Clinical trial results:
A randomised, double-blind, cross-over study to evaluate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (5/5 g) compared with tiotropium (5 g), both delivered by the Respimat® Inhaler, on breathlessness during the three minute Constant Speed Shuttle Test (3min CSST) in patients with Chronic Obstructive Pulmonary Disease (COPD).

Summary

EudraCT number	2015-002974-20
Trial protocol	BE NL
Global end of trial date	14 August 2017

Results information

Result version number	v1 (current)
This version publication date	29 August 2018
First version publication date	29 August 2018

Trial information

Trial identification

Sponsor protocol code	1237.28

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02853123
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2017
Global end of trial reached?	Yes
Global end of trial date	14 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effect of tiotropium + olodaterol fixed dose combination (FDC) compared to tiotropium monotherapy on the intensity of breathlessness during the 3minute (min) Constant Speed Shuttle Test (CSST).

Protection of trial subjects:

Only participants that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All participants were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all participants was adhered to throughout the trial conduct. Rescue medication was allowed for all participants as required. The terms and conditions of the insurance coverage were available to the investigator and the patients in the investigator site file (ISF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2016
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	Canada: 31
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Netherlands: 28
Worldwide total number of subjects	130
EEA total number of subjects	99

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)	59
From 65 to 84 years	71
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A randomized, double-blind, active-controlled, 2-period crossover, Phase IV study to evaluate the effects of tiotropium+olodaterol fixed dose combination compared with tiotropium on the intensity of breathlessness in patients with Chronic Obstructive Pulmonary Disease. Total of 130 patients were enrolled, 106 patients were entered and randomized.

Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. Patients attended specialist sites which then ensured that all patients met all inclusion/exclusion criteria. Patients were not to be randomized to trial treatment if any specific entry criteria were violated.

Period 1

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

Blinding implementation details:

This is Randomised and controlled trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Tiotropium 5 microgram (µg)/ Tiotropium + Olodaterol 5/5 µg

Arm description:

Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium (Tio) inhalation solution (2.5 µg per actuation) once a day, in the morning for a period of 6 weeks in period 1 followed by a 3 week washout period. In period 2, patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium + Olodaterol (Tio+Olo) fixed dose combination (FDC) inhalation solution (2.5/2.5 µg per actuation) once a day, in the morning for a period of 6 weeks.

Arm type	Treatment sequence
Investigational medicinal product name	Tiotropium + Olodaterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

2 puffs from the Respimat® Inhaler of the Tiotropium + Olodaterol Fixed Dose Combination (FDC) inhalation solution (2.5/2.5 µg per actuation) once a day, in the morning for a period of 6 weeks

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

Dosage and administration details:

2 puffs from the Respimat® Inhaler of the Tiotropium inhalation solution (2.5 µg per actuation) once a day, in the morning for a period of 6 weeks

Arm title	Tiotropium + Olodaterol 5/5 µg/Tiotropium 5 µg

Arm description:

Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium + Olodaterol (Tio+Olo) fixed dose combination (FDC) inhalation solution (2.5/2.5 µg per actuation) once a day, in the morning for a period of 6 weeks in period 1 followed by a 3 week washout period. In period 2, patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium (Tio) inhalation solution (2.5 µg per actuation) once a day, in

the morning for a period of 6 weeks.

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

Dosage and administration details:

2 puffs from the Respimat® Inhaler of the Tiotropium inhalation solution (2.5 µg per actuation) once a day, in the morning for a period of 6 weeks

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

Dosage and administration details:

2 puffs from the Respimat® Inhaler of the Tiotropium + Olodaterol Fixed Dose Combination (FDC) inhalation solution (2.5/2.5 µg per actuation) once a day, in the morning for a period of 6 weeks

Number of subjects in period 1[1]	Tiotropium 5 microgram (µg)/ Tiotropium + Olodaterol 5/5 µg	Tiotropium + Olodaterol 5/5 µg/Tiotropium 5 µg
Started	52	54
Completed	51	48
Not completed	1	6
Worsening COPD	-	3
Adverse event, non-fatal	1	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Period 2

Period 2 title	Period 2 (Treatment period)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

This is Randomised and controlled trial.

Arms

Are arms mutually exclusive?	No

Arm title	Tiotropium 5 microgram (µg)

Arm description:

Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium (Tio) inhalation solution (2.5 µg per actuation) once a day, in the morning for a period of 6 weeks.

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

Dosage and administration details:

2 puffs from the Respimat® Inhaler of the Tiotropium inhalation solution (2.5 µg per actuation) once a day, in the morning for a period of 6 weeks

Arm title	Tiotropium + Olodaterol 5/5 µg

Arm description:

Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium + Olodaterol (Tio+Olo) fixed dose combination (FDC) inhalation solution (2.5/2.5 µg per actuation) once a day, in the morning for a period of 6 weeks.

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

Dosage and administration details:

Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium + Olodaterol Fixed Doce Combination (FDC) inhalation solution (2.5/2.5 µg per actuation) once a day, in the morning for a period of 6 weeks

Number of subjects in period 2	Tiotropium 5 microgram (µg)	Tiotropium + Olodaterol 5/5 µg
Started	100	105
Completed	100	102
Not completed	0	3
Adverse event, non-fatal	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Period 1 (Overall trial by sequence)

Reporting group description:

This patient set was nested within the randomized set (RS) and included all patients who were dispensed study medication and were documented to have taken any dose of study medication.

Reporting group values	Period 1 (Overall trial by sequence)	Total	
Number of subjects	106	106	
Age categorical Units: Subjects			

Age Continuous			
The age data are presented by years. Treated set (TS): This patient set was nested within the RS and included all patients who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: years			
arithmetic mean	63.6		
standard deviation	± 7.2	-	
Sex: Female, Male			
The sex data are presented by count of participants. TS			
Units: Subjects			
Male	66	66	
Female	40	40	
Race (NIH/OMB)			
The race data are presented by count of participants. Ethnicity was not captured in this trial.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	105	105	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Tiotropium 5 microgram (µg)/ Tiotropium + Olodaterol 5/5 µg
Reporting group description:	
Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium (Tio) inhalation solution (2.5 µg per actuation) once a day, in the morning for a period of 6 weeks in period 1 followed by a 3 week washout period. In period 2, patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium + Olodaterol (Tio+Olo) fixed dose combination (FDC) inhalation solution (2.5/2.5 µg per actuation) once a day, in the morning for a period of 6 weeks.	
Reporting group title	Tiotropium + Olodaterol 5/5 µg/Tiotropium 5 µg
Reporting group description:	
Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium + Olodaterol (Tio+Olo) fixed dose combination (FDC) inhalation solution (2.5/2.5 µg per actuation) once a day, in the morning for a period of 6 weeks in period 1 followed by a 3 week washout period. In period 2, patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium (Tio) inhalation solution (2.5 µg per actuation) once a day, in the morning for a period of 6 weeks.	
Reporting group title	Tiotropium 5 microgram (µg)
Reporting group description:	
Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium (Tio) inhalation solution (2.5 µg per actuation) once a day, in the morning for a period of 6 weeks.	
Reporting group title	Tiotropium + Olodaterol 5/5 µg
Reporting group description:	
Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium + Olodaterol (Tio+Olo) fixed dose combination (FDC) inhalation solution (2.5/2.5 µg per actuation) once a day, in the morning for a period of 6 weeks.	

Primary: Change from baseline in intensity of breathlessness measured using the Modified Borg Scale at the end of the 3 minute Constant Speed Shuttle Test after 6 weeks of treatment.

End point title	Change from baseline in intensity of breathlessness measured using the Modified Borg Scale at the end of the 3 minute Constant Speed Shuttle Test after 6 weeks of treatment.
End point description:	
At 3 min or end of exercise (if 3 min not achieved), patients were asked to estimate the intensity of breathing discomfort that they were experiencing by matching their subjective estimate to descriptive phrases that best described the intensity of each sensation using the Modified Borg Scale (MBS-S). Measure type is actually Adjusted Mean Change from Baseline. Full analysis set (FAS): This patient set was nested within the Treated set (TS) and included patients who had baseline measurement and at least one post-baseline measurement for the primary endpoint.	
End point type	Primary
End point timeframe:	
Baseline and week 6	

End point values	Tiotropium 5 microgram (µg)	Tiotropium + Olodaterol 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[1]	101[2]		
Units: Unit on Scale				
least squares mean (standard error)	-0.968 (± 0.137)	-1.325 (± 0.136)		

Notes:
[1] - FAS
[2] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The adjusted means (SE) are obtained from fitting an Mixed-effects Model Repeated Measures (MMRM) model including treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates, compound symmetry covariance structure for within−patient variation.

Comparison groups	Tiotropium 5 microgram (µg) v Tiotropium + Olodaterol 5/5 µg
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0217 [4]
Method	Mixed Effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.357
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.661
upper limit	-0.053
Variability estimate	Standard error of the mean
Dispersion value	0.153

Notes:

[3] - Mean difference means the treatment difference vs. Tiotropium (i.e. Tiotropium/Olodaterol - Tiotropium).

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (201) does not reflect the actual number. The number of subjects in FAS is 105.
[4] - Kenward−Roger approximation of denominator was used for degrees of freedom.

Secondary: Change from baseline after 6 weeks of treatment for inspiratory capacity measured prior to exercise

End point title	Change from baseline after 6 weeks of treatment for inspiratory capacity measured prior to exercise

End point description:

Inspiratory Capacity (IC) is a standard measurement for the assessment of lung function. IC measurements were performed prior to the 3min Constant Speed Shuttle Test (CSST) (at rest). Measure type is actually Adjusted Mean Change from Baseline.

End point type	Secondary

End point timeframe:

Baseline and week 6

End point values	Tiotropium 5 microgram (µg)	Tiotropium + Olodaterol 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[5]	101[6]		
Units: Litre (L)				
least squares mean (standard error)	0.279 (± 0.040)	0.464 (± 0.039)		

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

IC measured prior to exercise, the adjusted means (SE) are obtained from fitting an Mixed-effects Model Repeated Measures (MMRM) model including treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates, compound symmetry covariance structure for within−patient variation.

Comparison groups	Tiotropium 5 microgram (µg) v Tiotropium + Olodaterol 5/5 µg
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001 [8]
Method	Mixed Effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	0.185
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.106
upper limit	0.265
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

[7] - Mean difference means the treatment difference vs. Tiotropium (i.e. Tiotropium/Olodaterol - Tiotropium).

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (201) does not reflect the actual number. The number of subjects in FAS is 105.

[8] - Kenward−Roger approximation of denominator was used for degrees of freedom.

Secondary: Change from baseline after 6 weeks of treatment for inspiratory capacity measured at the end of exercise

End point title	Change from baseline after 6 weeks of treatment for inspiratory capacity measured at the end of exercise

End point description:

Inspiratory Capacity (IC) is a standard measurement for the assessment of lung function. IC measurements were performed at the end of the 3min Constant Speed Shuttle Test (CSST). Measure type is actually Adjusted Mean Change from Baseline.

End point type	Secondary

End point timeframe:

Baseline and week 6

End point values	Tiotropium 5 microgram (µg)	Tiotropium + Olodaterol 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98[9]	100[10]		
Units: Litre (L)				
least squares mean (standard error)	0.256 (± 0.034)	0.322 (± 0.034)		

Notes:

[9] - FAS

[10] - FAS

Statistical analyses

Statistical analysis title	Statistical Annalysis 3

Statistical analysis description:

IC measured end of exercise, the adjusted means (SE) are obtained from fitting an Mixed-effects Model Repeated Measures (MMRM) model including treatment and period as fixed effects, patient as a random effect,
and period baseline and patient baseline as covariates, compound symmetry covariance structure for within−patient variation

Comparison groups	Tiotropium 5 microgram (µg) v Tiotropium + Olodaterol 5/5 µg
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.0852 [12]
Method	Mixed Effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	0.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.009
upper limit	0.141
Variability estimate	Standard error of the mean
Dispersion value	0.038

Notes:

[11] - Mean difference means the treatment difference vs. Tiotropium (i.e. Tiotropium/Olodaterol - Tiotropium).

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (198) does not reflect the actual number. The number of subjects in FAS is 105.

[12] - Kenward−Roger approximation of denominator was used for degrees of freedom.

Secondary: Change from baseline after 6 weeks of treatment for 1 hour post-dose Forced Expiratory Volume in 1st second

End point title	Change from baseline after 6 weeks of treatment for 1 hour post-dose Forced Expiratory Volume in 1st second

End point description:

Forced Expiratory Volume in 1st second (FEV1) is a standard measurement for the assessment of lung function. The best of 3 efforts was defined as the highest FEV1, each obtained on any of 3 manoeuvres meeting the American Thoracic Society (ATS) criteria (to a maximum of 5 attempts). Measure type is

actually Adjusted Mean Change from Baseline.

End point type	Secondary

End point timeframe:

Baseline and week 6

End point values	Tiotropium 5 microgram (µg)	Tiotropium + Olodaterol 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[13]	103[14]		
Units: Litre (L)				
least squares mean (standard error)	0.163 (± 0.021)	0.318 (± 0.021)		

Notes:

[13] - FAS

[14] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

The adjusted means (SE) are obtained from fitting an Mixed-effects Model Repeated Measures (MMRM) model including treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates, compound symmetry covariance structure for within−patient variation.

Comparison groups	Tiotropium 5 microgram (µg) v Tiotropium + Olodaterol 5/5 µg
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	Mixed Effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	0.155
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.117
upper limit	0.194
Variability estimate	Standard error of the mean
Dispersion value	0.02

Notes:

[15] - Mean difference means the treatment difference vs. Tiotropium (i.e. Tiotropium/Olodaterol - Tiotropium).

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (202) does not reflect the actual number. The number of subjects in FAS is 105.

[16] - Kenward−Roger approximation of denominator was used for degrees of freedom.

Secondary: Change from baseline after 6 weeks of treatment for 1 hour post-dose Forced Vital Capacity

End point title	Change from baseline after 6 weeks of treatment for 1 hour post-dose Forced Vital Capacity

End point description:

Forced Vital Capacity (FVC) is a standard measurement for the assessment of lung function. The best of 3 efforts was defined as the highest FVC, each obtained on any of 3 manoeuvres meeting the American Thoracic Society (ATS) criteria (to a maximum of 5 attempts). Measure type is actually Adjusted Mean Change from Baseline.

End point type	Secondary

End point timeframe:

Baseline and week 6

End point values	Tiotropium 5 microgram (µg)	Tiotropium + Olodaterol 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[17]	103[18]		
Units: Litre (L)				
least squares mean (standard error)	0.258 (± 0.040)	0.459 (± 0.039)		

Notes:

[17] - FAS

[18] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

The adjusted means (SE) are obtained from fitting an Mixed-effects Model Repeated Measures (MMRM) model including treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates, compound symmetry covariance structure for within−patient variation.

Comparison groups	Tiotropium 5 microgram (µg) v Tiotropium + Olodaterol 5/5 µg
Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001 [20]
Method	Mixed Effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	0.201
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.134
upper limit	0.267
Variability estimate	Standard error of the mean
Dispersion value	0.034

Notes:

[19] - Mean difference means the treatment difference vs. Tiotropium (i.e. Tiotropium/Olodaterol - Tiotropium).

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (202) does not reflect the actual number. The number of subjects in FAS is 105.

[20] - Kenward−Roger approximation of denominator was used for degrees of freedom.

Secondary: Change from baseline after 6 weeks of treatment for intensity of breathlessness (MBS-S) at 1, 2 and 2.5 minute (min) during the 3 min Constant Speed Shuttle Test

End point title	Change from baseline after 6 weeks of treatment for intensity of breathlessness (MBS-S) at 1, 2 and 2.5 minute (min) during the 3 min Constant Speed Shuttle Test

End point description:

At 1, 2 and 2.5 min during exercise, patients were asked to estimate the intensity of breathing discomfort that they were experiencing by matching their subjective estimate to descriptive phrases that best described the intensity of each sensation using the Modified Borg Scale (MBS-S). Measure type is actually Adjusted Mean Change from Baseline.

End point type	Secondary

End point timeframe:

Baseline and week 6

End point values	Tiotropium 5 microgram (µg)	Tiotropium + Olodaterol 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[21]	101[22]		
Units: Unit on Scale				
least squares mean (standard error)				
1 min	-0.685 (± 0.081)	-0.793 (± 0.081)		
2 min	-0.839 (± 0.102)	-1.079 (± 0.101)		
2.5 min	-0.846 (± 0.127)	-1.164 (± 0.126)		

Notes:

[21] - FAS

[22] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

1 min, the adjusted means (SE) are obtained from fitting an Mixed-effects Model Repeated Measures (MMRM) model including treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates, compound symmetry covariance structure for within−patient variation.

Comparison groups	Tiotropium 5 microgram (µg) v Tiotropium + Olodaterol 5/5 µg
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.2645 [24]
Method	Mixed Effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.108
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.083

Variability estimate	Standard error of the mean
Dispersion value	0.096

Notes:

[23] - Mean difference means the treatment difference vs. Tiotropium (i.e. Tiotropium/Olodaterol - Tiotropium).

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (201) does not reflect the actual number. The number of subjects in FAS is 105.
[24] - Kenward−Roger approximation of denominator was used for degrees of freedom.

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

2 min, the adjusted means (SE) are obtained from fitting an Mixed-effects Model Repeated Measures (MMRM) model including treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates, compound symmetry covariance structure for within−patient variation.

Comparison groups	Tiotropium 5 microgram (µg) v Tiotropium + Olodaterol 5/5 µg
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.0267 [26]
Method	Mixed Effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.452
upper limit	-0.028
Variability estimate	Standard error of the mean
Dispersion value	0.107

Notes:

[25] - Mean difference means the treatment difference vs. Tiotropium (i.e. Tiotropium/Olodaterol - Tiotropium).

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (201) does not reflect the actual number. The number of subjects in FAS is 105.
[26] - Kenward−Roger approximation of denominator was used for degrees of freedom.

Statistical analysis title	Statistical Analysis 8

Statistical analysis description:

2.5 min, the adjusted means (SE) are obtained from fitting an Mixed-effects Model Repeated Measures (MMRM) model including treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates, compound symmetry covariance structure for within−patient variation.

Comparison groups	Tiotropium 5 microgram (µg) v Tiotropium + Olodaterol 5/5 µg
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.0258 [28]
Method	Mixed Effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.318
Confidence interval	
level	95 %

sides	2-sided
lower limit	-0.596
upper limit	-0.039
Variability estimate	Standard error of the mean
Dispersion value	0.14

Notes:

[27] - Mean difference means the treatment difference vs. Tiotropium (i.e. Tiotropium/Olodaterol - Tiotropium).

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (201) does not reflect the actual number. The number of subjects in FAS is 105.

[28] - Kenward−Roger approximation of denominator was used for degrees of freedom.

Secondary: Change from baseline after 6 weeks of treatment for Chronic Respiratory Questionnaire - Self Administered Individualized dyspnoea domain score

End point title	Change from baseline after 6 weeks of treatment for Chronic Respiratory Questionnaire - Self Administered Individualized dyspnoea domain score

End point description:

Patients completed the Chronic Respiratory Questionnaire - Self Administered Individualized (CRQ-SAI) questionnaire, which contained a dyspnoea domain individualized to each patient. The patients were asked to select the 5 activities among 26 activities associated with breathlessness that they performed frequently and were most important to them. Measure type is actually Adjusted Mean Change from Baseline.

End point type	Secondary

End point timeframe:

Baseline and week 6

End point values	Tiotropium 5 microgram (µg)	Tiotropium + Olodaterol 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93[29]	96[30]		
Units: Unit on Scale				
least squares mean (standard error)	0.640 (± 0.091)	0.610 (± 0.089)		

Notes:

[29] - FAS

[30] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 9

Statistical analysis description:

The adjusted means (SE) are obtained from fitting an Mixed-effects Model Repeated Measures (MMRM) model including treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates, compound symmetry covariance structure for within−patient variation.

Comparison groups	Tiotropium 5 microgram (µg) v Tiotropium + Olodaterol 5/5 µg
Number of subjects included in analysis	189
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.8025 [32]

Method	Mixed Effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.268
upper limit	0.208
Variability estimate	Standard error of the mean
Dispersion value	0.12

Notes:

[31] - Mean difference means the treatment difference vs. Tiotropium (i.e. Tiotropium/Olodaterol - Tiotropium).

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (189) does not reflect the actual number. The number of subjects in FAS is 105.

[32] - Kenward−Roger approximation of denominator was used for degrees of freedom.

Secondary: Change from baseline after 6 weeks of treatment for Chronic Respiratory Questionnaire - Self Administered Standardized dyspnoea domain score

End point title	Change from baseline after 6 weeks of treatment for Chronic Respiratory Questionnaire - Self Administered Standardized dyspnoea domain score

End point description:

The Chronic Respiratory Questionnaire - Self Administered Standardized (CRQ-SAS) is a questionnaire that assesses the patients' perception of their COPD and measures the impact of COPD on their life and contains 20 standardized questions. The first part of the questionnaire contains 5 standardized activities and the patients had to indicate how much shortness of breath they had experienced while performing each of the activities. Measure type is actually Adjusted Mean Change from Baseline.

End point type	Secondary

End point timeframe:

Baseline and week 6

End point values	Tiotropium 5 microgram (µg)	Tiotropium + Olodaterol 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[33]	102[34]		
Units: Unit on Scale				
least squares mean (standard error)	0.325 (± 0.088)	0.415 (± 0.087)		

Notes:

[33] - FAS

[34] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 10

Statistical analysis description:

The adjusted means (SE) are obtained from fitting an Mixed-effects Model Repeated Measures (MMRM) model including treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates, compound symmetry covariance structure for within−patient variation.

Comparison groups	Tiotropium 5 microgram (µg) v Tiotropium + Olodaterol 5/5 µg

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	= 0.3634 [36]
Method	Mixed Effect Model Repeated Measures
Parameter estimate	Mean difference (final values)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.106
upper limit	0.286
Variability estimate	Standard error of the mean
Dispersion value	0.099

Notes:

[35] - Mean difference means the treatment difference vs. Tiotropium (i.e. Tiotropium/Olodaterol - Tiotropium).

As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (202) does not reflect the actual number. The number of subjects in FAS is 105.

[36] - Kenward−Roger approximation of denominator was used for degrees of freedom.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 21 days after last drug administration, up to 18 weeks.

Adverse event reporting additional description:

Treated set (TS) (This patient set was nested within the Randomised set (RS) and included all patients who were dispensed study medication and were documented to have taken any dose of study medication.) was used for patient safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Tiotropium 5 microgram (µg)

Reporting group description:

Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium (Tio) inhalation solution (2.5 µg per actuation)
once a day, in the morning for a period of 6 weeks.

Reporting group title	Total subjects

Reporting group description:

This patient set was nested within the randomized set (RS) and included all patients who were dispensed study medication and were documented to have taken any dose of study medication.

Reporting group title	Tiotropium + Olodaterol 5/5 µg

Reporting group description:

Patients inhaled 2 puffs from the Respimat® Inhaler of the Tiotropium + Olodaterol (Tio+Olo) fixed dose combination
(FDC) inhalation solution (2.5/2.5 µg per actuation) once a day, in the morning for a period of 6 weeks.

Serious adverse events	Tiotropium 5 microgram (µg)	Total subjects	Tiotropium + Olodaterol 5/5 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 100 (1.00%)	6 / 106 (5.66%)	5 / 105 (4.76%)
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)			
Colon neoplasm			
subjects affected / exposed	0 / 100 (0.00%)	1 / 106 (0.94%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 100 (0.00%)	1 / 106 (0.94%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 100 (1.00%)	1 / 106 (0.94%)	0 / 105 (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
Coma			
subjects affected / exposed	0 / 100 (0.00%)	1 / 106 (0.94%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 100 (0.00%)	1 / 106 (0.94%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 106 (0.94%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 106 (0.94%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	0 / 100 (0.00%)	1 / 106 (0.94%)	1 / 105 (0.95%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Tiotropium 5 microgram (µg)	Total subjects	Tiotropium + Olodaterol 5/5 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 100 (21.00%)	44 / 106 (41.51%)	31 / 105 (29.52%)

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	10 / 100 (10.00%)	22 / 106 (20.75%)	14 / 105 (13.33%)
occurrences (all)	12	30	18
Cough			
subjects affected / exposed	2 / 100 (2.00%)	6 / 106 (5.66%)	5 / 105 (4.76%)
occurrences (all)	2	7	5
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	13 / 100 (13.00%)	23 / 106 (21.70%)	14 / 105 (13.33%)
occurrences (all)	13	27	14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported