olo 2.5/5 QD vs Tio 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 2.5/5 µg QD minus Tio 5 µg QD

Comparison groups	Tiotropium 5 µg QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.047
upper limit	0.147

Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[11] - The actual number of subjects analyzed is 212. 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 (420) does not reflect the actual number.

Primary: Endurance Time During Constant Work Rate Cycle Ergometry to Symptom Limitation at 75% Wcap

End point title	Endurance Time During Constant Work Rate Cycle Ergometry to Symptom Limitation at 75% Wcap

End point description:

Endurance time during constant work rate cycle ergometry (CWRCE) to symptom limitation at 75% Wcap
Wcap was defined as the maximum work rate achieved for at least 30 seconds during the incremental cycle ergometry performed at Visit 1.
The presented means are adjusted mean from the MMRM model.

End point type	Primary

End point timeframe:

6 weeks

End point values	Placebo QD	Olodaterol 5 µg QD	Tiotropium 5 µg QD	Tiotropium + Olodaterol 2.5/5 QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	205[12]	207[13]	209[14]	212[15]
Units: second(s)				
geometric mean (standard error)	410.77 (± 12.009)	419.06 (± 12.207)	446.5 (± 12.958)	460.66 (± 13.31)

Notes:

[12] - FAS

[13] - FAS

[14] - FAS

[15] - FAS

End point values	Tiotropium + Olodaterol 5/5 QD			
Subject group type	Reporting group			
Number of subjects analysed	216[16]			
Units: second(s)				
geometric mean (standard error)	465.68 (± 13.359)			

Notes:

[16] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5/5 QD / placebo QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model for log10 (endurance time[sec])with fixed effects of treatment and period, log10 (study baseline endurance time) as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. Mean and 95% confidence limits are transformed from log10 back to the original scale. Standard error is

calculated using delta method.
Ratio calculated as Tio+Olo 5/5 µg QD divided by placebo QD.

Comparison groups	Tiotropium + Olodaterol 5/5 QD v Placebo QD
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	ratio
Point estimate	1.134
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.065
upper limit	1.206
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[17] - The actual number of subjects analyzed is 218. 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 (421) does not reflect the actual number.

Statistical analysis title	Tio+Olo 5/5 QD/ Olo 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model for log10 (endurance time[sec])with fixed effects of treatment and period, log10 (study baseline endurance time) as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. Mean and 95% confidence limits are transformed from log10 back to the original scale. Standard error is calculated using delta method.
Ratio calculated as Tio+Olo 5/5 µg QD divided by Olo 5 µg QD.

Comparison groups	Olodaterol 5 µg QD v Tiotropium + Olodaterol 5/5 QD
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.0009
Method	Mixed models analysis
Parameter estimate	ratio
Point estimate	1.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.045
upper limit	1.182
Variability estimate	Standard error of the mean
Dispersion value	0.035

Notes:

[18] - The actual number of subjects analyzed is 218. 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 (423) does not reflect the actual number.

Statistical analysis title	Tio+Olo 5/5 QD / Tio 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model for log10 (endurance time[sec])with fixed effects of treatment and period, log10 (study baseline endurance time) as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. Mean and 95% confidence limits are transformed from log10 back to the original scale. Standard error is

calculated using delta method.
Ratio calculated as Tio+Olo 5/5 µg QD divided by Tio 5 µg QD.

Comparison groups	Tiotropium 5 µg QD v Tiotropium + Olodaterol 5/5 QD
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.1807
Method	Mixed models analysis
Parameter estimate	Ratio
Point estimate	1.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.981
upper limit	1.109
Variability estimate	Standard error of the mean
Dispersion value	0.033

Notes:

[19] - The actual number of subjects analyzed is 218. 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 (425) does not reflect the actual number.

Statistical analysis title	Tio+Olo 2.5/5 QD / placebo QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model for log10 (endurance time[sec])with fixed effects of treatment and period, log10 (study baseline endurance time) as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. Mean and 95% confidence limits are transformed from log10 back to the original scale. Standard error is calculated using delta method.
Ratio calculated as Tio+Olo 2.5/5 µg QD divided by Placebo QD.

Comparison groups	Placebo QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	Ratio
Point estimate	1.121
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.054
upper limit	1.193
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[20] - The actual number of subjects analyzed is 212. 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 (417) does not reflect the actual number.

Statistical analysis title	Tio+Olo 2.5/5 QD/ Olo 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model for log10 (endurance time[sec])with fixed effects of treatment and period, log10 (study baseline endurance time) as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. Mean and 95% confidence limits are transformed from log10 back to the original scale. Standard error is

calculated using delta method.
Ratio calculated as Tio+Olo 2.5/5 µg QD divided by Olo 5 µg QD.

Comparison groups	Olodaterol 5 µg QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.0029
Method	Mixed models analysis
Parameter estimate	Ratio
Point estimate	1.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.033
upper limit	1.17
Variability estimate	Standard error of the mean
Dispersion value	0.035

Notes:

[21] - The actual number of subjects analyzed is 212. 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 (419) does not reflect the actual number.

Statistical analysis title	Tio+Olo 2.5/5 QD/ Tio 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model for log10 (endurance time[sec])with fixed effects of treatment and period, log10 (study baseline endurance time) as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. Mean and 95% confidence limits are transformed from log10 back to the original scale. Standard error is calculated using delta method.
Ratio calculated as Tio+Olo 2.5/5 µg QD divided by Tio 5 µg QD.

Comparison groups	Tiotropium 5 µg QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.324
Method	Mixed models analysis
Parameter estimate	Ratio
Point estimate	1.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.098
Variability estimate	Standard error of the mean
Dispersion value	0.033

Notes:

[22] - The actual number of subjects analyzed is 212. 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 (421) does not reflect the actual number.

Secondary: Slope of the Intensity of Breathing Discomfort (Borg Scale) During Constant Work Rate Cycle Ergometry to Symptom Limitation at 75% Wcap

End point title	Slope of the Intensity of Breathing Discomfort (Borg Scale) During Constant Work Rate Cycle Ergometry to Symptom Limitation at 75% Wcap

End point description:

Slope of the intensity of breathing discomfort (Borg Scale) during CWRCE to symptom limitation at 75% Wcap. The intensity of breathing discomfort was rated using the modified Borg scale with ratings from 0 (nothing at all) to 10 (maximal).
Slope is defined as : (intensity of breathing discomfort at the end of exercise minus intensity of breathing discomfort at rest) / endurance time. A decrease in slope indicates improvement. The presented means are adjusted means from MMRM model.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Placebo QD	Olodaterol 5 µg QD	Tiotropium 5 µg QD	Tiotropium + Olodaterol 2.5/5 QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	205[23]	207[24]	208[25]	212[26]
Units: Borg scale unit(s)/second				
least squares mean (standard error)	0.018 (± 0.001)	0.017 (± 0.001)	0.015 (± 0.001)	0.014 (± 0.001)

Notes:

[23] - FAS

[24] - FAS

[25] - FAS

[26] - FAS

End point values	Tiotropium + Olodaterol 5/5 QD			
Subject group type	Reporting group			
Number of subjects analysed	216[27]			
Units: Borg scale unit(s)/second				
least squares mean (standard error)	0.015 (± 0.001)			

Notes:

[27] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5/5 QD vs placebo QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 5/5 µg QD minus Placebo QD

Comparison groups	Placebo QD v Tiotropium + Olodaterol 5/5 QD

Number of subjects included in analysis	421
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	-0.002
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[28] - The actual number of subjects analyzed is 218. 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 (421) does not reflect the actual number.

Statistical analysis title	Tio+Olo 5/5 QD vs Olo 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 5/5 µg QD minus Olo 5 µg QD

Comparison groups	Olodaterol 5 µg QD v Tiotropium + Olodaterol 5/5 QD
Number of subjects included in analysis	423
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.0033
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	-0.001
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[29] - The actual number of subjects analyzed is 218. 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 (423) does not reflect the actual number.

Statistical analysis title	Tio+Olo 5/5 QD vs Tio 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 5/5 µg QD minus Tio 5 µg QD

Comparison groups	Tiotropium 5 µg QD v Tiotropium + Olodaterol 5/5 QD

Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.2306
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.001
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[30] - The actual number of subjects analyzed is 218. 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 (424) does not reflect the actual number.

Statistical analysis title	Tio+Olo 2.5/5 QD vs placebo QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 2.5/5 µg QD minus Placebo QD

Comparison groups	Placebo QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	-0.002
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[31] - The actual number of subjects analyzed is 212. 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 (417) does not reflect the actual number.

Statistical analysis title	Tio+Olo 2.5/5 QD vs Olo 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 2.5/5 µg QD minus Olo 5 µg QD

Comparison groups	Olodaterol 5 µg QD v Tiotropium + Olodaterol 2.5/5 QD

Number of subjects included in analysis	419
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	-0.001
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[32] - The actual number of subjects analyzed is 212. 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 (419) does not reflect the actual number.

Statistical analysis title	Tio+Olo 2.5/5 QD vs Tio 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period, study baseline as covariate, patient as a random effect, and compound symmetry as a covariance structure for within−patient variation. N is the number of patients contributing to the MMRM model.

Difference calculated as Tiotropium + olodaterol 2.5/5 µg QD minus Tio 5 µg QD

Comparison groups	Tiotropium 5 µg QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	420
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.1206
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[33] - The actual number of subjects analyzed is 212. 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 (420) does not reflect the actual number.

Secondary: FEV1 (1 Hour Post-dose)

End point title	FEV1 (1 Hour Post-dose)

End point description:

Forced Expiratory Volume in 1 Second (FEV1)(one hour post-dose). The presented means are adjusted means from MMRM model.

All patients in FAS with available FEV1 data at baseline and week 6 are included in the analysis.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Placebo QD	Olodaterol 5 µg QD	Tiotropium 5 µg QD	Tiotropium + Olodaterol 2.5/5 QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	210[34]	215[35]	211[36]	215[37]
Units: litre(s)				
least squares mean (standard error)	1.548 (± 0.016)	1.742 (± 0.016)	1.741 (± 0.016)	1.852 (± 0.016)

Notes:

[34] - FAS

[35] - FAS

[36] - FAS

[37] - FAS

End point values	Tiotropium + Olodaterol 5/5 QD			
Subject group type	Reporting group			
Number of subjects analysed	219[38]			
Units: litre(s)				
least squares mean (standard error)	1.876 (± 0.016)			

Notes:

[38] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5/5 QD vs placebo QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of denominator degrees of freedom.

Difference calculated as Tiotropium + olodaterol 5/5 µg QD minus Placebo QD

Comparison groups	Placebo QD v Tiotropium + Olodaterol 5/5 QD
Number of subjects included in analysis	429
Analysis specification	Pre-specified
Analysis type	superiority[39]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.329
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.294
upper limit	0.364

Variability estimate	Standard error of the mean
Dispersion value	0.018

Notes:

[39] - The actual number of subjects analyzed is 218. 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 (429) does not reflect the actual number.

Statistical analysis title	Tio+Olo 5/5 QD vs Olo 5 QD

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of denominator degrees of freedom.

Difference calculated as Tiotropium + olodaterol 5/5 µg QD minus Olo 5 µg QD

Comparison groups	Olodaterol 5 µg QD v Tiotropium + Olodaterol 5/5 QD
Number of subjects included in analysis	434
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.134
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.099
upper limit	0.169
Variability estimate	Standard error of the mean
Dispersion value	0.018

Notes:

[40] - The actual number of subjects analyzed is 218. 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 (434) does not reflect the actual number.

Statistical analysis title	T+O 5/5 vs Tio 5

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of denominator degrees of freedom.

Difference calculated as Tiotropium + olodaterol 5/5 µg QD minus Tio 5 µg QD

Comparison groups	Tiotropium 5 µg QD v Tiotropium + Olodaterol 5/5 QD
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.17

Variability estimate	Standard error of the mean
Dispersion value	0.018

Notes:

[41] - The actual number of subjects analyzed is 218. 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 (430) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of denominator degrees of freedom.

Difference calculated as Tiotropium + olodaterol 2.5/5 µg QD minus placebo QD

Comparison groups	Placebo QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.305
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.269
upper limit	0.34
Variability estimate	Standard error of the mean
Dispersion value	0.018

Notes:

[42] - The actual number of subjects analyzed is 212. 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 (425) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs Olo 5

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of denominator degrees of freedom.

Difference calculated as Tiotropium + olodaterol 2.5/5 µg QD minus Olo 5 µg QD

Comparison groups	Olodaterol 5 µg QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	430
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.075
upper limit	0.145

Variability estimate	Standard error of the mean
Dispersion value	0.018

Notes:

[43] - The actual number of subjects analyzed is 212. 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 (430) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs Tio 5

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting an MMRM model including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of denominator degrees of freedom.

Difference calculated as Tiotropium + olodaterol 2.5/5 µg QD minus Tio 5 µg QD

Comparison groups	Tiotropium 5 µg QD v Tiotropium + Olodaterol 2.5/5 QD
Number of subjects included in analysis	426
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.076
upper limit	0.146
Variability estimate	Standard error of the mean
Dispersion value	0.018

Notes:

[44] - The actual number of subjects analyzed is 212. 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 (426) does not reflect the actual number.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From drug administration until 21 days after the last administration, up to 139 days	
Adverse event reporting additional description:	
One patient received treatment for 118 days, rather than 6 weeks, due to non-compliance with study visit requirements.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Oral inhalation of placebo, 2 puffs from the Respimat inhaler, once daily, in the morning.	
Reporting group title	Olodaterol 5 µg
Reporting group description:	
Oral inhalation of Olodaterol fixed dose 5 µg (2.5 µg per actuation), 2 puffs from the Respimat inhaler, once daily, in the morning.	
Reporting group title	Tiotropium 5 µg
Reporting group description:	
Oral inhalation of Tiotropium fixed dose 5 µg (2.5 µg per actuation), 2 puffs from the Respimat inhaler, once daily, in the morning.	
Reporting group title	Tiotropium + Olodaterol 2.5/5
Reporting group description:	
Oral inhalation of fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg (Tiotropium: 1.25 µg per actuation and Olodaterol: 2.5 µg per actuation), 2 puffs from the Respimat inhaler, once daily, in the morning.	
Reporting group title	Tiotropium + Olodaterol 5/5
Reporting group description:	
Oral inhalation of fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg (Tiotropium: 2.5 µg per actuation and Olodaterol: 2.5 µg per actuation), 2 puffs from the Respimat inhaler, once daily, in the morning.	

Serious adverse events	Placebo	Olodaterol 5 µg	Tiotropium 5 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 214 (1.40%)	3 / 218 (1.38%)	8 / 218 (3.67%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric neoplasm			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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

Prostate cancer			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	0 / 214 (0.00%)	1 / 218 (0.46%)	0 / 218 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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
Contusion			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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
Overdose			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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
Road traffic accident			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sick sinus syndrome			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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
Suicide attempt			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pain			
subjects affected / exposed	0 / 214 (0.00%)	1 / 218 (0.46%)	0 / 218 (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
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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

Diarrhoea			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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
Nausea			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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
Vomiting			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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			
Acute respiratory failure			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 214 (0.93%)	0 / 218 (0.00%)	2 / 218 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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
Infections and infestations			
Acute tonsillitis			

subjects affected / exposed	1 / 214 (0.47%)	0 / 218 (0.00%)	0 / 218 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis gangrenous			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	0 / 218 (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
Parainfluenzae virus infection			
subjects affected / exposed	0 / 214 (0.00%)	0 / 218 (0.00%)	1 / 218 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 214 (0.00%)	1 / 218 (0.46%)	0 / 218 (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	Tiotropium + Olodaterol 2.5/5	Tiotropium + Olodaterol 5/5	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 219 (1.37%)	4 / 224 (1.79%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric neoplasm			
subjects affected / exposed	1 / 219 (0.46%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			

subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sick sinus syndrome			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 219 (0.46%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 219 (0.00%)	1 / 224 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Acute tonsillitis			

subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis gangrenous			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 219 (0.46%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 219 (0.00%)	0 / 224 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Olodaterol 5 µg	Tiotropium 5 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 214 (19.16%)	42 / 218 (19.27%)	48 / 218 (22.02%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	17 / 214 (7.94%)	25 / 218 (11.47%)	19 / 218 (8.72%)
occurrences (all)	17	26	21
Cough			
subjects affected / exposed	11 / 214 (5.14%)	5 / 218 (2.29%)	8 / 218 (3.67%)
occurrences (all)	12	5	8
Dyspnoea			

subjects affected / exposed	12 / 214 (5.61%)	6 / 218 (2.75%)	13 / 218 (5.96%)
occurrences (all)	12	6	13
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 214 (4.67%)	15 / 218 (6.88%)	13 / 218 (5.96%)
occurrences (all)	10	16	14

Non-serious adverse events	Tiotropium + Olodaterol 2.5/5	Tiotropium + Olodaterol 5/5	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 219 (16.44%)	40 / 224 (17.86%)	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	15 / 219 (6.85%)	20 / 224 (8.93%)	
occurrences (all)	15	22	
Cough			
subjects affected / exposed	4 / 219 (1.83%)	3 / 224 (1.34%)	
occurrences (all)	5	3	
Dyspnoea			
subjects affected / exposed	6 / 219 (2.74%)	6 / 224 (2.68%)	
occurrences (all)	6	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	18 / 219 (8.22%)	16 / 224 (7.14%)	
occurrences (all)	19	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2012	Body plethysmography at Visit 1 (baseline) was introduced to characterise the patients' static hyperinflation. Furthermore, procedures to be completed in the case of early withdrawal from the trial were specified as well as individual withdrawal criteria. It was clarified that the adjudication committee reviewed all serious adverse events (SAEs) and not only fatal SAEs. On recommendation from local (German) authorities, the trial population was restricted to patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Stage II to III (instead of Stage II to IV) including a lower limit of FEV1 > 30% of predicted normal. For safety reasons, chronic respiratory failure was added to the exclusion criteria. A specification that SAEs needed to be reported until 21 days after the last administration of study medication was added and a list of "always serious" AEs was included to comply with a new Boehringer Ingelheim (BI) internal procedure.
03 December 2012	Instructions were added for the clinical evaluation of potential Drug-induced Liver Injury (DILI) to comply with FDA guidance for industry "Drug-Induced Liver Injury: Premarketing Clinical Evaluation". The period during which a pregnancy test after end of treatment was to be performed was specified. It was clarified that mortality and SAE adjudication were to be conducted separately. Furthermore, the order of the endpoint hypothesis testing strategy was changed and the testing for the key secondary endpoint of breathing discomfort was included to be aligned with the testing strategy for the programme and for monoproducts with the FDC product.
10 June 2013	The definition of primary endpoint of IC was changed from being determined at isotime to being determined at rest (prior to exercise) to avoid introducing a bias. This was due to the incomplete cross-over design, which had the possibility for treatment comparisons at isotime to be at different time points. The original primary endpoint 'IC determined at isotime' and the original key-secondary endpoint 'intensity of breathing discomfort at isotime' were included among the 'further' efficacy endpoints. The slope of the intensity of breathing discomfort during CWRCE to symptom limitation at 75% Wcap after 6 weeks of treatment and FEV1 (1 h post-dose) after 6 weeks of treatment were included as secondary endpoints (slope defined as [intensity of breathing discomfort at the end of exercise minus intensity of breathing discomfort at rest]/endurance time). FEV1 (1 h post-dose) on Day 1 of treatment, Forced Vital Capacity (FVC) (1 h post-dose) on Day 1 and after 6 weeks of treatment, and FEV1, FVC (trough) after 6 weeks of treatment were added as "further" efficacy endpoints. Intensity of breathing discomfort and intensity of leg discomfort (Borg scale) were changed to be determined at isotime and not during exercise. The trial protocol had specified that the effect of Tio+Olo FDC was to be tested at the 1-sided 0.025 level. This is the same as testing at the 2-sided 0.05 level if the treatment effect is in favour of Tio+Olo FDC compared with placebo. To aid in the interpretation of the results, 1-sided superiority hypothesis testing was changed to 2-sided hypothesis testing, and the corresponding 1-sided type I error rate of 0.025 was changed to 2-sided type I error rate of 0.05. Statistical significance was therefore declared if hypothesis tests were significant at the 2-sided 0.05 level, the treatment effect favoured Tio+Olo FDC, and all previous hypothesis tests in the hierarchy had shown statistical superiority.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported