



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	2013-002243-29
Trial protocol	FI GB CZ ES DK BE
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	1237.25
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01964352
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, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim Pharma GmbH & Co. KG, QRPE Processes and Systems Coordination, Clinical Trial, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	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	29 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	Belgium: 42
Country: Number of subjects enrolled	Canada: 58
Country: Number of subjects enrolled	Czech Republic: 45
Country: Number of subjects enrolled	Denmark: 58
Country: Number of subjects enrolled	Finland: 52
Country: Number of subjects enrolled	Germany: 159
Country: Number of subjects enrolled	South Africa: 64
Country: Number of subjects enrolled	Spain: 81
Country: Number of subjects enrolled	United Kingdom: 49
Country: Number of subjects enrolled	United States: 446
Worldwide total number of subjects	1054
EEA total number of subjects	486

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)	505
From 65 to 84 years	541
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

814 were entered and randomized. One patient randomized to Tiotropium 5 µg was not treated. One patient entered the study with 2 different patient numbers. This patient was counted twice in the randomized set but only once in the treated set. Thus a total of 812 unique patients were 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
Arm title	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.

Arm title	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.

Arm title	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	
Arm title	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	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 5 µg.

Number of subjects in period 1^[1]	Placebo	Tiotropium 5 µg	Tiotropium 2.5 µg+ Olodaterol 5 µg
Started	204	203	202
Completed	178	192	196
Not completed	26	11	6
Adverse event, serious fatal	-	2	-
Consent withdrawn by subject	4	2	1
Adverse event, non-fatal	13	1	4
Lost to follow-up	1	-	-
Lack of efficacy	6	-	-
Protocol deviation	2	4	-
Other than stated above	-	2	1

Number of subjects in period 1^[1]	Tiotropium 5 µg + Olodaterol 5 µg
Started	203
Completed	195
Not completed	8
Adverse event, serious fatal	-
Consent withdrawn by subject	-
Adverse event, non-fatal	3
Lost to follow-up	1
Lack of efficacy	-
Protocol deviation	2
Other than stated above	2

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	204	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	65.1	64.9	64.7
standard deviation	± 8.3	± 8.2	± 8.2
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	77	79	86
Male	127	124	116

Reporting group values	Tiotropium 5 µg + Olodaterol 5 µg	Total	
Number of subjects	203	812	
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	64.7		
standard deviation	± 8.9	-	

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	89	331	
Male	114	481	

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	204 ^[1]	203 ^[2]	202 ^[3]	202 ^[4]
Units: Liter				
arithmetic mean (standard error)	-0.014 (± 0.014)	0.205 (± 0.013)	0.285 (± 0.013)	0.316 (± 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

Statistical analysis title	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	406
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	0.331
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.293
upper limit	0.369
Variability estimate	Standard error of the mean
Dispersion value	0.019

Statistical analysis title	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	405
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	0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.075
upper limit	0.148

Variability estimate	Standard error of the mean
Dispersion value	0.019

Statistical analysis title	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	406
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	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.262
upper limit	0.337
Variability estimate	Standard error of the mean
Dispersion value	0.019

Statistical analysis title	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	405
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	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.044
upper limit	0.116
Variability estimate	Standard error of the mean
Dispersion value	0.018

Statistical analysis title	Statistical analysis 5
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	407
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	0.219
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.181
upper limit	0.258
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	Statistical analysis 6
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	404
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0872
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.031
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.067
Variability estimate	Standard error of the mean
Dispersion value	0.018

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.

End point type	Primary
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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	198 ^[5]	200 ^[6]	201 ^[7]	200 ^[8]
Units: Liter				
arithmetic mean (standard error)	0.001 (± 0.014)	0.135 (± 0.014)	0.151 (± 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
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Number of subjects included in analysis	398
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	< 0.0001
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Method	Mixed Effects Model for Repeated Measure
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Parameter estimate	Mean difference (net)
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Point estimate	0.162
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Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0124
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.019

Statistical analysis title	Statistical analysis 2
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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	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1381
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.009
upper limit	0.066
Variability estimate	Standard error of the mean
Dispersion value	0.019

Statistical analysis title	Statistical analysis 3
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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	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	0.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.113
upper limit	0.188
Variability estimate	Standard error of the mean
Dispersion value	0.019

Statistical analysis title	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	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3872
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.054
Variability estimate	Standard error of the mean
Dispersion value	0.019

Statistical analysis title	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	398
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	0.134

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.096
upper limit	0.172
Variability estimate	Standard error of the mean
Dispersion value	0.019

Statistical analysis title	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 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	Tiotropium 2.5 µg+ Olodaterol 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	= 0.5333
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.049
Variability estimate	Standard error of the mean
Dispersion value	0.019

Primary: St. George's Respiratory Questionnaire (SGRQ) total score

End point title	St. George's Respiratory Questionnaire (SGRQ) total score
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End point description:

This endpoint was evaluated based on the data from this individual trial. 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. 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.

End point type	Primary
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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	186 ^[9]	192 ^[10]	199 ^[11]	196 ^[12]
Units: units on a scale				
arithmetic mean (standard error)	42.038 (± 0.738)	39.637 (± 0.717)	37.916 (± 0.708)	37.144 (± 0.71)

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

[12] - 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 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	382
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	-4.894
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.904
upper limit	-2.884
Variability estimate	Standard error of the mean
Dispersion value	1.024

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 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	388
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0136
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-2.493
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.473
upper limit	-0.513
Variability estimate	Standard error of the mean
Dispersion value	1.009

Statistical analysis title	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	385
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	-4.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.129
upper limit	-2.114
Variability estimate	Standard error of the mean
Dispersion value	1.023

Statistical analysis title	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
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Number of subjects included in analysis	391
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.088
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-1.721
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.698
upper limit	0.256
Variability estimate	Standard error of the mean
Dispersion value	1.008

Statistical analysis title	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 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	378
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0198
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-2.401
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.419
upper limit	-0.382
Variability estimate	Standard error of the mean
Dispersion value	1.029

Statistical analysis title	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 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	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4415
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	-0.772
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.741
upper limit	1.196
Variability estimate	Standard error of the mean
Dispersion value	1.003

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

End point title	Trough forced vital capacity (FVC) response (change from baseline)
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
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	198 ^[13]	200 ^[14]	201 ^[15]	200 ^[16]
Units: Liter				
arithmetic mean (standard error)	0.025 (± 0.023)	0.223 (± 0.023)	0.233 (± 0.022)	0.244 (± 0.022)

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
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	398
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	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.157
upper limit	0.282
Variability estimate	Standard error of the mean
Dispersion value	0.032

Statistical analysis title	Statistical analysis 2
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	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5052
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.041
upper limit	0.084
Variability estimate	Standard error of the mean
Dispersion value	0.032

Statistical analysis title	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	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	0.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.146
upper limit	0.271
Variability estimate	Standard error of the mean
Dispersion value	0.032

Statistical analysis title	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	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7566
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.052
upper limit	0.072
Variability estimate	Standard error of the mean
Dispersion value	0.032

Statistical analysis title	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	398
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	0.198
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.136
upper limit	0.261
Variability estimate	Standard error of the mean
Dispersion value	0.032

Statistical analysis title	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	401
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7199
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.051
upper limit	0.073
Variability estimate	Standard error of the mean
Dispersion value	0.032

Secondary: TDI focal score

End point title	TDI focal score
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End point description:

This endpoint was evaluated based on the data from this individual trial. 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. 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.

End point type	Secondary
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	187 ^[17]	193 ^[18]	199 ^[19]	196 ^[20]
Units: Units on a scale				
arithmetic mean (standard error)	-0.113 (± 0.196)	1.332 (± 0.192)	1.839 (± 0.189)	1.939 (± 0.19)

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
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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	383
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	2.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.516
upper limit	2.588
Variability estimate	Standard error of the mean
Dispersion value	0.273

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	= 0.0246
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	0.607
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.078
upper limit	1.137
Variability estimate	Standard error of the mean
Dispersion value	0.27

Statistical analysis title	Statistical analysis 3
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	386
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	1.952
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.417
upper limit	2.487
Variability estimate	Standard error of the mean
Dispersion value	0.272

Statistical analysis title	Statistical analysis 4
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
Number of subjects included in analysis	392
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0599
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	0.507
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	1.035
Variability estimate	Standard error of the mean
Dispersion value	0.269

Statistical analysis title	Statistical analysis 5
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	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	1.445
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.907
upper limit	1.983
Variability estimate	Standard error of the mean
Dispersion value	0.274

Statistical analysis title	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 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
Number of subjects included in analysis	395
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7081
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.425
upper limit	0.626
Variability estimate	Standard error of the mean
Dispersion value	0.268

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	204 ^[21]	203 ^[22]	202 ^[23]	202 ^[24]
Units: Liter				
arithmetic mean (standard error)	-0.011 (± 0.025)	0.286 (± 0.024)	0.387 (± 0.023)	0.446 (± 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

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 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	406
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	0.457
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.524
Variability estimate	Standard error of the mean
Dispersion value	0.034

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 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	405
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	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.095
upper limit	0.225

Variability estimate	Standard error of the mean
Dispersion value	0.033

Statistical analysis title	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	406
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	0.398
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.331
upper limit	0.465
Variability estimate	Standard error of the mean
Dispersion value	0.034

Statistical analysis title	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	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.101
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.036
upper limit	0.165
Variability estimate	Standard error of the mean
Dispersion value	0.033

Statistical analysis title	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	407
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	0.297
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.229
upper limit	0.365
Variability estimate	Standard error of the mean
Dispersion value	0.035

Statistical analysis title	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	404
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0701
Method	Mixed Effects Model for Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.123
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 2.5 µg tiotropium 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	11 / 204 (5.39%)	6 / 203 (2.96%)	4 / 202 (1.98%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm of unknown primary site			
subjects affected / exposed	0 / 204 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 204 (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

Cervical vertebral fracture			
subjects affected / exposed	0 / 204 (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
Clavicle fracture			
subjects affected / exposed	0 / 204 (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
Road traffic accident			
subjects affected / exposed	0 / 204 (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
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 204 (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
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 204 (0.49%)	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	2 / 204 (0.98%)	0 / 203 (0.00%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 204 (0.49%)	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
Cardiomyopathy			
subjects affected / exposed	1 / 204 (0.49%)	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

Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 204 (0.49%)	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
Myocardial infarction			
subjects affected / exposed	0 / 204 (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 / 1	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 204 (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 / 1	0 / 0
Convulsion			
subjects affected / exposed	0 / 204 (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
Lumbar radiculopathy			
subjects affected / exposed	1 / 204 (0.49%)	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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 204 (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
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 204 (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
Hepatobiliary disorders			
Autoimmune hepatitis			

subjects affected / exposed	1 / 204 (0.49%)	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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 204 (1.47%)	1 / 203 (0.49%)	1 / 202 (0.50%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 204 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 204 (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 failure			
subjects affected / exposed	1 / 204 (0.49%)	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
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	0 / 204 (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
Bipolar disorder			
subjects affected / exposed	0 / 204 (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
Depression			
subjects affected / exposed	0 / 204 (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

Suicide attempt			
subjects affected / exposed	0 / 204 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 204 (0.98%)	1 / 203 (0.49%)	0 / 202 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 204 (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
Erysipelas			
subjects affected / exposed	0 / 204 (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
Gangrene			
subjects affected / exposed	0 / 204 (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
Gastrointestinal bacterial infection			
subjects affected / exposed	0 / 204 (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
Localised infection			
subjects affected / exposed	0 / 204 (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
Pneumonia			
subjects affected / exposed	0 / 204 (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

Pneumonia bacterial			
subjects affected / exposed	0 / 204 (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
Sinusitis			
subjects affected / exposed	1 / 204 (0.49%)	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
Viral infection			
subjects affected / exposed	1 / 204 (0.49%)	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

Serious adverse events	Treatment period Tiotropium 5 µg + Olodaterol 5 µg		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 203 (4.93%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm of unknown primary site			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical vertebral fracture			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			

subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Road traffic accident			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiomyopathy			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Convulsion			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar radiculopathy			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bipolar disorder			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicide attempt			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Osteoarthritis			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gangrene			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal bacterial infection			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 203 (0.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinusitis			

subjects affected / exposed	0 / 203 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	0 / 203 (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 %

Non-serious adverse events	Treatment period placebo	Treatment period Tiotropium 5 µg	Treatment period Tiotropium 2.5 µg + Olodaterol 5 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 204 (15.69%)	25 / 203 (12.32%)	25 / 202 (12.38%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	20 / 204 (9.80%)	19 / 203 (9.36%)	16 / 202 (7.92%)
occurrences (all)	22	21	16
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 204 (5.88%)	9 / 203 (4.43%)	9 / 202 (4.46%)
occurrences (all)	12	9	9

Non-serious adverse events	Treatment period Tiotropium 5 µg + Olodaterol 5 µg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 203 (7.88%)		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	9 / 203 (4.43%)		
occurrences (all)	10		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 203 (3.45%)		
occurrences (all)	7		

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: