



## Clinical trial results:

**A randomised, double-blind, placebo- and active-controlled parallel group study to assess the efficacy of 12 weeks of once daily treatment of two doses of orally inhaled tiotropium + olodaterol fixed dose combination (delivered by the RespiMat® inhaler) in patients with moderate to severe Chronic Obstructive Pulmonary Disease (COPD)**

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

## Summary

EudraCT number	2013-002264-24
Trial protocol	SE AT SK GR
Global end of trial date	24 November 2014

## Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

## Trial information

### Trial identification

Sponsor protocol code	1237.26
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02006732
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	Boehringer Ingelheim Pharma GmbH & Co. KG, QRPE Processes and Systems Coordination, Clinical Trial, +1 8002430127, <a href="mailto:clintriage.rdg@boehringer-ingelheim.com">clintriage.rdg@boehringer-ingelheim.com</a>
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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	13 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2014
Global end of trial reached?	Yes
Global end of trial date	24 November 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This trial was 1 of 2 randomised, double-blind, placebo- and active-controlled parallel group Phase IIIb trials with identical protocols (replicate trials with BI trial numbers 1237.25 and 1237.26) The objective of this trial was to evaluate maximal treatment effect in forced expiratory volume in one second (FEV1) response and St. George's Respiratory Questionnaire (SGRQ) total score and safety after 12 weeks of treatment with 2 different doses of tiotropium + olodaterol fixed dose combination solution (2.5/5µg and 5/5µg) delivered by the RESPIMAT® inhaler by comparison with placebo in patients with moderate to severe COPD.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 November 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	Australia: 65
Country: Number of subjects enrolled	Austria: 58
Country: Number of subjects enrolled	Canada: 65
Country: Number of subjects enrolled	Germany: 213
Country: Number of subjects enrolled	Greece: 39
Country: Number of subjects enrolled	New Zealand: 16
Country: Number of subjects enrolled	Norway: 49
Country: Number of subjects enrolled	Slovakia: 39
Country: Number of subjects enrolled	South Africa: 27
Country: Number of subjects enrolled	Sweden: 48
Country: Number of subjects enrolled	United States: 488
Worldwide total number of subjects	1107
EEA total number of subjects	446

Notes:

<b>Subjects enrolled per age group</b>	
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)	541
From 65 to 84 years	557
85 years and over	9

## Subject disposition

### Recruitment

Recruitment details:

809 patients were randomised and treated.

### Pre-assignment

Screening details:

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

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Once daily 2 puffs solution of placebo for inhalation with Respimat

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

Dosage and administration details:

2 actuations once daily in the morning. Dose not applicable.

<b>Arm title</b>	Tiotropium 5 µg
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Arm description:

Once daily 2 puffs solution of 2.5 µg tiotropium for inhalation with Respimat

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

Dosage and administration details:

2 actuations once daily in the morning, for a total dose of 5 µg.

<b>Arm title</b>	Tiotropium 2.5 µg+ Olodaterol 5 µg
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Arm description:

Once daily 2 puffs solution of 1.25 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler.

Arm type	Experimental
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Investigational medicinal product name	Olodaterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
2 actuations once daily in the morning for a total dose of 5 µg	
Investigational medicinal product name	Tiotropium Bromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
2 actuations once daily in the morning for a total dose of 2.5 µg	
<b>Arm title</b>	Tiotropium 5 µg + Olodaterol 5 µg

Arm description:

Once daily 2 puffs solution of 2.5 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler.

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

Dosage and administration details:

2 actuations once daily in the morning, for a total dose of 5 µg.

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

Dosage and administration details:

2 actuations once daily in the morning, for a total dose of 5 µg.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Placebo	Tiotropium 5 µg	Tiotropium 2.5 µg+ Olodaterol 5 µg
Started	202	203	202
Completed	182	191	193
Not completed	20	12	9
Consent withdrawn by subject	3	-	4
Adverse event, non-fatal	10	7	4
Lost to follow-up	-	1	-
Lack of efficacy	6	3	1
Protocol deviation	1	1	-

<b>Number of subjects in period 1</b>	Tiotropium 5 µg + Olodaterol 5 µg
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[1]	
Started	202
Completed	198
Not completed	4
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Lost to follow-up	-
Lack of efficacy	1
Protocol deviation	-

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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 the patients who were randomized after successfully completing the screening period and received at least one of the trial medication.

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description: Once daily 2 puffs solution of placebo for inhalation with Respimat	
Reporting group title	Tiotropium 5 µg
Reporting group description: Once daily 2 puffs solution of 2.5 µg tiotropium for inhalation with Respimat	
Reporting group title	Tiotropium 2.5 µg+ Olodaterol 5 µg
Reporting group description: Once daily 2 puffs solution of 1.25 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler.	
Reporting group title	Tiotropium 5 µg + Olodaterol 5 µg
Reporting group description: Once daily 2 puffs solution of 2.5 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler.	

Reporting group values	Placebo	Tiotropium 5 µg	Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects	202	203	202
Age categorical			
Units: Subjects			

Age Continuous			
Treated set (TS) which included all randomised patients who received at least one dose of trial medication represents the baseline analysis population.			
Units: years			
arithmetic mean	64	64.7	64.4
standard deviation	± 8.3	± 8.4	± 8.6
Gender, Male/Female			
Treated set (TS) which included all randomised patients who received at least one dose of trial medication represents the baseline analysis population.			
Units: participants			
Female	85	73	76
Male	117	130	126

Reporting group values	Tiotropium 5 µg + Olodaterol 5 µg	Total	
Number of subjects	202	809	
Age categorical			
Units: Subjects			

Age Continuous			
Treated set (TS) which included all randomised patients who received at least one dose of trial medication represents the baseline analysis population.			
Units: years			
arithmetic mean	65.2		
standard deviation	± 8.5	-	

Gender, Male/Female			
Treated set (TS) which included all randomised patients who received at least one dose of trial medication represents the baseline analysis population.			
Units: participants			
Female	69	303	
Male	133	506	



## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description: Once daily 2 puffs solution of placebo for inhalation with Respimat	
Reporting group title	Tiotropium 5 µg
Reporting group description: Once daily 2 puffs solution of 2.5 µg tiotropium for inhalation with Respimat	
Reporting group title	Tiotropium 2.5 µg+ Olodaterol 5 µg
Reporting group description: Once daily 2 puffs solution of 1.25 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler.	
Reporting group title	Tiotropium 5 µg + Olodaterol 5 µg
Reporting group description: Once daily 2 puffs solution of 2.5 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat as a fixed combination with a single inhaler.	

### Primary: FEV1 AUC0-3h response (change from baseline)

End point title	FEV1 AUC0-3h response (change from baseline)
End point description: Forced expiratory volume in one second (FEV1) Area under the curve (AUC) 0-3h was calculated as the area under the FEV1-time curve from 0 to 3h post-dose using the trapezoidal rule, divided by the duration (3h) to report in litres. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom. The Full Analysis set (FAS) included all patients in the TS who had a baseline and at least one postbaseline measurement for any of the primary efficacy endpoints.	
End point type	Primary
End point timeframe: baseline and 12 weeks	

End point values	Placebo	Tiotropium 5 µg	Tiotropium 2.5 µg+ Olodaterol 5 µg	Tiotropium 5 µg + Olodaterol 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	199 <sup>[1]</sup>	201 <sup>[2]</sup>	200 <sup>[3]</sup>	200 <sup>[4]</sup>
Units: Liter				
arithmetic mean (standard error)	-0.006 (± 0.014)	0.188 (± 0.013)	0.279 (± 0.014)	0.293 (± 0.013)

Notes:

[1] - FAS including patients with available endpoint data at week 12

[2] - FAS including patients with available endpoint data at week 12

[3] - FAS including patients with available endpoint data at week 12

[4] - FAS including patients with available endpoint data at week 12

### Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis 1
Statistical analysis description:	
Placebo vs. Tiotropium 5 µg + Olodaterol 5 µg. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and standard error (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Placebo v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.299
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.261
upper limit	0.336
Variability estimate	Standard error of the mean
Dispersion value	0.019

<b>Statistical analysis title</b>	Statistical analysis 2
Statistical analysis description:	
Tiotropium 5 µg vs. Tiotropium 5 µg + 5 µg Olodaterol. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and SE are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.069
upper limit	0.141
Variability estimate	Standard error of the mean
Dispersion value	0.019

<b>Statistical analysis title</b>	Statistical analysis 3
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**Statistical analysis description:**

Placebo vs. Tiotropium 2.5 µg + Olodaterol 5 µg. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and SE are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.284
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.246
upper limit	0.323
Variability estimate	Standard error of the mean
Dispersion value	0.02

<b>Statistical analysis title</b>	Statistical analysis 4
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**Statistical analysis description:**

Tiotropium 5 µg vs. Tiotropium 2.5 µg + Olodaterol 5 µg. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and SE are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.053
upper limit	0.128
Variability estimate	Standard error of the mean
Dispersion value	0.019

<b>Statistical analysis title</b>	Statistical analysis 5
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**Statistical analysis description:**

Placebo vs. Tiotropium 5 µg. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and SE are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 5 µg
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.156
upper limit	0.232
Variability estimate	Standard error of the mean
Dispersion value	0.019

<b>Statistical analysis title</b>	Statistical analysis 6
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Statistical analysis description:

Tiotropium 2.5 µg + Olodaterol 5 µg vs. Tiotropium 5 µg + Olodaterol 5 µg. FEV1 AUC0-3h response was defined as FEV1 AUC0-3h minus baseline FEV1. The adjusted mean and SE are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4499
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.023
upper limit	0.051
Variability estimate	Standard error of the mean
Dispersion value	0.019

### **Primary: Trough FEV1 response (change from baseline)**

End point title	Trough FEV1 response (change from baseline)
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End point description:

Trough FEV1 was defined as the FEV1 value at the end of the dosing interval (24 hours). It was calculated as the mean of the 2 FEV1 measurements performed 23 h and at 23 h 50 min after inhalation

of study medication at day 85. Trough FEV1 response was defined as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom. The Full Analysis set (FAS) included all patients in the TS who had a baseline and at least one postbaseline measurement for any of the primary efficacy endpoints.

End point type	Primary
End point timeframe: baseline and 12 weeks	

End point values	Placebo	Tiotropium 5 µg	Tiotropium 2.5 µg+ Olodaterol 5 µg	Tiotropium 5 µg + Olodaterol 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	193 <sup>[5]</sup>	197 <sup>[6]</sup>	200 <sup>[7]</sup>	199 <sup>[8]</sup>
Units: Liter				
arithmetic mean (standard error)	-0.003 (± 0.014)	0.124 (± 0.013)	0.166 (± 0.013)	0.163 (± 0.013)

Notes:

[5] - FAS including patients with available endpoint data at week 12

[6] - FAS including patients with available endpoint data at week 12

[7] - FAS including patients with available endpoint data at week 12

[8] - FAS including patients with available endpoint data at week 12

## Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

Placebo vs. Tiotropium 5 µg + Olodaterol 5 µg. Trough FEV1 response was defined as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.129
upper limit	0.203
Variability estimate	Standard error of the mean
Dispersion value	0.019

<b>Statistical analysis title</b>	Statistical analysis 2
Statistical analysis description:	
Tiotropium 5 µg vs. Tiotropium 5 µg + Olodaterol 5 µg. Trough FEV1 response was defines as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within–patient errors and Kenward–Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0395
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.076
Variability estimate	Standard error of the mean
Dispersion value	0.019

<b>Statistical analysis title</b>	Statistical analysis 3
Statistical analysis description:	
Placebo vs. Tiotropium 2.5 µg + Olodaterol 5 µg. Trough FEV1 response was defines as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within–patient errors and Kenward–Roger approximation of denominator degrees of freedom.	
Comparison groups	Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.169
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.132
upper limit	0.207
Variability estimate	Standard error of the mean
Dispersion value	0.019

<b>Statistical analysis title</b>	Statistical analysis 4
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**Statistical analysis description:**

Tiotropium 5 µg vs. Tiotropium 2.5 µg + Olodaterol 5 µg. Trough FEV1 response was defines as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0269
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.005
upper limit	0.079
Variability estimate	Standard error of the mean
Dispersion value	0.019

<b>Statistical analysis title</b>	Statistical analysis 5
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**Statistical analysis description:**

Placebo vs. Tiotropium 5 µg. Trough FEV1 response was defines as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 5 µg
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.127
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.165
Variability estimate	Standard error of the mean
Dispersion value	0.019

<b>Statistical analysis title</b>	Statistical analysis 6
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**Statistical analysis description:**

Tiotropium 2.5 µg + Olodaterol 5 µg vs. Tiotropium 5 µg + Olodaterol 5 µg. Trough FEV1 response was defines as trough FEV1 minus baseline FEV1. The adjusted mean (SE) are obtained from fitting an

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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8669
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.034
Variability estimate	Standard error of the mean
Dispersion value	0.019

### Primary: St. George's Respiratory Questionnaire (SGRQ) total score based on data from this individual study

End point title	St. George's Respiratory Questionnaire (SGRQ) total score based on data from this individual study
End point description:	
<p>The SGRQ ranges from 0 (no impairment of quality of life) to 100 (highest impairment of quality of life). The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom. An additional combined endpoint is defined and analysed for trial 1237.25 and 1237.26, however due to the platform limitations those could not be provided. Results can be found on CT.gov study number: NCT02006732.</p>	
End point type	Primary
End point timeframe:	
12 weeks treatment	

End point values	Placebo	Tiotropium 5 µg	Tiotropium 2.5 µg+ Olodaterol 5 µg	Tiotropium 5 µg + Olodaterol 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	184 <sup>[9]</sup>	192 <sup>[10]</sup>	195 <sup>[11]</sup>	197 <sup>[12]</sup>
Units: units on a scale				
arithmetic mean (standard error)	42.575 (± 0.711)	39.729 (± 0.694)	38.909 (± 0.691)	38.011 (± 0.683)

Notes:

[9] - FAS including patients with available endpoint data at week 12

[10] - FAS including patients with available endpoint data at week 12

[11] - FAS including patients with available endpoint data at week 12



**Statistical analyses**

<b>Statistical analysis title</b>	Statistical analysis 1
Statistical analysis description:	
Placebo vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Placebo v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-4.564
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.499
upper limit	-2.629
Variability estimate	Standard error of the mean
Dispersion value	0.986

<b>Statistical analysis title</b>	Statistical analysis 2
Statistical analysis description:	
Tiotropium 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-1.717
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.628
upper limit	0.193

Variability estimate	Standard error of the mean
Dispersion value	0.974

<b>Statistical analysis title</b>	Statistical analysis 3
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Statistical analysis description:

Placebo vs. Tiotropium 2.5 µg + Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-3.666
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.611
upper limit	-1.721
Variability estimate	Standard error of the mean
Dispersion value	0.991

<b>Statistical analysis title</b>	Statistical analysis 4
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Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4028
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.741
upper limit	1.102
Variability estimate	Standard error of the mean
Dispersion value	0.974

<b>Statistical analysis title</b>	Statistical analysis 5
Statistical analysis description:	
Placebo vs. Tiotropium 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Placebo v Tiotropium 5 µg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0042
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-2.846
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.796
upper limit	-0.897
Variability estimate	Standard error of the mean
Dispersion value	0.993

<b>Statistical analysis title</b>	Statistical analysis 6
Statistical analysis description:	
Tiotropium 2.5 µg+ Olodaterol 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3555
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-0.898
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.804
upper limit	1.008
Variability estimate	Standard error of the mean
Dispersion value	0.971

## Secondary: Trough forced vital capacity (FVC) response (change from baseline)

End point title	Trough forced vital capacity (FVC) response (change from baseline)
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End point description:

Trough FVC was defined as the FVC value at the end of the dosing interval (24 hours). It was calculated as the mean of the 2 FVC measurements performed 23 h and at 23 h 50 min after inhalation of study medication at day 85. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

End point type	Secondary
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End point timeframe:

baseline and 12 weeks

End point values	Placebo	Tiotropium 5 µg	Tiotropium 2.5 µg+ Olodaterol 5 µg	Tiotropium 5 µg + Olodaterol 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	193 <sup>[13]</sup>	197 <sup>[14]</sup>	200 <sup>[15]</sup>	199 <sup>[16]</sup>
Units: Liter				
arithmetic mean (standard error)	-0.021 (± 0.024)	0.17 (± 0.023)	0.284 (± 0.023)	0.231 (± 0.023)

Notes:

[13] - FAS including patients with available endpoint data at week 12

[14] - FAS including patients with available endpoint data at week 12

[15] - FAS including patients with available endpoint data at week 12

[16] - FAS including patients with available endpoint data at week 12

## Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

Placebo vs. Tiotropium 5 µg+ Olodaterol 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.252

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.187
upper limit	0.317
Variability estimate	Standard error of the mean
Dispersion value	0.033

<b>Statistical analysis title</b>	Statistical analysis 2
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Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0614
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.061

<b>Statistical analysis title</b>	Statistical analysis 3
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Statistical analysis description:

Placebo vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects included in analysis	393
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.305

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.033

<b>Statistical analysis title</b>	Statistical analysis 4
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Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects included in analysis	397
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.049
upper limit	0.178
Variability estimate	Standard error of the mean
Dispersion value	0.033

<b>Statistical analysis title</b>	Statistical analysis 5
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Statistical analysis description:

Placebo vs. Tiotropium 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 5 µg
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.191

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.126
upper limit	0.256
Variability estimate	Standard error of the mean
Dispersion value	0.033

<b>Statistical analysis title</b>	Statistical analysis 6
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Statistical analysis description:

Tiotropium 2.5 µg+ Olodaterol 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. Trough FVC response was defined as trough FVC minus baseline FVC. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1089
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.117
upper limit	0.012
Variability estimate	Standard error of the mean
Dispersion value	0.033

## Secondary: TDI focal score based on data from this individual study

End point title	TDI focal score based on data from this individual study
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End point description:

Mahler Transitional Dyspnoea Index (TDI) focal score was performed to measure the effect of the treatment on patients' dyspnoea. (Rating scale of 3 components - change in functional impairment, change in magnitude of tasks, change in magnitude of efforts. Worst score = -9, best score = +9). The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom. An additional combined endpoint is defined and analysed for trial 1237.25 and 1237.26, however due to the platform limitations those could not be provided. Results can be found on CT.gov study number: NCT02006732.

End point type	Secondary
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End point timeframe:

12 weeks

End point values	Placebo	Tiotropium 5 µg	Tiotropium 2.5 µg+ Olodaterol 5 µg	Tiotropium 5 µg + Olodaterol 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	183 <sup>[17]</sup>	192 <sup>[18]</sup>	195 <sup>[19]</sup>	197 <sup>[20]</sup>
Units: Units on a scale				
arithmetic mean (standard error)	0.337 (± 0.195)	0.95 (± 0.191)	1.599 (± 0.189)	1.531 (± 0.187)

Notes:

[17] - FAS including patients with available endpoint data at week 12

[18] - FAS including patients with available endpoint data at week 12

[19] - FAS including patients with available endpoint data at week 12

[20] - FAS including patients with available endpoint data at week 12

## Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Placebo vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Placebo v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	380
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	1.195
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.665
upper limit	1.725
Variability estimate	Standard error of the mean
Dispersion value	0.27

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Tiotropium 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg



Number of subjects included in analysis	389
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0296
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	0.582
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.058
upper limit	1.106
Variability estimate	Standard error of the mean
Dispersion value	0.267

<b>Statistical analysis title</b>	Statistical analysis 3
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Statistical analysis description:

Placebo vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects included in analysis	378
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	1.263
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.796
Variability estimate	Standard error of the mean
Dispersion value	0.272

<b>Statistical analysis title</b>	Statistical analysis 4
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Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg
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Number of subjects included in analysis	387
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0159
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.122
upper limit	1.178
Variability estimate	Standard error of the mean
Dispersion value	0.269

<b>Statistical analysis title</b>	Statistical analysis 5
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Statistical analysis description:

Placebo vs. Tiotropium 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 5 µg
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0248
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	0.613
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.078
upper limit	1.148
Variability estimate	Standard error of the mean
Dispersion value	0.273

<b>Statistical analysis title</b>	Statistical analysis 6
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Statistical analysis description:

Tiotropium 2.5 µg+ Olodaterol 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting an 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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
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Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7984
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-0.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	0.454
Variability estimate	Standard error of the mean
Dispersion value	0.266

### Secondary: FVC AUC0-3h response (change from baseline)

End point title	FVC AUC0-3h response (change from baseline)
End point description:	
The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
End point type	Secondary
End point timeframe:	
baseline and 12 weeks	

End point values	Placebo	Tiotropium 5 µg	Tiotropium 2.5 µg+ Olodaterol 5 µg	Tiotropium 5 µg + Olodaterol 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	199 <sup>[21]</sup>	201 <sup>[22]</sup>	200 <sup>[23]</sup>	200 <sup>[24]</sup>
Units: Liter				
arithmetic mean (standard error)	-0.018 (± 0.025)	0.266 (± 0.023)	0.436 (± 0.024)	0.414 (± 0.023)

Notes:

[21] - FAS including patients with available endpoint data at week 12

[22] - FAS including patients with available endpoint data at week 12

[23] - FAS including patients with available endpoint data at week 12

[24] - FAS including patients with available endpoint data at week 12

### Statistical analyses

Statistical analysis title	Statistical analysis 1
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Statistical analysis description:

Placebo vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.432
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.366
upper limit	0.498
Variability estimate	Standard error of the mean
Dispersion value	0.033

<b>Statistical analysis title</b>	Statistical analysis 2
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Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.148
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.084
upper limit	0.212
Variability estimate	Standard error of the mean
Dispersion value	0.033

<b>Statistical analysis title</b>	Statistical analysis 3
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Statistical analysis description:

Placebo vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 2.5 µg+ Olodaterol 5 µg
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Number of subjects included in analysis	399
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.455
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.387
upper limit	0.522
Variability estimate	Standard error of the mean
Dispersion value	0.034

<b>Statistical analysis title</b>	Statistical analysis 4
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Statistical analysis description:

Tiotropium 5 µg vs. Tiotropium 2.5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 5 µg v Tiotropium 2.5 µg+ Olodaterol 5 µg
Number of subjects included in analysis	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.171
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.105
upper limit	0.236
Variability estimate	Standard error of the mean
Dispersion value	0.034

<b>Statistical analysis title</b>	Statistical analysis 5
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Statistical analysis description:

Placebo vs. Tiotropium 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Placebo v Tiotropium 5 µg
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Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.284
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.217
upper limit	0.35
Variability estimate	Standard error of the mean
Dispersion value	0.034

<b>Statistical analysis title</b>	Statistical analysis 6
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Statistical analysis description:

Tiotropium 2.5 µg+ Olodaterol 5 µg vs. Tiotropium 5 µg+ Olodaterol 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (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; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium 2.5 µg+ Olodaterol 5 µg v Tiotropium 5 µg + Olodaterol 5 µg
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4974
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.087
upper limit	0.042
Variability estimate	Standard error of the mean
Dispersion value	0.033

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first drug administration to the last drug administration plus 21 days up to 112 days.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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### Reporting groups

Reporting group title	Treatment period Placebo
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Reporting group description:

Once daily 2 puffs solution of placebo for inhalation with Respimat

Reporting group title	Treatment period Tiotropium 5 µg
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Reporting group description:

Once daily 2 puffs solution of 2.5 µg tiotropium for inhalation with Respimat

Reporting group title	Treatment period Tiotropium 2.5 µg+ Olodaterol 5 µg
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Reporting group description:

Once daily 2 puffs solution of 1.25 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat.

Reporting group title	Treatment period Tiotropium 5 µg+ Olodaterol 5 µg
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Reporting group description:

Once daily 2 puffs solution of 2.5 µg tiotropium / 2.5 µg olodaterol for inhalation with Respimat.

Serious adverse events	Treatment period Placebo	Treatment period Tiotropium 5 µg	Treatment period Tiotropium 2.5 µg+ Olodaterol 5 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 202 (1.98%)	12 / 203 (5.91%)	4 / 202 (1.98%)
number of deaths (all causes)	0	0	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 / 202 (0.00%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	0 / 202 (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
Squamous cell carcinoma			

subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 202 (0.00%)	0 / 203 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	0 / 202 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	0 / 202 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 202 (0.00%)	0 / 203 (0.00%)	0 / 202 (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	1 / 202 (0.50%)	0 / 203 (0.00%)	0 / 202 (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
Atrial fibrillation			
subjects affected / exposed	0 / 202 (0.00%)	0 / 203 (0.00%)	0 / 202 (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
Myocardial infarction			
subjects affected / exposed	0 / 202 (0.00%)	2 / 203 (0.99%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0



Supraventricular tachycardia subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	0 / 202 (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 / 202 (0.00%)	0 / 203 (0.00%)	0 / 202 (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
Eye disorders			
Blindness subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Large intestine polyp subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	0 / 202 (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
Nausea subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	0 / 202 (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
Umbilical hernia subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	0 / 202 (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			
Acute respiratory failure subjects affected / exposed	0 / 202 (0.00%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 202 (0.50%)	1 / 203 (0.49%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 202 (0.00%)	0 / 203 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 202 (0.00%)	0 / 203 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 202 (0.00%)	1 / 203 (0.49%)	0 / 202 (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
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 202 (0.00%)	2 / 203 (0.99%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 202 (0.00%)	0 / 203 (0.00%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 202 (0.50%)	0 / 203 (0.00%)	0 / 202 (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

<b>Serious adverse events</b>	Treatment period Tiotropium 5 µg+ Olodaterol 5 µg		
Total subjects affected by serious			

adverse events			
subjects affected / exposed	6 / 202 (2.97%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 202 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			

subjects affected / exposed	1 / 202 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 202 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 202 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Supraventricular tachycardia			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 202 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Large intestine polyp			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nausea			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 202 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 202 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			

subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
Cellulitis			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Diverticulitis</b>			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Treatment period Placebo	Treatment period Tiotropium 5 µg	Treatment period Tiotropium 2.5 µg+ Olodaterol 5 µg
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	34 / 202 (16.83%)	15 / 203 (7.39%)	25 / 202 (12.38%)
<b>Respiratory, thoracic and mediastinal disorders</b>			
Chronic obstructive pulmonary disease			
subjects affected / exposed	14 / 202 (6.93%)	7 / 203 (3.45%)	17 / 202 (8.42%)
occurrences (all)	14	7	17
Dyspnoea			
subjects affected / exposed	14 / 202 (6.93%)	4 / 203 (1.97%)	4 / 202 (1.98%)
occurrences (all)	14	4	4
Cough			
subjects affected / exposed	12 / 202 (5.94%)	5 / 203 (2.46%)	5 / 202 (2.48%)
occurrences (all)	12	5	5

<b>Non-serious adverse events</b>	Treatment period Tiotropium 5 µg+ Olodaterol 5 µg		
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	14 / 202 (6.93%)		
<b>Respiratory, thoracic and mediastinal disorders</b>			

Chronic obstructive pulmonary disease			
subjects affected / exposed	9 / 202 (4.46%)		
occurrences (all)	9		
Dyspnoea			
subjects affected / exposed	2 / 202 (0.99%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	3 / 202 (1.49%)		
occurrences (all)	3		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2014	In this administrative revision of the trial protocol, medication restrictions and washout periods for bronchodilator medications were updated to define washout periods for bronchodilator medications marketed after finalisation of original protocol. Web cast training was added for sites that did not participate in hands-on training of MasterScope equipment during the investigator meeting to ensure that at least one staff member at each site was fully trained in the use of the ERT equipment.
28 August 2014	In this administrative revision of the trial protocol, the hypothesis testing strategy, text describing the hypothesis testing strategy and corresponding figure were updated to maintain consistency within the project. It was made explicit that safety laboratory tests and ECGs were to be performed locally and not collected in the database, and hence would not be analysed. Further details were added to provide clear guidance on visit rescheduling for patients recovering from acute exacerbations of COPD.

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.

Additional combined primary and secondary endpoints are defined and analysed for trial 1237.25 and 1237.26, however due to the platform limitations those could not be provided. Results can be found on CT.gov study number: NCT02006732.

Notes: