

**Clinical trial results:**

An exploratory, 12 week, randomised, partially double-blinded, placebo-controlled parallel group trial to explore the effects of once daily treatments of orally inhaled tiotropium + olodaterol fixed dose combination or tiotropium (both delivered by Respimat® inhaler), supervised exercise training and behavior modification on exercise capacity and physical activity in patients with Chronic Obstructive Pulmonary Disease (COPD).

Summary

EudraCT number	2013-002671-18
Trial protocol	GB DK BE PT DE AT PL
Global end of trial date	31 October 2015

Results information

Result version number	v1 (current)
This version publication date	15 October 2016
First version publication date	15 October 2016

Trial information**Trial identification**

Sponsor protocol code	1237.16
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02085161
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, clintrriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintrriage.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	15 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2015
Global end of trial reached?	Yes
Global end of trial date	31 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective of this trial was to explore the effects of bronchodilator monotherapy (tiotropium) plus behavioural modification, bronchodilator combination therapy (tiotropium + olodaterol fixed dose combination [FDC]) plus behavioural modification, and bronchodilator combination therapy (tiotropium + olodaterol FDC) plus exercise training plus behavioural modification on exercise capacity and physical activity in COPD patients.

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. Patients in placebo arm have used their maintenance inhaled corticosteroids through the study, have been, as all patients in the trial, provided with a short acting bronchodilator for rescue use, had to be clinically stable 4 weeks prior to randomization, and were withdrawn from the trial in case of COPD exacerbation requiring extensive treatment and/or hospitalization.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2014
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	Austria: 21
Country: Number of subjects enrolled	Australia: 36
Country: Number of subjects enrolled	Belgium: 53
Country: Number of subjects enrolled	Canada: 57
Country: Number of subjects enrolled	Germany: 134
Country: Number of subjects enrolled	Denmark: 27
Country: Number of subjects enrolled	New Zealand: 14
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	United States: 40

Worldwide total number of subjects	448
EEA total number of subjects	301

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)	182
From 65 to 84 years	266
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

An exploratory, randomised, partially double-blinded, placebo-controlled, parallel group trial to explore the effects of tiotropium + olodaterol fixed dose combination (FDC) or tiotropium, supervised exercise training and behaviour modification on exercise capacity and physical activity in patients with Chronic Obstructive Pulmonary Disease (COPD)

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended a specialist site which ensured that they met all strictly implemented inclusion/exclusion criteria. Subjects were not to be entered to trial treatment if any one of the specific entry criteria were violated.

Period 1

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

Blinding implementation details:

Patients in this partially double-blind trial remained blinded with regard to the randomised treatment assignments until after database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo with behavioural modification (BM)

Arm description:

Placebo matching tiotropium + olodaterol FDC or tiotropium solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks. In total 76 subjects were randomised for this arm but one subject was not treated and hence the number of subjects started is 75.

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

Dosage and administration details:

Placebo matching tiotropium + olodaterol FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

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

Dosage and administration details:

Placebo matching tiotropium solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

Arm title	Tiotropium (Tio) 5 micro-grams (μg) with BM
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Arm description:

Tiotropium 5 μg solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

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

Dosage and administration details:

Tiotropium 5 µg solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

Arm title	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
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Arm description:

Tiotropium 5 µg plus olodaterol 5 µg FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

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

Dosage and administration details:

Tiotropium 5 µg plus olodaterol 5 µg FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

Arm title	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
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Arm description:

Tiotropium 5 µg plus olodaterol 5 µg FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks; ET was conducted for 8 weeks.

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

Dosage and administration details:

Tiotropium 5 µg plus olodaterol 5 µg FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks; ET was conducted for 8 weeks.

Number of subjects in period 1^[1]	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micro-grams (µg) with BM	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Started	75	76	76
Completed	64	66	71
Not completed	11	10	5
Adverse event, serious fatal	1	-	1
Consent withdrawn by subject	2	4	-
Adverse event, non-fatal	7	5	3
Other Reason	1	-	1
Protocol deviation	-	1	-

Number of subjects in period 1	Tio+Olo (5/5 µg) FDC with exercise
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[1]	training (ET) and BM
Started	76
Completed	66
Not completed	10
Adverse event, serious fatal	-
Consent withdrawn by subject	3
Adverse event, non-fatal	5
Other Reason	1
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups

Reporting group title	Placebo with behavioural modification (BM)
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Reporting group description:

Placebo matching tiotropium + olodaterol FDC or tiotropium solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks. In total 76 subjects were randomised for this arm but one subject was not treated and hence the number of subjects started is 75.

Reporting group title	Tiotropium (Tio) 5 micro-grams (μg) with BM
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Reporting group description:

Tiotropium 5 μg solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

Reporting group title	Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM
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Reporting group description:

Tiotropium 5 μg plus olodaterol 5 μg FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

Reporting group title	Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM
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Reporting group description:

Tiotropium 5 μg plus olodaterol 5 μg FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks; ET was conducted for 8 weeks.

Reporting group values	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micro-grams (μg) with BM	Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM
Number of subjects	75	76	76
Age categorical Units: Subjects			

Age Continuous			
Treated set (TS): This patient set included all patients of the Randomised set (All patients who signed informed consent form and were also randomised, regardless whether the patient was treated with study medication or not) who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: Years			
arithmetic mean	64.4	65.1	65
standard deviation	± 6.6	± 6.4	± 6.9
Gender, Male/Female			
Treated set (TS): This patient set included all patients of the Randomised set (All patients who signed informed consent form and were also randomised, regardless whether the patient was treated with study medication or not) who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: Participants			
Female	23	21	28
Male	52	55	48

Reporting group values	Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM	Total	
Number of subjects	76	303	
Age categorical Units: Subjects			

Age Continuous			
Treated set (TS): This patient set included all patients of the Randomised set (All patients who signed informed consent form and were also randomised, regardless whether the patient was treated with study medication or not) who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: Years			
arithmetic mean	64.7		
standard deviation	± 6.5	-	
Gender, Male/Female			
Treated set (TS): This patient set included all patients of the Randomised set (All patients who signed informed consent form and were also randomised, regardless whether the patient was treated with study medication or not) who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: Participants			
Female	31	103	
Male	45	200	

End points

End points reporting groups

Reporting group title	Placebo with behavioural modification (BM)
Reporting group description: Placebo matching tiotropium + olodaterol FDC or tiotropium solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks. In total 76 subjects were randomised for this arm but one subject was not treated and hence the number of subjects started is 75.	
Reporting group title	Tiotropium (Tio) 5 micro-grams (μg) with BM
Reporting group description: Tiotropium 5 μg solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.	
Reporting group title	Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM
Reporting group description: Tiotropium 5 μg plus olodaterol 5 μg FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.	
Reporting group title	Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM
Reporting group description: Tiotropium 5 μg plus olodaterol 5 μg FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks; ET was conducted for 8 weeks.	

Primary: Endurance time during Endurance Shuttle Walk Test (ESWT) to symptom limitation after 8 weeks

End point title	Endurance time during Endurance Shuttle Walk Test (ESWT) to symptom limitation after 8 weeks
End point description: Endurance time during ESWT to symptom limitation at walking speed corresponding to 85% of predicted maximum oxygen consumption (VO_2 peak) after 8 weeks of pharmacological treatment and non-pharmacological intervention. The numerical value of endurance time in seconds was transformed in log ₁₀ scale to correct for skewness and then an analysis of covariance (ANCOVA) was fitted to the log ₁₀ -transformed data and the least square means (LSMean) and standard error (SE) were obtained. To present the results in a way easier for interpretation, the least square mean from the ANCOVA fitted to the log ₁₀ -transformed data were transformed back taking 10 to the power of the least square estimate to obtain the geometric mean and the corresponding SE was transformed using delta method to get the corresponding SE of the geometric mean. Full analysis set (FAS): This patient set included all patients in the TS who had baseline measurement and at least 1 post-baseline measurement for the primary endpoint	
End point type	Primary
End point timeframe: Week 8	

End point values	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micro-grams (μg) with BM	Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM	Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65 ^[1]	67 ^[2]	72 ^[3]	70 ^[4]
Units: Second				
geometric mean (standard error)	244.07 (\pm 17.666)	254.18 (\pm 18.099)	315.32 (\pm 21.671)	355.73 (\pm 24.787)

Notes:

[1] - FAS. Patients assigned after implementation of data handling rules that set measurements to missing.

[2] - FAS. Patients assigned after implementation of data handling rules that set measurements to missing.

[3] - FAS. Patients assigned after implementation of data handling rules that set measurements to missing.

[4] - FAS. Patients assigned after implementation of data handling rules that set measurements to missing.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
This treatment comparison is the first one in the alpha-protected hierarchical testing chain. ANCOVA model with categorical effect of treatment and baseline as covariate. Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was back transformed using the delta method. Ratio of means calculated as back transformation of difference on log 10 scale between Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Placebo with behavioural modification (BM).	
Comparison groups	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM v Placebo with behavioural modification (BM)
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.458
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.196
upper limit	1.777
Variability estimate	Standard error of the mean
Dispersion value	0.147

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
This treatment comparison is the second one in the alpha-protected hierarchical testing chain. ANCOVA model with categorical effect of treatment and baseline as covariate. Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was back transformed using the delta method. Ratio of means calculated as back transformation of difference on log 10 scale between Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Placebo with behavioural modification (BM).	
Comparison groups	Placebo with behavioural modification (BM) v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0109
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.292

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.061
upper limit	1.573
Variability estimate	Standard error of the mean
Dispersion value	0.129

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

This treatment comparison is the third one in the alpha-protected hierarchical testing chain. ANCOVA model with categorical effect of treatment and baseline as covariate. Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was back transformed using the delta method. Ratio of means calculated as back transformation of difference on log 10 scale between Tiotropium (Tio) 5 micro-grams (μg) with BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tiotropium (Tio) 5 micro-grams (μg) with BM
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6895 ^[5]
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.853
upper limit	1.272
Variability estimate	Standard error of the mean
Dispersion value	0.106

Notes:

[5] - Since the p-value for this treatment comparison is >0.05 , the hierarchical testing chain is broken and all of the following hypothesis tests in this hierarchical chain are considered as descriptive only.

Statistical analysis title	Statistical Analysis 4
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Statistical analysis description:

ANCOVA model with categorical effect of treatment and baseline as covariate. Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was back transformed using the delta method. Ratio of means calculated as back transformation of difference on log 10 scale between Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM minus Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM.

Comparison groups	Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM v Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2188
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.128

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.931
upper limit	1.368
Variability estimate	Standard error of the mean
Dispersion value	0.11

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

ANCOVA model with categorical effect of treatment and baseline as covariate. Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was back transformed using the delta method. Ratio of means calculated as back transformation of difference on log 10 scale between Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Tiotropium (Tio) 5 micro-grams (µg) with BM.

Comparison groups	Tiotropium (Tio) 5 micro-grams (µg) with BM v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0303
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.241
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.021
upper limit	1.507
Variability estimate	Standard error of the mean
Dispersion value	0.123

Secondary: Average daily walking time measured by the activity monitor in the week prior to Week 12

End point title	Average daily walking time measured by the activity monitor in the week prior to Week 12
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End point description:

Average daily walking time measured by the activity monitor in the week prior to Week 12. Full analysis set (FAS): This patient set included all patients in the TS who had baseline measurement and at least 1 post-baseline measurement for the primary endpoint. Patients were assigned to the FAS after implementation of any data handling rules that set measurements to missing. Patients with available data were included.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micrograms (µg) with BM	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55 ^[6]	57 ^[7]	60 ^[8]	57 ^[9]
Units: Second				
least squares mean (standard error)	4670.78 (± 211.798)	4145.85 (± 207.351)	4831.85 (± 202.261)	4338.8 (± 207.252)

Notes:

[6] - FAS

[7] - FAS

[8] - FAS

[9] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Placebo with behavioural modification (BM).	
Comparison groups	Placebo with behavioural modification (BM) v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2639
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	-331.975
Confidence interval	
level	95 %
sides	2-sided
lower limit	-916.015
upper limit	252.064
Variability estimate	Standard error of the mean
Dispersion value	296.375

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Placebo with behavioural modification (BM).	
Comparison groups	Placebo with behavioural modification (BM) v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM

Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5837
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	161.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	-417.314
upper limit	739.459
Variability estimate	Standard error of the mean
Dispersion value	293.506

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tiotropium (Tio) 5 micro-grams (μg) with BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tiotropium (Tio) 5 micro-grams (μg) with BM
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0783
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	-524.926
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1109.806
upper limit	59.954
Variability estimate	Standard error of the mean
Dispersion value	296.802

Statistical analysis title	Statistical Analysis 4
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM minus Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM.

Comparison groups	Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM v Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM
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Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	-493.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1063.67
upper limit	77.575
Variability estimate	Standard error of the mean
Dispersion value	289.566

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Tiotropium (Tio) 5 micro-grams (µg) with BM.

Comparison groups	Tiotropium (Tio) 5 micro-grams (µg) with BM v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0186
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	685.998
Confidence interval	
level	95 %
sides	2-sided
lower limit	115.635
upper limit	1256.362
Variability estimate	Standard error of the mean
Dispersion value	289.435

Secondary: Average daily walking intensity measured by the activity monitor in the week prior to 12 weeks of treatment

End point title	Average daily walking intensity measured by the activity monitor in the week prior to 12 weeks of treatment
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End point description:

Average daily walking intensity measured by the activity monitor in the week prior to 12 weeks of treatment. Full analysis set (FAS): This patient set included all patients in the TS who had baseline measurement and at least 1 post-baseline measurement for the primary endpoint. Patients were assigned to the FAS after implementation of any data handling rules that set measurements to missing. Patients with available data were included.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micrograms (μg) with BM	Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM	Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54 ^[10]	56 ^[11]	58 ^[12]	57 ^[13]
Units: Gravitational acceleration (g)				
least squares mean (standard error)	0.2 (\pm 0.003)	0.2 (\pm 0.003)	0.2 (\pm 0.003)	0.2 (\pm 0.003)

Notes:

[10] - FAS

[11] - FAS

[12] - FAS

[13] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LS Mean Difference is calculated as Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5186
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.005
Variability estimate	Standard error of the mean
Dispersion value	0.004

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LS Mean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM
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Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6436
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.006
upper limit	0.009
Variability estimate	Standard error of the mean
Dispersion value	0.004

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tiotropium (Tio) 5 micro-grams (μg) with BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tiotropium (Tio) 5 micro-grams (μg) with BM
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1081
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	-0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.001
Variability estimate	Standard error of the mean
Dispersion value	0.004

Statistical analysis title	Statistical Analysis 4
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM minus Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM.

Comparison groups	Tiotropium + olodaterol (Olo) (5/5 μg) FDC with BM v Tio+Olo (5/5 μg) FDC with exercise training (ET) and BM
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Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2612
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	-0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.011
upper limit	0.003
Variability estimate	Standard error of the mean
Dispersion value	0.004

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Tiotropium (Tio) 5 micro-grams (µg) with BM.

Comparison groups	Tiotropium (Tio) 5 micro-grams (µg) with BM v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0361
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.015
Variability estimate	Standard error of the mean
Dispersion value	0.004

Secondary: Perceived difficulties as evaluated with Functional Performance Inventory (FPI) - Short Form (SF) total score at Week 12

End point title	Perceived difficulties as evaluated with Functional Performance Inventory (FPI) - Short Form (SF) total score at Week 12
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End point description:

Perceived difficulties as evaluated with Functional Performance Inventory (FPI) - Short Form (SF) total score at Week 12. The FPI-SF self-report questionnaire consists of 2 pages of questions relating to 6 dimensions: body care, household maintenance, physical exercise, recreation, spiritual activities, and social activities. Five answer options were possible: "Do with no difficulty, do with some difficulty, do with great difficulty, don't do because of health reasons, and don't do because choose not to". Domain scores and total scores were calculated from the answers. Full analysis set (FAS): This patient set included all patients in the TS who had baseline measurement and at least 1 post-baseline measurement for the primary endpoint. Patients were assigned to the FAS after implementation of any data handling

rules that set measurements to missing. Patients with available data were included.

End point type	Secondary
End point timeframe:	
Week 12	

End point values	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micrograms (µg) with BM	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64 ^[14]	65 ^[15]	71 ^[16]	67 ^[17]
Units: Units on a scale				
least squares mean (standard error)	2.191 (± 0.04)	2.207 (± 0.04)	2.335 (± 0.038)	2.268 (± 0.039)

Notes:

[14] - FAS

[15] - FAS

[16] - FAS

[17] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1727
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.187
Variability estimate	Standard error of the mean
Dispersion value	0.056

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Placebo with

behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0097
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.035
upper limit	0.252
Variability estimate	Standard error of the mean
Dispersion value	0.055

Statistical analysis title

Statistical Analysis 3

Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tiotropium (Tio) 5 micro-grams (µg) with BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tiotropium (Tio) 5 micro-grams (µg) with BM
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7815
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.095
upper limit	0.126
Variability estimate	Standard error of the mean
Dispersion value	0.056

Statistical analysis title

Statistical Analysis 4

Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM.

Comparison groups	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
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Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2183
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	-0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.174
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.054

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

An ANCOVA model with categorical effects of treatment and baseline as covariate. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Tiotropium (Tio) 5 micro-grams (µg) with BM

Comparison groups	Tiotropium (Tio) 5 micro-grams (µg) with BM v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0203
Method	ANCOVA
Parameter estimate	LSMean Difference
Point estimate	0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.236
Variability estimate	Standard error of the mean
Dispersion value	0.055

Secondary: Endurance time during Endurance Shuttle Walk Test (ESWT) to symptom limitation after 12 weeks

End point title	Endurance time during Endurance Shuttle Walk Test (ESWT) to symptom limitation after 12 weeks
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End point description:

Endurance time during ESWT to symptom limitation at walking speed corresponding to 85% of maximum oxygen consumption (VO₂peak) after 12 weeks of pharmacological treatment and non-pharmacological intervention. The numerical value of endurance time in seconds was transformed in log₁₀ scale to correct for skewness and then the ANCOVA was fitted to the log₁₀-transformed data and the least square means and SE were obtained. To present the results in a way easier for interpretation, the least square mean from the ANCOVA fitted to the log₁₀-transformed data were transformed back taking 10 to the power of the least square estimate to obtain the geometric mean and the corresponding SE was transformed using delta method to get the corresponding SE of the geometric mean. Full

analysis set (FAS): This patient set included all patients in the TS who had baseline measurement and at least 1 post-baseline measurement for the primary endpoint. Patients with available data were included.

End point type	Secondary
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End point timeframe:

Week 12

End point values	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micrograms (µg) with BM	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62 ^[18]	64 ^[19]	71 ^[20]	66 ^[21]
Units: Second				
geometric mean (standard error)	243.3 (± 18.68)	255.67 (± 19.292)	302.61 (± 21.691)	324.21 (± 24.095)

Notes:

[18] - FAS. Patients assigned after implementation of data handling rules that set measurements to missing.

[19] - FAS. Patients assigned after implementation of data handling rules that set measurements to missing.

[20] - FAS. Patients assigned after implementation of data handling rules that set measurements to missing.

[21] - FAS. Patients assigned after implementation of data handling rules that set measurements to missing.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

ANCOVA model with categorical effect of treatment and baseline as covariate. Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was back transformed using the delta method. Ratio of means calculated as back transformation of difference on log 10 scale between Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0077
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.333
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	1.645
Variability estimate	Standard error of the mean
Dispersion value	0.142

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
ANCOVA model with categorical effect of treatment and baseline as covariate. Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was back transformed using the delta method. Ratio of means calculated as back transformation of difference on log 10 scale between Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Placebo with behavioural modification (BM).	
Comparison groups	Placebo with behavioural modification (BM) v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.244
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.011
upper limit	1.53
Variability estimate	Standard error of the mean
Dispersion value	0.131

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
ANCOVA model with categorical effect of treatment and baseline as covariate. Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was back transformed using the delta method. Ratio of means calculated as back transformation of difference on log 10 scale between Tiotropium (Tio) 5 micro-grams (µg) with BM minus Placebo with behavioural modification (BM).	
Comparison groups	Placebo with behavioural modification (BM) v Tiotropium (Tio) 5 micro-grams (µg) with BM
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6452
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.299
Variability estimate	Standard error of the mean
Dispersion value	0.113

Statistical analysis title	Statistical Analysis 4
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Statistical analysis description:

ANCOVA model with categorical effect of treatment and baseline as covariate. Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was back transformed using the delta method. Ratio of means calculated as back transformation of difference on log 10 scale between Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM.

Comparison groups	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5048
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.874
upper limit	1.313
Variability estimate	Standard error of the mean
Dispersion value	0.111

Statistical analysis title

Statistical Analysis 5

Statistical analysis description:

ANCOVA model with categorical effect of treatment and baseline as covariate. Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was back transformed using the delta method. Ratio of means calculated as back transformation of difference on log 10 scale between Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Tiotropium (Tio) 5 micro-grams (µg) with BM.

Comparison groups	Tiotropium (Tio) 5 micro-grams (µg) with BM v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1066
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.184
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.964
upper limit	1.453
Variability estimate	Standard error of the mean
Dispersion value	0.123

Secondary: One hour, Post-dose Forced Expiratory Volume in One Second (FEV1) after 8 weeks of treatment

End point title	One hour, Post-dose Forced Expiratory Volume in One Second (FEV1) after 8 weeks of treatment
End point description:	One hour, Post-dose Forced Expiratory Volume in One Second (FEV1) after 8 weeks of treatment. Full analysis set (FAS): This patient set included all patients in the TS who had baseline measurement and at least 1 post-baseline measurement for the primary endpoint. Patients were assigned to the FAS after implementation of any data handling rules that set measurements to missing. Patients with available data were included.
End point type	Secondary
End point timeframe:	Week 8

End point values	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micrograms (µg) with BM	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65 ^[22]	67 ^[23]	72 ^[24]	70 ^[25]
Units: Liter				
least squares mean (standard error)	1.375 (± 0.027)	1.55 (± 0.027)	1.731 (± 0.026)	1.705 (± 0.026)

Notes:

[22] - FAS

[23] - FAS

[24] - FAS

[25] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	Mixed effect Model Repeat Measurement (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Placebo with behavioural modification (BM).
Comparison groups	Placebo with behavioural modification (BM) v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.329
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.255
upper limit	0.403
Variability estimate	Standard error of the mean
Dispersion value	0.038

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Placebo with behavioural modification (BM).	
Comparison groups	Placebo with behavioural modification (BM) v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.356
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.282
upper limit	0.429
Variability estimate	Standard error of the mean
Dispersion value	0.037

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tiotropium (Tio) 5 micro-grams (µg) with BM minus Placebo with behavioural modification (BM).	
Comparison groups	Placebo with behavioural modification (BM) v Tiotropium (Tio) 5 micro-grams (µg) with BM
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.174
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.099
upper limit	0.249
Variability estimate	Standard error of the mean
Dispersion value	0.038

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM.	
Comparison groups	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4677
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	-0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.099
upper limit	0.045
Variability estimate	Standard error of the mean
Dispersion value	0.037

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Tiotropium (Tio) 5 micro-grams (µg) with BM.	
Comparison groups	Tiotropium (Tio) 5 micro-grams (µg) with BM v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.182
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.109
upper limit	0.255
Variability estimate	Standard error of the mean
Dispersion value	0.037

Secondary: One hour, Post-dose Forced Vital Capacity (FVC) after 8 weeks of treatment

End point title	One hour, Post-dose Forced Vital Capacity (FVC) after 8 weeks of treatment
End point description:	One hour, Post-dose Forced Vital Capacity (FVC) after 8 weeks of treatment. Full analysis set (FAS): This patient set included all patients in the TS who had baseline measurement and at least 1 post-baseline measurement for the primary endpoint. Patients were assigned to the FAS after implementation of any data handling rules that set measurements to missing. Patients with available data were included.
End point type	Secondary
End point timeframe:	Week 8

End point values	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micrograms (µg) with BM	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	65 ^[26]	67 ^[27]	72 ^[28]	70 ^[29]
Units: Liter				
least squares mean (standard error)	2.974 (± 0.047)	3.259 (± 0.046)	3.504 (± 0.044)	3.452 (± 0.045)

Notes:

[26] - FAS

[27] - FAS

[28] - FAS

[29] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	Mixed effect Model Repeat Measurement (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Placebo with behavioural modification (BM).
Comparison groups	Placebo with behavioural modification (BM) v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.478

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.606
Variability estimate	Standard error of the mean
Dispersion value	0.065

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.403
upper limit	0.657
Variability estimate	Standard error of the mean
Dispersion value	0.064

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tiotropium (Tio) 5 micro-grams (µg) with BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tiotropium (Tio) 5 micro-grams (µg) with BM
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.286

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.157
upper limit	0.415
Variability estimate	Standard error of the mean
Dispersion value	0.066

Statistical analysis title	Statistical Analysis 4
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Statistical analysis description:

MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM.

Comparison groups	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4107
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	-0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.176
upper limit	0.072
Variability estimate	Standard error of the mean
Dispersion value	0.063

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Tiotropium (Tio) 5 micro-grams (µg) with BM.

Comparison groups	Tiotropium (Tio) 5 micro-grams (µg) with BM v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.244

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.119
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.064

Secondary: Resting inspiratory capacity (IC) measured at 1.5 hours post dose after 8 weeks of treatment

End point title	Resting inspiratory capacity (IC) measured at 1.5 hours post dose after 8 weeks of treatment
End point description:	
Resting inspiratory capacity (IC) measured at 1.5 hours post dose after 8 weeks of treatment. Full analysis set (FAS): This patient set included all patients in the TS who had baseline measurement and at least 1 post-baseline measurement for the primary endpoint. Patients were assigned to the FAS after implementation of any data handling rules that set measurements to missing. Patients with available data were included.	
End point type	Secondary
End point timeframe:	
Week 8	

End point values	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micro-grams (µg) with BM	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	64 ^[30]	66 ^[31]	72 ^[32]	68 ^[33]
Units: Liter				
least squares mean (standard error)	2.452 (± 0.051)	2.627 (± 0.05)	2.755 (± 0.048)	2.771 (± 0.049)

Notes:

[30] - FAS

[31] - FAS

[32] - FAS

[33] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Mixed effect Model Repeat Measurement (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Placebo with behavioural modification (BM).	
Comparison groups	Placebo with behavioural modification (BM) v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM

Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.318
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.179
upper limit	0.457
Variability estimate	Standard error of the mean
Dispersion value	0.071

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.302
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.165
upper limit	0.439
Variability estimate	Standard error of the mean
Dispersion value	0.07

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tiotropium (Tio) 5 micro-grams (µg) with BM minus Placebo with behavioural modification (BM).

Comparison groups	Placebo with behavioural modification (BM) v Tiotropium (Tio) 5 micro-grams (µg) with BM
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Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0145
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.174
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.035
upper limit	0.314
Variability estimate	Standard error of the mean
Dispersion value	0.071

Statistical analysis title	Statistical Analysis 4
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Statistical analysis description:

MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM minus Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM.

Comparison groups	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM v Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.815
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.118
upper limit	0.151
Variability estimate	Standard error of the mean
Dispersion value	0.068

Statistical analysis title	Statistical Analysis 5
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Statistical analysis description:

MMRM model including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect. Compound symmetry covariance structure for within-patient variation and Kenward-Roger approximation of denominator degrees of freedom. The LSMean Difference is calculated as Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM minus Tiotropium (Tio) 5 micro-grams (µg) with BM.

Comparison groups	Tiotropium (Tio) 5 micro-grams (µg) with BM v Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
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Number of subjects included in analysis	138
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0642
Method	Mixed models analysis
Parameter estimate	LSMean Difference
Point estimate	0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.008
upper limit	0.263
Variability estimate	Standard error of the mean
Dispersion value	0.069

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study medication up to a period of 21 days after the last dose of study medication were assigned to the treatment period, up to 134 days.

Adverse event reporting additional description:

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e. from signing the informed consent onwards through the observational phase) were to be collected, documented and reported to the sponsor by the investigator on the appropriate electronic case report form / serious adverse event reporting forms.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Placebo with behavioural modification (BM)
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Reporting group description:

Placebo matching tiotropium + olodaterol FDC or tiotropium solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

Reporting group title	Tiotropium (Tio) 5 micro-grams (µg) with BM
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Reporting group description:

Tiotropium 5 µg solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

Reporting group title	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
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Reporting group description:

Tiotropium 5 µg plus olodaterol 5 µg FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks.

Reporting group title	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM
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Reporting group description:

Tiotropium 5 µg plus olodaterol 5 µg FDC solution was delivered to the patients orally once daily via RESPIMAT inhaler, with BM for 12 weeks; ET was conducted for 8 weeks.

Reporting group title	Total
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Reporting group description:

Total

Serious adverse events	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micro-grams (µg) with BM	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 75 (5.33%)	11 / 76 (14.47%)	3 / 76 (3.95%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			

subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Malignant genitourinary tract neoplasm			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Non-Hodgkin's lymphoma unspecified histology indolent stage IV			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	0 / 76 (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
Non-small cell lung cancer			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 76 (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
Pancreatic neoplasm			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Small cell lung cancer			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 76 (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
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural			

complications			
Alcohol poisoning			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 76 (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 / 75 (0.00%)	0 / 76 (0.00%)	0 / 76 (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			
Aortic aneurysm			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 76 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 76 (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
Angina pectoris			

subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 76 (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
Atrial fibrillation			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	0 / 76 (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
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Prostatitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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

Hepatotoxicity			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 75 (1.33%)	2 / 76 (2.63%)	1 / 76 (1.32%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Pulmonary embolism			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Pulmonary hilum mass			
subjects affected / exposed	1 / 75 (1.33%)	0 / 76 (0.00%)	0 / 76 (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
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 76 (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			
Abdominal abscess			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Urinary tract infection			
subjects affected / exposed	0 / 75 (0.00%)	1 / 76 (1.32%)	0 / 76 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 76 (0.00%)	0 / 76 (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	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM	Total	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 76 (10.53%)	26 / 303 (8.58%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant genitourinary tract neoplasm			

subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma unspecified histology indolent stage IV			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 76 (1.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 76 (1.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 76 (0.00%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rib fracture			
subjects affected / exposed	1 / 76 (1.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Road traffic accident subjects affected / exposed	1 / 76 (1.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease subjects affected / exposed	1 / 76 (1.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction subjects affected / exposed	1 / 76 (1.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris subjects affected / exposed	1 / 76 (1.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 76 (1.32%)	5 / 303 (1.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 76 (1.32%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hilum mass			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	1 / 76 (1.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 76 (1.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo with behavioural modification (BM)	Tiotropium (Tio) 5 micro-grams (µg) with BM	Tiotropium + olodaterol (Olo) (5/5 µg) FDC with BM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 75 (29.33%)	19 / 76 (25.00%)	16 / 76 (21.05%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	16 / 75 (21.33%)	10 / 76 (13.16%)	12 / 76 (15.79%)
occurrences (all)	18	13	14
Dyspnoea			
subjects affected / exposed	2 / 75 (2.67%)	6 / 76 (7.89%)	2 / 76 (2.63%)
occurrences (all)	2	6	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 75 (5.33%)	1 / 76 (1.32%)	2 / 76 (2.63%)
occurrences (all)	4	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 75 (10.67%)	9 / 76 (11.84%)	4 / 76 (5.26%)
occurrences (all)	9	11	5

Non-serious adverse events	Tio+Olo (5/5 µg) FDC with exercise training (ET) and BM	Total	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 76 (25.00%)	76 / 303 (25.08%)	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	13 / 76 (17.11%)	51 / 303 (16.83%)	
occurrences (all)	15	60	

Dyspnoea subjects affected / exposed occurrences (all)	2 / 76 (2.63%) 2	12 / 303 (3.96%) 12	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 76 (1.32%) 1	8 / 303 (2.64%) 8	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	10 / 76 (13.16%) 11	31 / 303 (10.23%) 36	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2014	This amendment includes the following; Waist circumference was removed from the measurements of moderating variables. Tiotropium was entered as a comparator product. SpO2 was entered under criteria for safety with exercise testing. Medical history was removed from the flowchart and in the main flowchart, timing of the trial follow-up visit was clarified. Medication washout check was entered also under Visit 2 for the washout of ipratropium in the main flowchart. Pedometer use was entered and MBS-S use corrected for the 6MWT. In the behavioural modification flowchart, visit windows were specified and names of questionnaires were corrected. Exercise capacity and physical activity were to be assessed after the end of supervised exercise training in the Tio+Olo 5/5 µg FDC + BM + ET arm. Patients were not to inhale trial medication on the morning of Visits 5 to 8. In safety laboratory urine examination added. Patient treatment preference assessment was added to the individual BM pre-session. Details on bronchodilator therapy required for treatment of GOLD Stage II and III patients were deleted. Intensity of breathing and leg discomfort recording during 6MWT was additionally specified, and timing of 6MWT after the ESWT on Visits 5 and 8 and IC measurement post dose on Visits 3, 5 and 8 was re-specified. Timing of baseline LF and exercise tests specified at Visit 3. Modified Borg Scale use during 6MWT has been clarified. Minor corrections and further clarifications were introduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported