Clinical trial results:
Randomized, double-blind, double-dummy, active-controlled, 4 period complete cross-over study to compare the effect on lung function of 6 weeks once daily treatment with orally inhaled Tiotropium+Olodaterol fixed dose combination delivered by the Respimat® inhaler vs. 6 weeks twice daily treatment with Fluticasone Propionate+Salmeterol fixed dose combination delivered by the Accuhaler® in patients with Chronic Obstructive Pulmonary Disease (COPD). [ENERGITO™]

Summary

EudraCT number	2013-000808-41
Trial protocol	ES NL CZ BE DK SE HU DE
Global end of trial date	04 February 2015

Results information

Result version number	v2 (current)
This version publication date	16 September 2016
First version publication date	01 July 2016
Version creation reason	• Correction of full data set One value for endpoint "FEV1 AUC (12−24h) Change from Patient Baseline after 6 Weeks of Treatment" needs correction

Trial information

Trial identification

Sponsor protocol code	1237.11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01969721
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	20 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2015
Global end of trial reached?	Yes
Global end of trial date	04 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the trial is to compare the lung function profile of once daily treatment with Tiotropium+Olodaterol (Tio+Olo) Fixed Dose Combination (FDC) [2.5/5µg and 5/5µg] delivered by the Respimat® with the lung function profile of twice daily treatment with Fluticasone propionate+Salmeterol (F+S) FDC [250/50µg and 500/50µg] delivered by the Accuhaler® after 6 weeks of treatment in patients with COPD.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were 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.

Background therapy: -

Evidence for comparator:

Placebo matching Tiotropium + Olodaterol inhalation solution via Respimat® inhaler inhaled orally. Fluticasone+Salmeterol FDC (inhalation powder) via Accuhaler® inhaled orally as 250 µg/50 µg or 500 µg/50 µg per inhalation, twice daily. Placebo matching Fluticasone+Salmeterol inhalation powder via Accuhaler® inhaled orally.

Actual start date of recruitment	29 October 2013
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	Belgium: 16
Country: Number of subjects enrolled	Czech Republic: 39
Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Hungary: 36
Country: Number of subjects enrolled	Netherlands: 78
Country: Number of subjects enrolled	Sweden: 19
Worldwide total number of subjects	288
EEA total number of subjects	288

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)	159
From 65 to 84 years	129
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomized, double-blind, double-dummy, active-controlled, 4-treatment, 4-period, complete cross-over design. The treatments were A: T+O 2.5/5; B: T+O 5/5; C: F+S 250/50; D: F+S 500/50. ABCD, BDAC, CADB, and DCBA were four treatment sequences.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist sites to ensure that they met all implemented inclusion/exclusion criteria. Subjects were not randomised to trial drug if any of the specific entry criteria was violated. In this study, 288 subjects were enrolled.

Period 1

Period 1 title	Overall trial by sequence
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	T+O 2.5/5 / T+O 5/5 / F+S 250/50 / F+S 500/50

Arm description:

Tiotropium+Olodaterol (T+O) FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching Fluticasone propionate+Salmeterol (F+S) FDC inhalation powder via Accuhaler® twice daily in period 1, followed with T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 2, followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 3, then followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 4. Each treatment period was 6 weeks (wks) and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

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 administered via the Respimat® inhaler once daily.

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 administered via the Respimat® inhaler once daily.

Investigational medicinal product name	Fluticasone propionate 250 µg / Salmeterol 50 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder

Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol (250/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

Investigational medicinal product name	Fluticasone propionate 500 µg / Salmeterol 50 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol (500/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

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

Dosage and administration details:

Tiotropium+Olodaterol placebo inhalation solution was administered via the Respimat® inhaler once daily.

Investigational medicinal product name	Placebo matching Fluticasone propionate / Salmeterol_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol placebo inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

Arm title	T+O 5/5 / F+S 500/50 / T+O 2.5/5 / F+S 250/50

Arm description:

Tiotropium+Olodaterol (T+O) FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching Fluticasone propionate+Salmeterol (F+S) FDC inhalation powder via Accuhaler® twice daily in period 1, followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily followed and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 2, followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 3, then followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

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 administered via the Respimat® inhaler once daily.

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 (2.5/5 µg) FDC inhalation solution was administered via the Respimat® inhaler once daily.

Investigational medicinal product name	Fluticasone propionate 250 µg / Salmeterol 50 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol (250/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

Investigational medicinal product name	Fluticasone propionate 500 µg / Salmeterol 50 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol (500/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

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

Dosage and administration details:

Tiotropium+Olodaterol placebo inhalation solution was administered via the Respimat® inhaler once daily.

Investigational medicinal product name	Placebo matching Fluticasone propionate / Salmeterol_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol placebo inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

Arm title	F+S 250/50 / T+O 2.5/5 / F+S 500/50 / T+O 5/5

Arm description:

Fluticasone propionate+Salmeterol (F+S) FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching Tiotropium+Olodaterol (T+O) FDC inhalation solution via Respimat® inhaler once daily in the morning in period 1, followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 2, followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 3, then followed T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning with placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

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:

Tiotropium+Olodaterol (5/5 µg) FDC inhalation solution was administered via the Respimat® inhaler once daily.

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 administered via the Respimat® inhaler once daily.

Investigational medicinal product name	Fluticasone propionate 250 µg / Salmeterol 50 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol (250/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

Investigational medicinal product name	Fluticasone propionate 500 µg / Salmeterol 50 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol (500/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

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

Dosage and administration details:

Tiotropium+Olodaterol placebo inhalation solution was administered via the Respimat® inhaler once daily.

Investigational medicinal product name	Placebo matching Fluticasone propionate / Salmeterol_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol placebo inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

Arm title	F+S 500/50 / F+S 250/50 / T+O 5/5 / T+O 2.5/5

Arm description:

Fluticasone propionate+Salmeterol (F+S) FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching Tiotropium+Olodaterol (T+O) FDC inhalation solution via Respimat® inhaler once daily in the morning in period 1, followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 2, followed with T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 3, then followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

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 administered via the Respimat® inhaler once daily.

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 administered via the Respimat® inhaler once daily.

Investigational medicinal product name	Fluticasone propionate 250 µg / Salmeterol 50 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol (250/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

Investigational medicinal product name	Fluticasone propionate 500 µg / Salmeterol 50 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol (500/50 µg) FDC inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

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

Dosage and administration details:

Tiotropium+Olodaterol placebo inhalation solution was administered via the Respimat® inhaler once daily.

Investigational medicinal product name	Placebo matching Fluticasone propionate / Salmeterol_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol placebo inhalation powder was inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

Number of subjects in period 1	T+O 2.5/5 / T+O 5/5 / F+S 250/50 / F+S 500/50	T+O 5/5 / F+S 500/50 / T+O 2.5/5 / F+S 250/50	F+S 250/50 / T+O 2.5/5 / F+S 500/50 / T+O 5/5
Started	58	69	50
Completed	54	57	45
Not completed	4	12	5
Adverse event, serious fatal	-	-	1
Non compliant with protocol	1	1	-
Adverse event, non-fatal	3	8	2
Other not defined	-	2	-
Discontinued during washout periods.	-	1	1
Lack of efficacy	-	-	1

Number of subjects in period 1	F+S 500/50 / F+S 250/50 / T+O 5/5 / T+O 2.5/5
Started	52
Completed	46
Not completed	6
Adverse event, serious fatal	-
Non compliant with protocol	2
Adverse event, non-fatal	2
Other not defined	-
Discontinued during washout periods.	2
Lack of efficacy	-

Period 2

Period 2 title	Overall trial (treatment period)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	No
Arm title	T+O 2.5/5 / F+S placebo

Arm description:

Subjects were administered with Fixed Dose Combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily. Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

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:

Tiotropium+Olodaterol (2.5/5 µg) FDC inhalation solutions were administered via the Respimat® inhaler once daily.

Investigational medicinal product name	Placebo matching Fluticasone propionate / Salmeterol_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

Arm title	T+O 5/5 / F+S placebo

Arm description:

Subjects were administered with Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily. Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Arm type	Active comparator
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 µg/5 µg) FDC inhalation solutions were administered via the Respimat® inhaler once daily.

Investigational medicinal product name	Placebo matching Fluticasone propionate / Salmeterol_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times.

Arm title	F+S 250/50 / T+O placebo

Arm description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 250 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone propionate 250 µg / Salmeterol 50 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol (250/50 µg) FDC inhalation powders were inhaled orally twice daily via Accuhaler®.

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

Dosage and administration details:

Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily.

Arm title	F+S 500/50 / T+O placebo

Arm description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 500 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Arm type	Active comparator
Investigational medicinal product name	Fluticasone propionate 500 µg / Salmeterol 50 µg_FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate+Salmeterol (500/50 µg) FDC inhalation powders were inhaled orally twice daily via Accuhaler®.

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

Dosage and administration details:

Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily.

Notes:

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

Justification: In this study, Period 1 evaluates by sequence and baseline characteristics is defined based on overall trial by treatment period, thus period 2 was selected as a baseline period to define the baseline characteristics of this trial.

Number of subjects in period 2	T+O 2.5/5 / F+S placebo	T+O 5/5 / F+S placebo	F+S 250/50 / T+O placebo
Started	215	221	212
Completed	210	213	209
Not completed	5	8	3
Adverse event, serious fatal	-	1	-
Non compliant with protocol	1	1	-
Adverse event, non-fatal	3	5	2
Other not defined	1	1	-
Lack of efficacy	-	-	1

Number of subjects in period 2	F+S 500/50 / T+O placebo
Started	219
Completed	212
Not completed	7
Adverse event, serious fatal	-
Non compliant with protocol	2
Adverse event, non-fatal	5
Other not defined	-
Lack of efficacy	-

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 dose of the trial medication.

Reporting group values	Overall trial (treatment period)	Total	
Number of subjects	229	229	
Age categorical Units: Subjects			

Age Continuous |			
Treated Set: All randomised patients who received any dose of the trial medication.			
Units: years			
arithmetic mean	63.6		
standard deviation	± 7.6	-	
Gender, Male/Female Units: Participants			
Female	81	81	
Male	148	148	

End points reporting groups

Reporting group title	T+O 2.5/5 / T+O 5/5 / F+S 250/50 / F+S 500/50

Reporting group description:

Tiotropium+Olodaterol (T+O) FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching Fluticasone propionate+Salmeterol (F+S) FDC inhalation powder via Accuhaler® twice daily in period 1, followed with T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 2, followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 3, then followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 4. Each treatment period was 6 weeks (wks) and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

Reporting group title	T+O 5/5 / F+S 500/50 / T+O 2.5/5 / F+S 250/50

Reporting group description:

Tiotropium+Olodaterol (T+O) FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching Fluticasone propionate+Salmeterol (F+S) FDC inhalation powder via Accuhaler® twice daily in period 1, followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily followed and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 2, followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 3, then followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

Reporting group title	F+S 250/50 / T+O 2.5/5 / F+S 500/50 / T+O 5/5

Reporting group description:

Fluticasone propionate+Salmeterol (F+S) FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching Tiotropium+Olodaterol (T+O) FDC inhalation solution via Respimat® inhaler once daily in the morning in period 1, followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 2, followed with F+S FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 3, then followed T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning with placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

Reporting group title	F+S 500/50 / F+S 250/50 / T+O 5/5 / T+O 2.5/5

Reporting group description:

Fluticasone propionate+Salmeterol (F+S) FDC (500 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching Tiotropium+Olodaterol (T+O) FDC inhalation solution via Respimat® inhaler once daily in the morning in period 1, followed with F+S FDC (250 µg/50 µg) inhalation powder via Accuhaler® twice daily and placebo matching T+O FDC inhalation solution via Respimat® inhaler once daily in the morning in period 2, followed with T+O FDC (5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 3, then followed with T+O FDC (2.5 µg/5 µg) inhalation solution via Respimat® inhaler once daily in the morning and placebo Diskus® matching F+S FDC inhalation powder via Accuhaler® twice daily in period 4. Each treatment period was 6 wks and washing-out period 3 wks. Treatment sequence was 33 wks including 4 treatment periods and 3 washing-out periods.

Reporting group title	T+O 2.5/5 / F+S placebo

Reporting group description:

Subjects were administered with Fixed Dose Combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily. Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Reporting group title	T+O 5/5 / F+S placebo

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily.

Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Reporting group title	F+S 250/50 / T+O placebo

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 250 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Reporting group title	F+S 500/50 / T+O placebo

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 500 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Primary: FEV1 AUC (0−12h) Change from Patient Baseline after 6 Weeks of Treatment

End point title	FEV1 AUC (0−12h) Change from Patient Baseline after 6 Weeks of Treatment

End point description:

Change from patient baseline in Forced Expiratory Volume in one second (FEV1) Area Under the FEV1-time Curve from 0 to 12hours post-dose (AUC 0-12h) [L] after 6 weeks of treatment. Measured values presented are actually adjusted means. The period baseline is defined as the pre-dose measurement taken at on the day 1 of each period. The patient baseline is defined as the mean of non-missing period baselines for each patient.
Full Analysis Set (FAS): Included all randomised patients who were documented to have had received any dose of trial medication and who had both period baseline and any evaluable post-baseline measurement for the primary efficacy endpoint.

End point type	Primary

End point timeframe:

Baseline and 6 weeks.

End point values	T+O 2.5/5 / F+S placebo	T+O 5/5 / F+S placebo	F+S 250/50 / T+O placebo	F+S 500/50 / T+O placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	214[1]	216[2]	211[3]	217[4]
Units: Litres				
arithmetic mean (standard error)	0.295 (± 0.014)	0.317 (± 0.014)	0.192 (± 0.015)	0.188 (± 0.014)

Notes:

[1] - Full Analysis Set (FAS)

[2] - Full Analysis Set (FAS)

[3] - Full Analysis Set (FAS)

[4] - Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Statistical analysis 1

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.

Comparison groups	T+O 5/5 / F+S placebo v F+S 250/50 / T+O placebo
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.0001 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.103
upper limit	0.147
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[5] - The actual number of subjects analyzed is 221. 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 (427) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S placebo - F+S 250/50 / T+O placebo adjusted mean FEV1 AUC 0-12h change from patient baseline (L).

[6] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 2

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.

Comparison groups	T+O 5/5 / F+S placebo v F+S 500/50 / T+O placebo
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.129
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.107
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[7] - The actual number of subjects analyzed is 221. 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 (433) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S placebo - F+S

500/50 / T+O placebo adjusted mean FEV1 AUC 0-12h change from patient baseline (L).

[8] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 3

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.

Comparison groups	T+O 2.5/5 / F+S placebo v F+S 250/50 / T+O placebo
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.081
upper limit	0.124
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[9] - The actual number of subjects analyzed is 221. 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. Difference calculated as T+O 2.5/5 / F+S placebo - F+S 250/50 / T+O placebo adjusted mean FEV1 AUC 0-12h change from patient baseline (L).
[10] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 4

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.

Comparison groups	T+O 2.5/5 / F+S placebo v F+S 500/50 / T+O placebo
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.085
upper limit	0.128
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[11] - The actual number of subjects analyzed is 219. 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 (431) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S placebo - F+S 500/50 / T+O placebo adjusted mean FEV1 AUC 0-12h change from patient baseline (L).

[12] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Secondary: FEV1 AUC (0−24h) Change from Patient Baseline after 6 Weeks of Treatment

End point title	FEV1 AUC (0−24h) Change from Patient Baseline after 6 Weeks of Treatment

End point description:

Change from patient baseline in Forced Expiratory Volume in one second (FEV1) Area Under the FEV1-time Curve from 0 to 24 hours post-dose (AUC 0-24h) [L] after 6 weeks of treatment. Measured values presented are actually adjusted means. The period baseline is defined as the pre-dose measurement taken at on the day 1 of each period. The patient baseline is defined as the mean of non-missing period baselines for each patient.

End point type	Secondary

End point timeframe:

Baseline and 6 weeks.

End point values	T+O 2.5/5 / F+S placebo	T+O 5/5 / F+S placebo	F+S 250/50 / T+O placebo	F+S 500/50 / T+O placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	214[13]	216[14]	211[15]	217[16]
Units: Litres				
arithmetic mean (standard error)	0.228 (± 0.014)	0.244 (± 0.014)	0.162 (± 0.014)	0.159 (± 0.014)

Notes:

[13] - Full Analysis Set (FAS)

[14] - Full Analysis Set (FAS)

[15] - Full Analysis Set (FAS)

[16] - Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Statistical analysis 1

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.

Comparison groups	T+O 5/5 / F+S placebo v F+S 250/50 / T+O placebo
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.0001 [18]
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.082

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.061
upper limit	0.103
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[17] - The actual number of subjects analyzed is 221. 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 (427) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean FEV1 AUC 0-24h change from patient baseline (L).

[18] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 2

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.

Comparison groups	T+O 5/5 / F+S placebo v F+S 500/50 / T+O placebo
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001 [20]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.065
upper limit	0.107
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[19] - The actual number of subjects analyzed is 221. 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 (433) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean FEV1 AUC 0-24h change from patient baseline (L).

[20] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 3

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.

Comparison groups	T+O 2.5/5 / F+S placebo v F+S 250/50 / T+O placebo

Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.0001 [22]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.045
upper limit	0.086
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[21] - The actual number of subjects analyzed is 215. 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. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean FEV1 AUC 0-24h change from patient baseline (L).
[22] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 4

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.

Comparison groups	T+O 2.5/5 / F+S placebo v F+S 500/50 / T+O placebo
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	< 0.0001 [24]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.048
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[23] - The actual number of subjects analyzed is 219. 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 (431) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean FEV1 AUC 0-24h change from patient baseline (L).
[24] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Secondary: Trough FEV1 Change from Patient Baseline after 6 Weeks of Treatment

End point title	Trough FEV1 Change from Patient Baseline after 6 Weeks of Treatment

End point description:

Change from patient baseline in trough Forced Expiratory Volume in one second (FEV1) after 6 weeks of treatment. Trough FEV1 was defined as the mean of the 23h and 23h 50min (minutes) post-dose FEV1 measurements. Measured values presented are actually adjusted means. The period baseline is defined as the pre-dose measurement taken at on the day 1 of each period. The patient baseline is defined as the mean of non-missing period baselines for each patient.

End point type	Secondary

End point timeframe:

Baseline and 6 weeks.

End point values	T+O 2.5/5 / F+S placebo	T+O 5/5 / F+S placebo	F+S 250/50 / T+O placebo	F+S 500/50 / T+O placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	214[25]	216[26]	211[27]	217[28]
Units: Litres				
arithmetic mean (standard error)	0.192 (± 0.014)	0.197 (± 0.014)	0.15 (± 0.014)	0.139 (± 0.014)

Notes:

[25] - Full Analysis Set (FAS)

[26] - Full Analysis Set (FAS)

[27] - Full Analysis Set (FAS)

[28] - Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Statistical analysis 1

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.

Comparison groups	T+O 5/5 / F+S placebo v F+S 250/50 / T+O placebo
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.0002 [30]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.071
Variability estimate	Standard error of the mean
Dispersion value	0.012

Notes:

[29] - The actual number of subjects analyzed is 221. 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 (427) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean trough FEV1 change from patient baseline (L).

[30] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 2

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.

Comparison groups	T+O 5/5 / F+S placebo v F+S 500/50 / T+O placebo
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.0001 [32]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.082
Variability estimate	Standard error of the mean
Dispersion value	0.012

Notes:

[31] - The actual number of subjects analyzed is 221. 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 (433) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean trough FEV1 change from patient baseline (L).
[32] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 3

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.

Comparison groups	T+O 2.5/5 / F+S placebo v F+S 250/50 / T+O placebo
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.0007 [34]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.067
Variability estimate	Standard error of the mean
Dispersion value	0.012

Notes:

[33] - The actual number of subjects analyzed is 215. 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. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean trough FEV1 change from patient baseline (L).

[34] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 4

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.

Comparison groups	T+O 2.5/5 / F+S placebo v F+S 500/50 / T+O placebo
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	< 0.0001 [36]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.054
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.078
Variability estimate	Standard error of the mean
Dispersion value	0.012

Notes:

[35] - The actual number of subjects analyzed is 219. 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 (431) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean trough FEV1 change from patient baseline (L).

[36] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Secondary: FEV1 AUC (12−24h) Change from Patient Baseline after 6 Weeks of Treatment

End point title	FEV1 AUC (12−24h) Change from Patient Baseline after 6 Weeks of Treatment

End point description:

Change from patient baseline in Forced Expiratory Volume in one second (FEV1) Area Under the FEV1-time Curve from 12 to 24 hours post-dose (AUC 12-24h) [L] after 6 weeks of treatment. Measured values presented are actually adjusted means. The period baseline is defined as the pre-dose measurement taken at on the day 1 of each period. The patient baseline is defined as the mean of non-missing period baselines for each patient.

End point type	Secondary

End point timeframe:

Baseline and 6 weeks.

End point values	T+O 2.5/5 / F+S placebo	T+O 5/5 / F+S placebo	F+S 250/50 / T+O placebo	F+S 500/50 / T+O placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	214[37]	216[38]	211[39]	217[40]
Units: Litres				
arithmetic mean (standard error)	0.164 (± 0.014)	0.172 (± 0.014)	0.132 (± 0.014)	0.129 (± 0.014)

Notes:

[37] - Full Analysis Set (FAS)

[38] - Full Analysis Set (FAS)

[39] - Full Analysis Set (FAS)

[40] - Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Statistical analysis 1

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.

Comparison groups	T+O 5/5 / F+S placebo v F+S 250/50 / T+O placebo
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	= 0.0007 [42]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.062
Variability estimate	Standard error of the mean
Dispersion value	0.012

Notes:

[41] - The actual number of subjects analyzed is 221. 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 (427) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean FEV1 AUC (12−24h) change from patient baseline (L).

[42] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 2

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.

Comparison groups	T+O 5/5 / F+S placebo v F+S 500/50 / T+O placebo

Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority[43]
P-value	= 0.0002 [44]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.021
upper limit	0.065
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[43] - The actual number of subjects analyzed is 221. 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 (433) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean FEV1 AUC (12−24h) change from patient baseline (L).
[44] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 3

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.

Comparison groups	T+O 2.5/5 / F+S placebo v F+S 250/50 / T+O placebo
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority[45]
P-value	= 0.0146 [46]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.051
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[45] - The actual number of subjects analyzed is 215. 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. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 250/50 / T+O Placebo adjusted mean FEV1 AUC (12−24h) change from patient baseline (L).
[46] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 4

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.

Comparison groups	T+O 2.5/5 / F+S placebo v F+S 500/50 / T+O placebo
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	= 0.0055 [48]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.054
Variability estimate	Standard error of the mean
Dispersion value	0.011

Notes:

[47] - The actual number of subjects analyzed is 219. 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 (431) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S Placebo - F+S 500/50 / T+O Placebo adjusted mean FEV1 AUC (12−24h) change from patient baseline (L).

[48] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Secondary: FEV1 Peak (0−3h) Change from Patient Baseline after 6 Weeks of Treatment

End point title	FEV1 Peak (0−3h) Change from Patient Baseline after 6 Weeks of Treatment

End point description:

Change from patient baseline in Forced Expiratory Volume in one second (FEV1) peak (0-3 hours) after 6 weeks of treatment. FEV1 peak (0-3 hours) was defined as the maximum FEV1 value measured within the first three hours post dosing. Measured values presented are actually adjusted means.

End point type	Secondary

End point timeframe:

Baseline and 6 weeks.

End point values	T+O 2.5/5 / F+S placebo	T+O 5/5 / F+S placebo	F+S 250/50 / T+O placebo	F+S 500/50 / T+O placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	214[49]	216[50]	211[51]	217[52]
Units: Litres				
arithmetic mean (standard error)	0.401 (± 0.016)	0.432 (± 0.016)	0.291 (± 0.016)	0.285 (± 0.015)

Notes:

[49] - Full Analysis Set (FAS)

[50] - Full Analysis Set (FAS)

[51] - Full Analysis Set (FAS)

[52] - Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Statistical analysis 1

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.

Comparison groups	T+O 5/5 / F+S placebo v F+S 250/50 / T+O placebo
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	< 0.0001 [54]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.142
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.118
upper limit	0.166
Variability estimate	Standard error of the mean
Dispersion value	0.012

Notes:

[53] - The actual number of subjects analyzed is 221. 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 (427) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S Placebo - F+S 250/50 / T+O placebo adjusted mean FEV1 peak (0−3h) change from patient baseline (L).
[54] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 2

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.

Comparison groups	T+O 5/5 / F+S placebo v F+S 500/50 / T+O placebo
Number of subjects included in analysis	433
Analysis specification	Pre-specified
Analysis type	superiority[55]
P-value	< 0.0001 [56]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.123
upper limit	0.171
Variability estimate	Standard error of the mean
Dispersion value	0.012

Notes:

[55] - The actual number of subjects analyzed is 221. 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 (433) does not reflect the actual number. Difference calculated as T+O 5/5 / F+S placebo - F+S

500/50 / T+O placebo adjusted mean FEV1 peak (0−3h) change from patient baseline (L).

[56] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 3

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.

Comparison groups	T+O 2.5/5 / F+S placebo v F+S 250/50 / T+O placebo
Number of subjects included in analysis	425
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	< 0.0001 [58]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.087
upper limit	0.135
Variability estimate	Standard error of the mean
Dispersion value	0.012

Notes:

[57] - The actual number of subjects analyzed is 215. 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. Difference calculated as T+O 2.5/5 / F+S placebo - F+S 250/50 / T+O placebo adjusted mean FEV1 peak (0−3h) change from patient baseline (L).
[58] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Statistical analysis title	Statistical analysis 4

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.

Comparison groups	T+O 2.5/5 / F+S placebo v F+S 500/50 / T+O placebo
Number of subjects included in analysis	431
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	< 0.0001 [60]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.116
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.092
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.012

Notes:

[59] - The actual number of subjects analyzed is 219. 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 (431) does not reflect the actual number. Difference calculated as T+O 2.5/5 / F+S placebo - F+S 500/50 / T+O placebo adjusted mean FEV1 peak (0−3h) change from patient baseline (L).

[60] - p-value is not adjusted for multiple comparisons. A priori threshold for statistical significance is two-sided alpha=0.05.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug intake until 21 days after last drug intake, up to 88 days.

Adverse event reporting additional description:

AEs are displayed by treatment, however in total patients were in the study for up to 223 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	T+O 2.5/5 / F+S placebo

Reporting group description:

Subjects were administered with Fixed Dose Combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily. Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Reporting group title	F+S 250/50 / T+O placebo

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 250 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Reporting group title	F+S 500/50 / T+O placebo

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Fluticasone propionate 500 µg and Salmeterol 50 µg. Fluticasone propionate+Salmeterol FDC inhalation powders were inhaled orally twice daily via Accuhaler®. Tiotropium+Olodaterol placebo inhalation solutions were administered via the Respimat® inhaler once daily. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Reporting group title	T+O 5/5 / F+S placebo

Reporting group description:

Subjects were administered with Fixed dose combination (FDC) of Tiotropium 5 µg and Olodaterol 5 µg. Tiotropium+Olodaterol FDC inhalation solutions were administered via the Respimat® inhaler once daily. Fluticasone propionate+Salmeterol placebo inhalation powders were inhaled orally twice daily via Accuhaler® in accordance with predefined treatment administration times. Treatments were taken for 6 weeks and each treatment period was separated by a washout period of at least 21 days.

Serious adverse events	T+O 2.5/5 / F+S placebo	F+S 250/50 / T+O placebo	F+S 500/50 / T+O placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 215 (2.79%)	4 / 212 (1.89%)	9 / 219 (4.11%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fibula fracture			

subjects affected / exposed	1 / 215 (0.47%)	0 / 212 (0.00%)	0 / 219 (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
Tibia fracture			
subjects affected / exposed	1 / 215 (0.47%)	0 / 212 (0.00%)	0 / 219 (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
Toxicity to various agents			
subjects affected / exposed	0 / 215 (0.00%)	1 / 212 (0.47%)	0 / 219 (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
Vascular graft occlusion			
subjects affected / exposed	1 / 215 (0.47%)	0 / 212 (0.00%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	1 / 219 (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
Atrial flutter			
subjects affected / exposed	1 / 215 (0.47%)	0 / 212 (0.00%)	0 / 219 (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
Cardiac failure			
subjects affected / exposed	1 / 215 (0.47%)	0 / 212 (0.00%)	0 / 219 (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
Myocardial infarction			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	1 / 219 (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
Myocardial ischaemia			

subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	0 / 219 (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
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	0 / 219 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 215 (0.00%)	1 / 212 (0.47%)	0 / 219 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	0 / 219 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	1 / 219 (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
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	0 / 219 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 215 (0.00%)	1 / 212 (0.47%)	0 / 219 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 215 (0.93%)	2 / 212 (0.94%)	4 / 219 (1.83%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	0 / 219 (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
Renal failure			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	0 / 219 (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
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	1 / 219 (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
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	0 / 219 (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
Lobar pneumonia			
subjects affected / exposed	0 / 215 (0.00%)	1 / 212 (0.47%)	0 / 219 (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
Osteomyelitis			
subjects affected / exposed	1 / 215 (0.47%)	0 / 212 (0.00%)	0 / 219 (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
Pneumonia			
subjects affected / exposed	0 / 215 (0.00%)	1 / 212 (0.47%)	1 / 219 (0.46%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sialoadenitis			
subjects affected / exposed	1 / 215 (0.47%)	0 / 212 (0.00%)	0 / 219 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 215 (0.00%)	0 / 212 (0.00%)	0 / 219 (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

Serious adverse events	T+O 5/5 / F+S placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 221 (3.17%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Toxicity to various agents			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular graft occlusion			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	1 / 221 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 221 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Transient ischaemic attack			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 221 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 221 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 221 (0.90%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 221 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 221 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 221 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lobar pneumonia			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sialoadenitis			
subjects affected / exposed	0 / 221 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 221 (0.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	T+O 2.5/5 / F+S placebo	F+S 250/50 / T+O placebo	F+S 500/50 / T+O placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 215 (9.77%)	19 / 212 (8.96%)	24 / 219 (10.96%)
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	10 / 215 (4.65%)	7 / 212 (3.30%)	15 / 219 (6.85%)
occurrences (all)	10	8	15
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 215 (5.58%)	13 / 212 (6.13%)	11 / 219 (5.02%)
occurrences (all)	12	13	11

Non-serious adverse events	T+O 5/5 / F+S placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 221 (12.67%)		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	18 / 221 (8.14%)		
occurrences (all)	20		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 221 (5.43%)		
occurrences (all)	12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2014	Global Amendment 1 included clarifications and administrative changes that did not require IRB/IEC/CA approval prior to implementation. Weather station, Accuhaler training and visit 10 for pregnancy testing was added. "patients taking Tiotropium prior to study entry" was changed to "patients taking a LAMA prior to study entry". Update with data from Phase III studies and Tiospir results. Further clarification of medication restrictions, dosing times and "rescheduling prior to randomisation" was provided. All hypotheses were changed to two-sided hypotheses with alpha=0.05. Handling of missing data and provided more details in the TSAP. Definition of period baseline was updated, correction to listedness section and comparator SPC was added.
04 February 2015	Amendment 2 was a change in the hierarchical testing strategy. The testing hierarchy was modified such that the primary and key secondary endpoints were first tested on the Tio+Olo 5/5 µg dose followed by the Tio+Olo 2.5/5 µg dose because Tio+Olo 5/5 µg was the dose planned for marketing. Global Amendment 2 did not require IRB/IEC/CA approval prior to implementation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

1 subject with missing information for number of enrolled subjects has been included in age range Elderly (From 65-84 years) as the missing category is not available.
Update initiated unnecessarily; Results in version 1 and version 2 are same.

Notes: