

**Clinical trial results:**

A randomised, double-blind, parallel group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium plus olodaterol fixed dose combination (2.5 g / 5 g; 5 g / 5 g) (delivered by the Respimat® Inhaler) compared with the individual components (2.5 g and 5 g tiotropium, 5 g olodaterol) (delivered by the Respimat® Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD)

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2009-010669-22
Trial protocol	NO SE ES SK BE DE HU IE AT GB
Global end of trial date	11 November 2013

Results information

Result version number	v2 (current)
This version publication date	01 July 2016
First version publication date	01 August 2015
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Data correction due to a system error in EudraCT- Results

Trial information**Trial identification**

Sponsor protocol code	1237.6
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01431287
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, +1 8002430127, clintrriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintrriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	09 December 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 April 2013
Global end of trial reached?	Yes
Global end of trial date	11 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the efficacy and safety of 52 weeks once daily treatment with orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg / 5 µg; 5 µg / 5 µg) (delivered by the Respimat® Inhaler) compared with the individual components (2.5 and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat® Inhaler) in patients with Chronic Obstructive Pulmonary Disease (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 without the need to provide a reason. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 68
Country: Number of subjects enrolled	Brazil: 178
Country: Number of subjects enrolled	Canada: 140
Country: Number of subjects enrolled	Colombia: 76
Country: Number of subjects enrolled	Croatia: 26
Country: Number of subjects enrolled	India: 94
Country: Number of subjects enrolled	Japan: 318
Country: Number of subjects enrolled	China: 362
Country: Number of subjects enrolled	Taiwan: 87
Country: Number of subjects enrolled	Russian Federation: 68
Country: Number of subjects enrolled	Romania: 72
Country: Number of subjects enrolled	Serbia: 99

Country: Number of subjects enrolled	Turkey: 128
Country: Number of subjects enrolled	United States: 643
Country: Number of subjects enrolled	South Africa: 122
Country: Number of subjects enrolled	Norway: 129
Country: Number of subjects enrolled	Slovakia: 22
Country: Number of subjects enrolled	Spain: 131
Country: Number of subjects enrolled	Sweden: 106
Country: Number of subjects enrolled	United Kingdom: 65
Country: Number of subjects enrolled	Austria: 108
Country: Number of subjects enrolled	Belgium: 101
Country: Number of subjects enrolled	Germany: 346
Country: Number of subjects enrolled	Ireland: 29
Worldwide total number of subjects	3518
EEA total number of subjects	1203

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)	1804
From 65 to 84 years	1706
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

A "Missing" category is unavailable for the age group breakdown of enrolled patients. Hence, 17 subjects with a missing data for age group have been added to age-category "18-64 years".

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, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Olodaterol (Olo) 5 µg

Arm description:

Oral inhalation of Olodaterol 5 µg (2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

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

Dosage and administration details:

5 µg Once daily with orally inhalation

Arm title	Tiotropium (Tio) 2.5 µg
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Arm description:

Oral inhalation of Tiotropium 2.5 µg (1.25 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

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:

2.5 µg once daily with oral inhalation

Arm title	Tiotropium (Tio) 5 µg
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Arm description:

Oral inhalation of Tiotropium 5 µg (2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning. One patient who was randomised to the Tiotropium 5 µg arm was not treated. Consequently, number of subjects that started is 507 but only 506 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

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:

5 µg once daily with oral inhalation

Arm title	Tio + Olo (T+O) 2.5/5 µg
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Arm description:

Oral inhalation of fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg (Tiotropium: 1.25 µg per actuation and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

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:

5 µg once daily with oral inhalation

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

Dosage and administration details:

2.5 µg once daily with oral inhalation

Arm title	Tio + Olo (T+O) 5/5 µg
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Arm description:

Oral inhalation of FDC of Tiotropium 5 µg and Olodaterol 5 µg (Tiotropium and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

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:

5 µg once daily with oral inhalation

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

Dosage and administration details:

5 µg once daily with oral inhalation

Number of subjects in period 1^[1]	Olodaterol (Olo) 5 µg	Tiotropium (Tio) 2.5 µg	Tiotropium (Tio) 5 µg
Started	510	507	506
Completed	412	409	410
Not completed	98	98	96
Adverse event, serious fatal	8	4	8
Consent withdrawn by subject	29	30	34
Adverse event, non-fatal	51	53	45
Lost to follow-up	-	3	2
Protocol deviation	6	6	5
not specified	4	2	2

Number of subjects in period 1^[1]	Tio + Olo (T+O) 2.5/5 µg	Tio + Olo (T+O) 5/5 µg
Started	508	507
Completed	445	430
Not completed	63	77
Adverse event, serious fatal	6	8
Consent withdrawn by subject	19	29
Adverse event, non-fatal	27	33
Lost to follow-up	3	1
Protocol deviation	6	5
not specified	2	1

Notes:

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

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

Baseline characteristics

Reporting groups

Reporting group title	Olodaterol (Olo) 5 µg
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Reporting group description:

Oral inhalation of Olodaterol 5 µg (2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

Reporting group title	Tiotropium (Tio) 2.5 µg
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Reporting group description:

Oral inhalation of Tiotropium 2.5 µg (1.25 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

Reporting group title	Tiotropium (Tio) 5 µg
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Reporting group description:

Oral inhalation of Tiotropium 5 µg (2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning. One patient who was randomised to the Tiotropium 5 µg arm was not treated.

Consequently, number of subjects that started is 507 but only 506 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

Reporting group title	Tio + Olo (T+O) 2.5/5 µg
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Reporting group description:

Oral inhalation of fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg (Tiotropium: 1.25 µg per actuation and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

Reporting group title	Tio + Olo (T+O) 5/5 µg
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Reporting group description:

Oral inhalation of FDC of Tiotropium 5 µg and Olodaterol 5 µg (Tiotropium and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

Reporting group values	Olodaterol (Olo) 5 µg	Tiotropium (Tio) 2.5 µg	Tiotropium (Tio) 5 µg
Number of subjects	510	507	506
Age categorical			
Units: Subjects			

Age continuous			
Treated Set (TS): This patient set included all patients in the randomised set who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: years			
arithmetic mean	64.7	63.9	63.5
standard deviation	± 8.3	± 8.7	± 8.7
Gender categorical			
Treated Set (TS): This patient set included all patients in the randomised set who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: Subjects			
Female	132	146	134
Male	378	361	372

Reporting group values	Tio + Olo (T+O) 2.5/5 µg	Tio + Olo (T+O) 5/5 µg	Total
Number of subjects	508	507	2538
Age categorical			
Units: Subjects			

Age continuous			
Treated Set (TS): This patient set included all patients in the randomised set who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: years			
arithmetic mean	64.1	62.7	
standard deviation	± 7.6	± 8.4	-
Gender categorical			
Treated Set (TS): This patient set included all patients in the randomised set who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: Subjects			
Female	140	158	710
Male	368	349	1828

End points

End points reporting groups

Reporting group title	Olodaterol (Olo) 5 µg
Reporting group description: Oral inhalation of Olodaterol 5 µg (2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.	
Reporting group title	Tiotropium (Tio) 2.5 µg
Reporting group description: Oral inhalation of Tiotropium 2.5 µg (1.25 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.	
Reporting group title	Tiotropium (Tio) 5 µg
Reporting group description: Oral inhalation of Tiotropium 5 µg (2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning. One patient who was randomised to the Tiotropium 5 µg arm was not treated. Consequently, number of subjects that started is 507 but only 506 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.	
Reporting group title	Tio + Olo (T+O) 2.5/5 µg
Reporting group description: Oral inhalation of fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg (Tiotropium: 1.25 µg per actuation and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.	
Reporting group title	Tio + Olo (T+O) 5/5 µg
Reporting group description: Oral inhalation of FDC of Tiotropium 5 µg and Olodaterol 5 µg (Tiotropium and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning.	

Primary: Forced Expiratory Volume in One Second (FEV1) Area Under the Curve (AUC) (0-3h) Response on Day 169.

End point title	Forced Expiratory Volume in One Second (FEV1) Area Under the Curve (AUC) (0-3h) Response on Day 169.
End point description: Area under the FEV-time curve from 0 to 3h post-dose (FEV1 AUC(0-3h)) was calculated using trapezoidal rule, divided by duration (3h) to report in litres. FEV1 AUC(0-3h) response was defined as FEV1 AUC(0-3h) minus baseline FEV1. Baseline was defined as the mean of 2 pre-dose measurements performed 1h & at 10 min prior to first dose at visit 2 (day1). The adjusted means (SE) were obtained by fitting MMRM model with fixed effects of treatment, planned test day, treatment-by-test day interaction, baseline & baseline-by-test day interaction, patient as random effect, & spatial power covariance structure for within-patient errors & Kenward-Roger approximation for denominator degrees of freedom. The Full analysis set (FAS) included all randomized patients, dispensed study medication, documented to have taken any dose of study medication & who had non-missing baseline & at least one non-missing post-baseline measurement for at least one primary or key secondary efficacy	
End point type	Primary
End point timeframe: 1 hour (h) and at 10 minutes (min) prior to dose on the first day of randomized treatment and on Day 169 and 5 min, 15 min, 30 min, 1 h, 2 h, 3 h post-dose on Day 169	

End point values	Olodaterol (Olo) 5 µg	Tiotropium (Tio) 2.5 µg	Tiotropium (Tio) 5 µg	Tio + Olo (T+O) 2.5/5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	507 ^[1]	504 ^[2]	500 ^[3]	506 ^[4]
Units: litre(s)				
least squares mean (standard error)	0.136 (± 0.009)	0.125 (± 0.009)	0.165 (± 0.009)	0.256 (± 0.009)

Notes:

[1] - Number of FAS (full analysis set) patients actually contributing to the model.

[2] - Number of FAS (full analysis set) patients actually contributing to the model.

[3] - Number of FAS (full analysis set) patients actually contributing to the model.

[4] - Number of FAS (full analysis set) patients actually contributing to the model.

End point values	Tio + Olo (T+O) 5/5 µg			
Subject group type	Reporting group			
Number of subjects analysed	502 ^[5]			
Units: litre(s)				
least squares mean (standard error)	0.268 (± 0.009)			

Notes:

[5] - Number of FAS (full analysis set) patients actually contributing to the model.

Statistical analyses

Statistical analysis title	T+O 5/5 vs Olo 5
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1009
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.108
upper limit	0.157
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 5
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day,

treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.078
upper limit	0.127
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Olo 5
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1013
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.121
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.096
upper limit	0.145
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 2.5
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1010
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.106
upper limit	0.155
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 5
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.066
upper limit	0.115
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs T+O 2.5/5
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
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Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3394
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.036
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 2.5
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.118
upper limit	0.167
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Olo 5
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
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Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0173
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.005
upper limit	0.054
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 2.5 vs Olo 5
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Statistical analysis description:

Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1011
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.421
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.035
upper limit	0.014
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
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Number of subjects included in analysis	1004
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.064
Variability estimate	Standard error of the mean
Dispersion value	0.012

Primary: Trough FEV1 response on day 170

End point title	Trough FEV1 response on day 170
End point description:	
<p>Trough FEV1 defined as the FEV1 value at the end of the dosing interval (24h)&calculated as mean of 2 FEV1 measurements performed at 23h &at 23h 50 min after inhalation of study medication at clinic visit on the previous day.Trough FEV1 response was defined as trough FEV1 minus baseline FEV1.Baseline was defined as mean of 2 pre-dose measurements performed 1h&at 10 min prior to administration of first dose at visit2(day 1).The adjusted means (SE) obtained by fitting mixed effect model repeated measures(MMRM) including fixed effects of treatment,planned test day,treatment-by-test day interaction,baseline&baseline-by-test day interaction,patient as random effect,&spatial power covariance structure for within-patient errors&Kenward- Roger approximation for denominator degrees of freedom.Since it is possible for patient to meet the data criterion for only a subset of the primary endpoints,it is possible that number of patients used in the FAS analysis for different endpoint will vary.</p>	
End point type	Primary
End point timeframe:	
<p>1 hours(h) and at 10 min prior to dose on the first day of randomized treatment (baseline) and at 23 h and at 23 h 50 min after inhalation of study medication on Day 170</p>	

End point values	Olodaterol (Olo) 5 µg	Tiotropium (Tio) 2.5 µg	Tiotropium (Tio) 5 µg	Tio + Olo (T+O) 2.5/5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	503 ^[6]	499 ^[7]	498 ^[8]	500 ^[9]
Units: litre(s)				
least squares mean (standard error)	0.057 (± 0.009)	0.062 (± 0.009)	0.096 (± 0.009)	0.125 (± 0.009)

Notes:

[6] - Number of FAS (full analysis set) patients actually contributing to the model.

[7] - Number of FAS (full analysis set) patients actually contributing to the model.

[8] - Number of FAS (full analysis set) patients actually contributing to the model.

[9] - Number of FAS (full analysis set) patients actually contributing to the model.

End point values	Tio + Olo (T+O) 5/5 µg			
Subject group type	Reporting group			
Number of subjects analysed	497 ^[10]			

Units: litre(s)				
least squares mean (standard error)	0.145 (± 0.009)			

Notes:

[10] - Number of FAS (full analysis set) patients actually contributing to the model.

Statistical analyses

Statistical analysis title	T+O 5/5 vs Olo 5
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.088
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.063
upper limit	0.113
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 5
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.024
upper limit	0.075

Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Olo 5
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Olodaterol (Olo) 5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	0.092
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 2.5
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.087
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 5
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0231
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.054
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs T+O 2.5/5
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1073
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.046
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 2.5
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.058
upper limit	0.108
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Olo 5
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	0.063
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 2.5 vs Olo 5
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6939
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0097
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.008
upper limit	0.058
Variability estimate	Standard error of the mean
Dispersion value	0.013

Secondary: FEV1 AUC (0-3h) response on Day 1, Day 85, and Day 365

End point title	FEV1 AUC (0-3h) response on Day 1, Day 85, and Day 365
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End point description:

FEV1 AUC(0-3h) was calculated as the area under the FEV1-time curve from 0 to 3 h post-dose using the trapezoidal rule, divided by the duration (3 h) to report in litres. FEV1 AUC(0-3h) response was defined as FEV1 AUC(0-3h) minus baseline FEV1. Baseline was defined as the mean of 2 pre-dose measurements performed 1 h & at 10 min prior to administration of the first dose of randomised treatment at Day 1. The adjusted means (SE) were obtained by fitting an Mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment-by-test day interaction, baseline & baseline-by-test day interaction, patient as random effect, & spatial power covariance structure for within-patient errors and Kenward-Roger approximation for denominator degrees of freedom. Since it is possible for the patient to meet the data criterion for only a subset of the primary endpoints, it is possible that the number of patients used in the FAS analysis for different endpoint will vary.

End point type	Secondary
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End point timeframe:

1 hour (h) and at 10 minutes (min) prior to dose on the first day of randomized treatment and on Days 85 and 365 and 5 min, 15 min, 30 min, 1 h, 2 h, 3 h post-dose on the first day of randomized treatment and on Days 85 and 365.

End point values	Olodaterol (Olo) 5 µg	Tiotropium (Tio) 2.5 µg	Tiotropium (Tio) 5 µg	Tio + Olo (T+O) 2.5/5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	507 ^[11]	504 ^[12]	500 ^[13]	506 ^[14]
Units: litre(s)				
least squares mean (standard error)				
Day 1	0.196 (± 0.009)	0.135 (± 0.009)	0.164 (± 0.009)	0.228 (± 0.009)
Day 85	0.153 (± 0.009)	0.165 (± 0.009)	0.187 (± 0.009)	0.272 (± 0.009)
Day 365	0.105 (± 0.01)	0.105 (± 0.01)	0.124 (± 0.01)	0.223 (± 0.009)

Notes:

[11] - Number of FAS (full analysis set) patients actually contributing to the model.

[12] - Number of FAS (full analysis set) patients actually contributing to the model.

[13] - Number of FAS (full analysis set) patients actually contributing to the model.

[14] - Number of FAS (full analysis set) patients actually contributing to the model.

End point values	Tio + Olo (T+O) 5/5 µg			
Subject group type	Reporting group			
Number of subjects analysed	502 ^[15]			
Units: litre(s)				
least squares mean (standard error)				
Day 1	0.229 (± 0.009)			
Day 85	0.297 (± 0.009)			
Day 365	0.237 (± 0.01)			

Notes:

[15] - Number of FAS (full analysis set) patients actually contributing to the model.

Statistical analyses

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 1
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1009
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0095
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.008
upper limit	0.058
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 1
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.09

Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 1
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1013
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0112
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.007
upper limit	0.058
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on Day 1
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1010
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.068
upper limit	0.119
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 1
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 1
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9514
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.026
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 1
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.069
upper limit	0.119
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Olo 5 on Day 1
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0131
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.057
upper limit	-0.007
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 1
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1011
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.086
upper limit	-0.036
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 1
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1004
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0243
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.054
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1009
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.145
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.119
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.085
upper limit	0.136
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1013
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.119
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.144
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1010
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.081
upper limit	0.132
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.059
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.051
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.107
upper limit	0.158
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Olo 5 on Day 85
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0083
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 85
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1011
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3329
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.038
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 85
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1004
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0958
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.047
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1009
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.105
upper limit	0.158
Variability estimate	Standard error of the mean
Dispersion value	0.014

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.086
upper limit	0.139
Variability estimate	Standard error of the mean
Dispersion value	0.014

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1013
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.092
upper limit	0.144
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1010
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.118
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.092
upper limit	0.144
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.098
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.072
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3008
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.105
upper limit	0.158
Variability estimate	Standard error of the mean
Dispersion value	0.014

Statistical analysis title	Tio 5 vs Olo 5 on Day 365
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1484
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.046
Variability estimate	Standard error of the mean
Dispersion value	0.014

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 365
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1011
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9981
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.027
Variability estimate	Standard error of the mean
Dispersion value	0.014

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 365
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1004
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.148
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.046
Variability estimate	Standard error of the mean
Dispersion value	0.013

Secondary: Trough FEV1 response on Days 15, 43, 85, 169 and 365

End point title	Trough FEV1 response on Days 15, 43, 85, 169 and 365
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End point description:

Trough FEV1 defined as the FEV1 value at the end of the dosing interval (24 hours), calculated as mean of the pre-dose measurements. Trough FEV1 response was defined as trough FEV1 minus baseline FEV1. Baseline was defined as mean of 2 pre-dose measurements performed 1h & at 10 min prior to administration of the first dose of randomised treatment at Day1. The adjusted means (SE) were obtained by MMRM model including fixed effects of treatment, planned test day, treatment-by-test day interaction, baseline & baseline-by-test day interaction, patient as random effect, & spatial power covariance structure for within-patient errors & Kenward-Roger approximation for denominator degrees of freedom. Since it is possible for the patient to meet the data criterion for only a subset of the primary endpoints, it is possible that number of patients used in the FAS analysis for different endpoint will vary.

End point type	Secondary
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End point timeframe:

1 hour (h) and at 10 minutes (min) prior to dose on the first day of randomized treatment and on Days 85, 169 and 365 and 10 minutes (min) prior to randomized treatment on days 15 and 43.

End point values	Olodaterol (Olo) 5 µg	Tiotropium (Tio) 2.5 µg	Tiotropium (Tio) 5 µg	Tio + Olo (T+O) 2.5/5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	503 ^[16]	499 ^[17]	498 ^[18]	500 ^[19]
Units: litre(s)				
least squares mean (standard error)				
Day 15	0.083 (± 0.009)	0.085 (± 0.009)	0.112 (± 0.009)	0.147 (± 0.009)
Day 43	0.07 (± 0.009)	0.085 (± 0.009)	0.103 (± 0.009)	0.146 (± 0.009)
Day 85	0.047 (± 0.009)	0.081 (± 0.009)	0.088 (± 0.009)	0.129 (± 0.009)
Day 169	0.034 (± 0.009)	0.041 (± 0.009)	0.068 (± 0.009)	0.111 (± 0.009)
Day 365	0.011 (± 0.009)	0.022 (± 0.009)	0.04 (± 0.009)	0.077 (± 0.009)

Notes:

[16] - Number of FAS (full analysis set) patients actually contributing to the model.

[17] - Number of FAS (full analysis set) patients actually contributing to the model.

[18] - Number of FAS (full analysis set) patients actually contributing to the model.

[19] - Number of FAS (full analysis set) patients actually contributing to the model.

End point values	Tio + Olo (T+O) 5/5 µg			
Subject group type	Reporting group			
Number of subjects analysed	497 ^[20]			
Units: litre(s)				
least squares mean (standard error)				
Day 15	0.148 (± 0.009)			
Day 43	0.15 (± 0.009)			
Day 85	0.147 (± 0.009)			

Day 169	0.119 (± 0.009)			
Day 365	0.093 (± 0.009)			

Notes:

[20] - Number of FAS (full analysis set) patients actually contributing to the model.

Statistical analyses

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 15
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 15
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.061

Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 15
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.089
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on Day 15
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.088
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 15
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0057
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	0.061
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 15
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9633
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.026
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 15
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.088
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Olo 5 on Day 15
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.054
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 15
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8949
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.023
upper limit	0.027
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 15
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0351
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.052
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 43
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	0.105
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 43
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.073
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 43
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.101
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on Day 43
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.036
upper limit	0.086
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 43
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.069
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 43
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7755
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.022
upper limit	0.029
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 43
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Olo 5 on Day 43
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0118
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.007
upper limit	0.058
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 43
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2416
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 43
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1792
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.008
upper limit	0.043
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.074
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.033
upper limit	0.084
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.057
upper limit	0.107
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.073
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0014
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.067
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1747
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.008
upper limit	0.043
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.091
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Olo 5 on Day 85
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.066
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 85
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0081
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 85
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.611
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.019
upper limit	0.032
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 169
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.059
upper limit	0.111
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 169
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.076
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 169
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.102
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on Day 169
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.044
upper limit	0.095
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 169
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.068
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 169
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5274
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.034
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 169
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.052
upper limit	0.103
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Olo 5 on Day 169
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0083
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 169
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5744
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.033
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 169
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0381
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.053
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	0.108
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.053
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.027
upper limit	0.079
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.091
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.081
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0052
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.063
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2273
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.042
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.045
upper limit	0.097
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Olo 5 on Day 365
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.055
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 365
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4327
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.016
upper limit	0.037
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 365
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1764
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.008
upper limit	0.044
Variability estimate	Standard error of the mean
Dispersion value	0.013

Secondary: Forced vital capacity (FVC) AUC (0-3h) response on Day 1, Day 85, Day

End point title	Forced vital capacity (FVC) AUC (0-3h) response on Day 1, Day 85, Day
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End point description:

FVC AUC(0-3h) calculated as area under FVC-time curve from 0to3h post-dose using trapezoidal rule,divided by duration(3h) to report in litres.FVC AUC(0-3h) response defined as FVC AUC(0-3h) minus baseline FVC.Baseline was defined as mean of 2 pre-dose measurements performed 1h&at10 min prior to administration of first dose at visit2(day 1).The adjusted means (SE) were obtained by fitting MMRM model including fixed effects of treatment,planned test day,treatment-by-test day interaction,baseline&baseline-by-test day interaction,patient as random effect,&spatial power covariance structure for within-patient errors&Kenward-Roger approximation for denominator degrees of freedom. Since it is possible for the patient to meet the data criterion for only a subset of the primary endpoints,it is possible that the number of patients used in the FAS analysis for different endpoints will vary.

End point type	Secondary
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End point timeframe:

1 hour (h) and at 10 minutes (min) prior to dose and 5 min, 15 min, 30 min, 1 h, 2 h, 3 h post-dose on the first day of randomized treatment and on each of the days specified in the title.

End point values	Olodaterol (Olo) 5 µg	Tiotropium (Tio) 2.5 µg	Tiotropium (Tio) 5 µg	Tio + Olo (T+O) 2.5/5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	507 ^[21]	504 ^[22]	500 ^[23]	506 ^[24]
Units: litre(s)				
least squares mean (standard error)				
Day 1	0.341 (± 0.018)	0.264 (± 0.018)	0.298 (± 0.018)	0.411 (± 0.018)
Day 85	0.25 (± 0.018)	0.306 (± 0.018)	0.326 (± 0.018)	0.46 (± 0.018)
Day 169	0.231 (± 0.018)	0.247 (± 0.018)	0.283 (± 0.018)	0.439 (± 0.018)
Day 365	0.18 (± 0.019)	0.216 (± 0.018)	0.198 (± 0.019)	0.397 (± 0.018)

Notes:

[21] - Number of FAS (full analysis set) patients actually contributing to the model.

[22] - Number of FAS (full analysis set) patients actually contributing to the model.

[23] - Number of FAS (full analysis set) patients actually contributing to the model.

[24] - Number of FAS (full analysis set) patients actually contributing to the model.

End point values	Tio + Olo (T+O) 5/5 µg			
Subject group type	Reporting group			
Number of subjects analysed	502 ^[25]			
Units: litre(s)				
least squares mean (standard error)				
Day 1	0.397 (± 0.018)			
Day 85	0.469 (± 0.018)			
Day 169	0.429 (± 0.018)			

Day 365	0.381 (\pm 0.019)			
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Notes:

[25] - Number of FAS (full analysis set) patients actually contributing to the model.

Statistical analyses

Statistical analysis title	T+O 5/5 vs Olo 5 Day 1
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1009
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0241
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.007
upper limit	0.105
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 5 Day 1
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.148

Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Olo 5 Day 1
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1013
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0049
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.021
upper limit	0.119
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 Day 1
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1010
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.147
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.098
upper limit	0.196
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 5 Day 1
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.113
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.064
upper limit	0.162
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 Day 1
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5831
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.063
upper limit	0.035
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 2.5 Day 1
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.133
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.084
upper limit	0.182
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Olo 5 Day 1
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0822
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.092
upper limit	0.006
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 2.5 vs Olo 5 Day 1
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1011
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.126
upper limit	-0.028
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Tio 2.5 Day 1
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1004
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1774
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.034
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.083
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Olo 5 Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1009
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.219
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.169
upper limit	0.268
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 5 Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.193
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Olo 5 Day 85
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1013
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.258
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 Day 85
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1010
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.153
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.104
upper limit	0.203
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 5 Day 85
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.134
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.084
upper limit	0.183
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6974
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.059
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 2.5 Day 85
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.114
upper limit	0.213
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Olo 5 Day 85
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 2.5 vs Olo 5 Day 85
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1011
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0269
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.105
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Tio 2.5 Day 85
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1004
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4343
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.069
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Olo 5 Day 169
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1009
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.198
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.148
upper limit	0.248
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Tio 5 Day 169
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.146
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.096
upper limit	0.197
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Olo 5 Day 169
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1013
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.158
upper limit	0.258
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 Day 169
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1010
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.193
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.143
upper limit	0.242
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 5 Day 169
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.106
upper limit	0.206
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 Day 169
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.698
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 2.5 Day 169
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.183
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.132
upper limit	0.233
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Olo 5 Day 169
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0442
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.102
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 2.5 vs Olo 5 Day 169
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within–patient errors and Kenward–Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1011
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5514
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.035
upper limit	0.065
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Tio 2.5 Day 169
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within–patient errors and Kenward–Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1004
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1569
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.086
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Olo 5 Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1009
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.253
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Tio 5 Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.183
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.132
upper limit	0.234
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Olo 5 Day 365
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1013
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.218
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.167
upper limit	0.269
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 Day 365
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1010
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.181
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.232
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Tio 5 Day 365
Statistical analysis description:	
Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.199
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.148
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5373
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.067
upper limit	0.035
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Tio 2.5 Day 365
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within–patient errors and Kenward–Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1006
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.165
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.114
upper limit	0.216
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Olo 5 Day 365
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within–patient errors and Kenward–Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1007
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4763
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 2.5 vs Olo 5 Day 365
Statistical analysis description:	
Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1011
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1613
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.088
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Tio 2.5 Day 365
Statistical analysis description:	
Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment, planned test day, treatment by test day interaction, baseline, and baseline by test day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	1004
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4908
Method	Mixed models analysis
Parameter estimate	adjusted mean difference
Point estimate	-0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.069
upper limit	0.033
Variability estimate	Standard error of the mean
Dispersion value	0.026

Secondary: Trough FVC response on Day 15, Day 43, Day 85, Day 170, and Day 365

End point title	Trough FVC response on Day 15, Day 43, Day 85, Day 170, and Day 365
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End point description:

Trough FVC defined as the FVC value at the end of the dosing interval (24 hours), calculated as mean of the pre-dose measurements. Trough FVC defined as FVC value at the end of the dosing interval (24 hours), calculated as mean of the pre-dose measurements. Trough FVC response defined as trough FVC minus baseline FVC. Baseline was defined as mean of 2 pre-dose measurements performed 1h and 10min prior to administration of first dose at visit 2 (day 1). The adjusted means (SE) were obtained by fitting MMRM including fixed effects of treatment, planned test day, treatment-by-test day interaction, baseline & baseline-by-test day interaction, patient as random effect, & spatial power covariance structure for within-patient errors & Kenward-Roger approximation for denominator degrees of freedom. Since it is possible for the patient to meet the data criterion for only a subset of the primary endpoints, it is possible that the number of patients used in the FAS analysis for different endpoints will vary.

End point type	Secondary
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End point timeframe:

1 h and at 10 min prior to dose on the first day of randomized treatment (baseline), day 85, day 365, at 10 min pre-dose on day 15 and 43 and at 23 h and at 23 h 50 min after inhalation of study medication on Day 170.

End point values	Olodaterol (Olo) 5 µg	Tiotropium (Tio) 2.5 µg	Tiotropium (Tio) 5 µg	Tio + Olo (T+O) 2.5/5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	503 ^[26]	499 ^[27]	498 ^[28]	500 ^[29]
Units: litre(s)				
least squares mean (standard error)				
Day 15	0.163 (± 0.018)	0.209 (± 0.018)	0.222 (± 0.018)	0.293 (± 0.018)
Day 43	0.129 (± 0.018)	0.206 (± 0.018)	0.222 (± 0.018)	0.281 (± 0.018)
Day 85	0.063 (± 0.018)	0.178 (± 0.018)	0.184 (± 0.018)	0.246 (± 0.018)
Day 170	0.116 (± 0.018)	0.163 (± 0.018)	0.202 (± 0.018)	0.266 (± 0.018)
Day 365	0.028 (± 0.019)	0.096 (± 0.019)	0.097 (± 0.019)	0.198 (± 0.019)

Notes:

[26] - Number of FAS (full analysis set) patients actually contributing to the model.

[27] - Number of FAS (full analysis set) patients actually contributing to the model.

[28] - Number of FAS (full analysis set) patients actually contributing to the model.

[29] - Number of FAS (full analysis set) patients actually contributing to the model.

End point values	Tio + Olo (T+O) 5/5 µg			
Subject group type	Reporting group			
Number of subjects analysed	497 ^[30]			
Units: litre(s)				
least squares mean (standard error)				
Day 15	0.285 (± 0.018)			
Day 43	0.293 (± 0.018)			

Day 85	0.274 (± 0.019)			
Day 170	0.274 (± 0.018)			
Day 365	0.184 (± 0.019)			

Notes:

[30] - Number of FAS (full analysis set) patients actually contributing to the model.

Statistical analyses

Statistical analysis title	T+O 5/5 vs Olo 5 Day 15
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.072
upper limit	0.173
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Tio 5 Day 15
Statistical analysis description:	
Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.	
Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0154
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.063

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.012
upper limit	0.113
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Olo 5 Day 15
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.181
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 Day 15
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.084

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.033
upper limit	0.134
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Tio 5 Day 15
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0061
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.121
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 Day 15
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7518
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.008

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.059
upper limit	0.042
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Tio 2.5 Day 15
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0034
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.126
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Olo 5 Day 15
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0209
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.059

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 2.5 vs Olo 5 Day 15
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Statistical analysis description:

Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0708
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.097
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Tio 2.5 Day 15
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6148
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.013

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.038
upper limit	0.064
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Olo 5 Day 43
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.164
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.114
upper limit	0.215
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Tio 5 Day 43
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0064
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.071

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.122
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Olo 5 Day 43
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.152
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.102
upper limit	0.203
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 Day 43
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.075

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.126
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Tio 5 Day 43
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0233
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.008
upper limit	0.109
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 Day 43
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6413
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.012

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.039
upper limit	0.063
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Tio 2.5 Day 43
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.088
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.138
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Olo 5 Day 43
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.094

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.043
upper limit	0.144
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 2.5 vs Olo 5 Day 43
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Statistical analysis description:

Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.127
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Tio 2.5 Day 43
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5159
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.017

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.068
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Olo 5 Day 85
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.159
upper limit	0.261
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Tio 5 Day 85
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.089

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.141
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Olo 5 Day 85
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.183
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.132
upper limit	0.234
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 Day 85
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0094
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.068

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.119
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Tio 5 Day 85
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0174
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.011
upper limit	0.113
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 Day 85
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2888
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.028

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.023
upper limit	0.079
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Tio 2.5 Day 85
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.044
upper limit	0.146
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Olo 5 Day 85
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.121

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.172
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 2.5 vs Olo 5 Day 85
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Statistical analysis description:

Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.064
upper limit	0.166
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Tio 2.5 Day 85
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8241
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.006

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.045
upper limit	0.057
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Olo 5 Day 170
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.158
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.108
upper limit	0.208
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 5 Day 170
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0048
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.072

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.122
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Olo 5 Day 170
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.101
upper limit	0.2
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 Day 170
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.103

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.053
upper limit	0.152
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 5 Day 170
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0116
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.113
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 Day 170
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7577
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.008

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.042
upper limit	0.058
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 2.5 Day 170
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.061
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Olo 5 Day 170
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.086

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.136
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 2.5 vs Olo 5 Day 170
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Statistical analysis description:

Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0621
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.097
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Tio 2.5 Day 170
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1266
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.039

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.011
upper limit	0.089
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Olo 5 Day 365
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.104
upper limit	0.209
Variability estimate	Standard error of the mean
Dispersion value	0.027

Statistical analysis title	T+O 5/5 vs Tio 5 Day 365
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	995
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.087

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.139
Variability estimate	Standard error of the mean
Dispersion value	0.027

Statistical analysis title	T+O 2.5/5 vs Olo 5 Day 365
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1003
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.118
upper limit	0.223
Variability estimate	Standard error of the mean
Dispersion value	0.027

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 Day 365
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	999
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.102

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.049
upper limit	0.154
Variability estimate	Standard error of the mean
Dispersion value	0.027

Statistical analysis title	T+O 2.5/5 vs Tio 5 Day 365
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Statistical analysis description:

Tio + Olo (T+O) 2.5/5 µg minus Tiotropium (Tio) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 2.5/5 µg v Tiotropium (Tio) 5 µg
Number of subjects included in analysis	998
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.048
upper limit	0.153
Variability estimate	Standard error of the mean
Dispersion value	0.027

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 Day 365
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tio + Olo (T+O) 2.5/5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tio + Olo (T+O) 2.5/5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6093
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.014

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.066
upper limit	0.039
Variability estimate	Standard error of the mean
Dispersion value	0.027

Statistical analysis title	T+O 5/5 vs Tio 2.5 Day 365
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Statistical analysis description:

Tio + Olo (T+O) 5/5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tio + Olo (T+O) 5/5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	996
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.088
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.035
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.027

Statistical analysis title	Tio 5 vs Olo 5 Day 365
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1001
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0095
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.123
Variability estimate	Standard error of the mean
Dispersion value	0.027

Statistical analysis title	Tio 2.5 vs Olo 5 Day 365
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Statistical analysis description:

Tiotropium (Tio) 2.5 µg minus Olodaterol (Olo) 5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 2.5 µg v Olodaterol (Olo) 5 µg
Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0108
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.069
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.121
Variability estimate	Standard error of the mean
Dispersion value	0.027

Statistical analysis title	Tio 5 vs Tio 2.5 Day 365
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Statistical analysis description:

Tiotropium (Tio) 5 µg minus Tiotropium (Tio) 2.5 µg. The adjusted means (SE) were 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 random effect, and spatial power covariance structure for within-patient errors and Kenward-Roger approximation of denominator degrees of freedom.

Comparison groups	Tiotropium (Tio) 5 µg v Tiotropium (Tio) 2.5 µg
Number of subjects included in analysis	997
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9627
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.001

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.051
upper limit	0.054
Variability estimate	Standard error of the mean
Dispersion value	0.027

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse events with an onset after the first dose of study medication up to a period of 21 days after the last dose of study medication were assigned to the treatment period for evaluation (Up to 459 days).

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Olodaterol (5 µg)
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Reporting group description:

Oral inhalation of Olodaterol 5 µg (2.5 µg per actuation) , 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

Reporting group title	Tiotropium (2.5 µg)
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Reporting group description:

Oral inhalation of Tiotropium 2.5 µg (1.25 µg per actuation) , 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

Reporting group title	Tiotropium (5 µg)
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Reporting group description:

Oral inhalation of Tiotropium 5 µg (2.5 µg per actuation) , 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

Reporting group title	Tio+Olo FDC (2.5/5 µg)
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Reporting group description:

Oral inhalation of fixed dose combination (FDC) of Tiotropium 2.5 µg and Olodaterol 5 µg (Tiotropium: 1.25 µg per actuation and Olodaterol: 2.5 µg per actuation) , 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

Reporting group title	Tio+Olo FDC (5/5 µg)
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Reporting group description:

Oral inhalation of FDC of Tiotropium 5 µg and Olodaterol 5 µg (Tiotropium and Olodaterol: 2.5 µg per actuation) , 2 puffs from the RESPIMAT inhaler, once daily, in the morning.

Serious adverse events	Olodaterol (5 µg)	Tiotropium (2.5 µg)	Tiotropium (5 µg)
Total subjects affected by serious adverse events			
subjects affected / exposed	106 / 510 (20.78%)	90 / 507 (17.75%)	93 / 506 (18.38%)
number of deaths (all causes)	13	5	11
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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

Basal cell carcinoma			
subjects affected / exposed	1 / 510 (0.20%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Bladder neoplasm			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Bronchial carcinoma			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Colon cancer			
subjects affected / exposed	2 / 510 (0.39%)	0 / 507 (0.00%)	0 / 506 (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
Endometrial cancer			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Gastric cancer			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Hepatic cancer			

subjects affected / exposed	0 / 510 (0.00%)	2 / 507 (0.39%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	1 / 510 (0.20%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma metastatic			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Lung cancer metastatic			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 510 (0.20%)	1 / 507 (0.20%)	2 / 506 (0.40%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to adrenals			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Metastases to central nervous system			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to liver			

subjects affected / exposed	2 / 510 (0.39%)	0 / 507 (0.00%)	0 / 506 (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
Neoplasm prostate			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal carcinoma			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Oropharyngeal cancer			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Penile cancer			

subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Prostate cancer			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Prostate cancer metastatic			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Rectal cancer			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Renal cancer metastatic			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the tongue			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Sweat gland tumour			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aneurysm			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Aortic aneurysm			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Aortic aneurysm rupture			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Arteritis			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Deep vein thrombosis			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Hypertension			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 510 (0.20%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leriche syndrome			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Peripheral artery aneurysm			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Shock			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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 discomfort			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 510 (0.20%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Device dislocation			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Drowning			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Generalised oedema			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Medical device complication			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Multi-organ failure			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Sudden death			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	4 / 506 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal prolapse			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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			
Acute respiratory failure			
subjects affected / exposed	2 / 510 (0.39%)	2 / 507 (0.39%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Analgesic asthma syndrome			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Bronchiectasis			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Bullous lung disease			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chronic obstructive pulmonary disease			
subjects affected / exposed	41 / 510 (8.04%)	37 / 507 (7.30%)	33 / 506 (6.52%)
occurrences causally related to treatment / all	0 / 48	1 / 45	1 / 38
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Dysphonia			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Dyspnoea			
subjects affected / exposed	0 / 510 (0.00%)	2 / 507 (0.39%)	2 / 506 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Epistaxis			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Haemoptysis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Hydrothorax			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Hypercapnia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Hypoxia			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Nasal polyps			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal turbinate hypertrophy			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Paranasal sinus discomfort			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Pleural effusion			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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 aspiration			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Pneumothorax			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	3 / 506 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			

subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 510 (0.39%)	2 / 507 (0.39%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary granuloma			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary infarction			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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 mass			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Pulmonary oedema			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Respiratory failure			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	3 / 506 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Rhonchi			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Vocal cord polyp			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Aggression			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Bipolar I disorder			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Confusional state			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Conversion disorder			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Delirium			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Depression			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Blood pressure decreased			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Troponin T increased			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acetabulum fracture			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Avulsion fracture			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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

Clavicle fracture			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Contusion			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Fall			
subjects affected / exposed	3 / 510 (0.59%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Femur fracture			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Head injury			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Hip fracture			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Humerus fracture			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			

subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Joint dislocation			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Liver contusion			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Patella fracture			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Rib fracture			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Skull fractured base			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Spinal compression fracture			

subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Stab wound			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Subdural haematoma			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Tendon rupture			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Traumatic haematoma			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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 pseudoaneurysm			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Malformation biliary			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Acute myocardial infarction			
subjects affected / exposed	2 / 510 (0.39%)	1 / 507 (0.20%)	0 / 506 (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
Angina pectoris			
subjects affected / exposed	3 / 510 (0.59%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Aortic valve stenosis			
subjects affected / exposed	0 / 510 (0.00%)	2 / 507 (0.39%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 510 (0.20%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac disorder			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	2 / 510 (0.39%)	0 / 507 (0.00%)	2 / 506 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 510 (0.20%)	2 / 507 (0.39%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Coronary artery disease			
subjects affected / exposed	2 / 510 (0.39%)	1 / 507 (0.20%)	3 / 506 (0.59%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrasystoles			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular dysfunction			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Palpitations			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Tachyarrhythmia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Acute polyneuropathy			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery aneurysm			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Carotid artery stenosis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Cerebellar haemorrhage			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	2 / 506 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular disorder			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Convulsion			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Dizziness			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Epilepsy			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Headache			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Neuromyopathy			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Spondylitic myelopathy			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Syncope			
subjects affected / exposed	1 / 510 (0.20%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	2 / 510 (0.39%)	0 / 507 (0.00%)	0 / 506 (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
Tremor			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Haemorrhagic anaemia			

subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Iron deficiency anaemia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Age-related macular degeneration			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Lacrimation increased			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Macular degeneration			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Retinal tear			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			

subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Abdominal pain upper			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Colitis			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Colitis ulcerative			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Crohn's disease			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Diverticulum intestinal			

subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Dysphagia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Gastritis			
subjects affected / exposed	0 / 510 (0.00%)	2 / 507 (0.39%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Ileus			

subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	3 / 510 (0.59%)	1 / 507 (0.20%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia strangulated			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Melaena			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Mesenteric artery stenosis			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Oesophageal achalasia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Oesophageal stenosis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Oral pain			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Biliary colic			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Cholecystitis			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Cholecystitis acute			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephritis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Renal failure acute			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal vasculitis			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Back pain			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Bone deformity			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Flank pain			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Foot deformity			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc degeneration			
subjects affected / exposed	1 / 510 (0.20%)	1 / 507 (0.20%)	0 / 506 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Monarthritis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Osteoarthritis			
subjects affected / exposed	2 / 510 (0.39%)	2 / 507 (0.39%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Spinal column stenosis			
subjects affected / exposed	0 / 510 (0.00%)	3 / 507 (0.59%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Spondylolisthesis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial cyst			

subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Anal abscess			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Appendicitis perforated			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Biliary sepsis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Bronchitis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	2 / 510 (0.39%)	0 / 507 (0.00%)	0 / 506 (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
Cellulitis			
subjects affected / exposed	2 / 510 (0.39%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis pharyngeal			

subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Dermatitis infected			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Diverticulitis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Escherichia bacteraemia			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Gastroenteritis			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	2 / 506 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Graft infection			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
H1N1 influenza			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Hepatitis B			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	2 / 510 (0.39%)	0 / 507 (0.00%)	0 / 506 (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
Influenza			
subjects affected / exposed	2 / 510 (0.39%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobar pneumonia			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Pelvic abscess			

subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	0 / 506 (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
Pneumococcal sepsis			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	6 / 510 (1.18%)	6 / 507 (1.18%)	2 / 506 (0.40%)
occurrences causally related to treatment / all	0 / 7	0 / 8	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Post procedural infection			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Postoperative abscess			
subjects affected / exposed	1 / 510 (0.20%)	0 / 507 (0.00%)	0 / 506 (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
Pyelonephritis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Respiratory tract infection			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Sepsis			
subjects affected / exposed	1 / 510 (0.20%)	1 / 507 (0.20%)	0 / 506 (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
Septic shock			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Sinusitis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Superinfection			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Urinary tract infection			
subjects affected / exposed	0 / 510 (0.00%)	1 / 507 (0.20%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Diabetes mellitus			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Diabetic ketoacidosis			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	0 / 506 (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
Gout			

subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 510 (0.00%)	0 / 507 (0.00%)	1 / 506 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tio+Olo FDC (2.5/5 µg)	Tio+Olo FDC (5/5 µg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 508 (17.13%)	82 / 507 (16.17%)	
number of deaths (all causes)	8	11	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colon adenoma			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma metastatic			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	2 / 508 (0.39%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to adrenals			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to liver			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm prostate			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			

subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal squamous cell carcinoma			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal cancer			
subjects affected / exposed	1 / 508 (0.20%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Penile cancer			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 508 (0.39%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal cancer			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer metastatic			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sweat gland tumour			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aneurysm			

subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Arteritis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leriche syndrome			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			

subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 508 (0.39%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 508 (0.20%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Generalised oedema			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 508 (0.00%)	2 / 507 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	2 / 508 (0.39%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anti-neutrophil cytoplasmic antibody positive vasculitis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 508 (0.20%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	2 / 508 (0.39%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Analgesic asthma syndrome			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bullous lung disease			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	30 / 508 (5.91%)	33 / 507 (6.51%)	
occurrences causally related to treatment / all	2 / 35	2 / 38	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dysphonia			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 508 (0.20%)	2 / 507 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Emphysema			

subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal turbinate hypertrophy			

subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranasal sinus discomfort			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 508 (0.59%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary granuloma			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary infarction			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 508 (0.00%)	3 / 507 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhonchi			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute stress disorder			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar I disorder			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conversion disorder			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure decreased			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin T increased			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal injury			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Avulsion fracture			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 508 (0.39%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver contusion			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 508 (0.00%)	2 / 507 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stab wound			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Malformation biliary			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 508 (0.20%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina unstable			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 508 (0.39%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac disorder			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 508 (0.20%)	2 / 507 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrasystoles			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 508 (0.39%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Acute polyneuropathy			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery aneurysm			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 508 (0.39%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 508 (0.00%)	2 / 507 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuromyopathy			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylitic myelopathy			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic cerebral infarction			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Age-related macular degeneration subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacrimation increased subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular degeneration subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery stenosis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal achalasia			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral pain			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 508 (0.39%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haematuria			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal vasculitis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone deformity			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	2 / 508 (0.39%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monarthritis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 508 (0.20%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
subjects affected / exposed	0 / 508 (0.00%)	2 / 507 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis pharyngeal			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis infected			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft infection			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	9 / 508 (1.77%)	9 / 507 (1.78%)	
occurrences causally related to treatment / all	0 / 9	1 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Post procedural infection			

subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 508 (0.20%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 508 (0.20%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 508 (0.00%)	2 / 507 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 508 (0.20%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 508 (0.00%)	1 / 507 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 508 (0.00%)	0 / 507 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Olodaterol (5 µg)	Tiotropium (2.5 µg)	Tiotropium (5 µg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	246 / 510 (48.24%)	228 / 507 (44.97%)	216 / 506 (42.69%)
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 510 (5.10%)	10 / 507 (1.97%)	10 / 506 (1.98%)
occurrences (all)	26	10	11
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	147 / 510 (28.82%)	146 / 507 (28.80%)	132 / 506 (26.09%)
occurrences (all)	216	226	204
Cough			
subjects affected / exposed	17 / 510 (3.33%)	27 / 507 (5.33%)	25 / 506 (4.94%)
occurrences (all)	20	29	27
Dyspnoea			
subjects affected / exposed	20 / 510 (3.92%)	22 / 507 (4.34%)	27 / 506 (5.34%)
occurrences (all)	23	27	36
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	66 / 510 (12.94%)	59 / 507 (11.64%)	54 / 506 (10.67%)
occurrences (all)	87	83	72
Upper respiratory tract infection			
subjects affected / exposed	32 / 510 (6.27%)	31 / 507 (6.11%)	27 / 506 (5.34%)
occurrences (all)	43	40	32

Non-serious adverse events	Tio+Olo FDC (2.5/5 µg)	Tio+Olo FDC (5/5 µg)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	223 / 508 (43.90%)	214 / 507 (42.21%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 508 (3.74%)	12 / 507 (2.37%)	
occurrences (all)	22	14	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	118 / 508 (23.23%)	129 / 507 (25.44%)	
occurrences (all)	168	208	

Cough subjects affected / exposed occurrences (all)	29 / 508 (5.71%) 30	24 / 507 (4.73%) 24	
Dyspnoea subjects affected / exposed occurrences (all)	21 / 508 (4.13%) 22	20 / 507 (3.94%) 22	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	70 / 508 (13.78%) 105	61 / 507 (12.03%) 82	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	29 / 508 (5.71%) 33	29 / 507 (5.72%) 38	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2011	<p>Significant changes to the trial protocol introduced by this revision were a change in timing of Visit 7* and the addition of trough PFT measurements to this visit to ensure FEV1 AUC0-3h and trough FEV1 at Visit 7 (primary efficacy endpoints after 24 weeks of treatment) both came from the same dosing interval. Furthermore, instructions were added to report any related SAEs that occurred after the defined observational period.</p> <p>Note: The last amendment to the protocol dated 28-Oct-2013 has been made after the global end of trial date (19-Sep-2013). In this administrative revision, assessment days and time points were added to the lists of primary, secondary and further endpoints. Several endpoints were split into secondary and further endpoints and 10 endpoints were moved from secondary to further endpoints. The list of further endpoints concerning COPD exacerbations was extended, with any, moderate/severe, and severe COPD exacerbations to be analysed as separate endpoints. Each endpoint related to COPD exacerbations was to be analysed for the entire population and for the subset of patients with a history of exacerbation. FPI was to be regarded as a further endpoint. The TDI component scores on Day 169 originally were inadvertently left out of the list of further endpoints. As with other TDI data, these endpoints were to be examined for data from 1237.5+1237.6 combined. A definition of patients to be considered having a history of exacerbation was added. The 1-sided superiority hypothesis testing was changed to 2-sided hypothesis testing, and the corresponding 1-sided type I error rate of 0.025 was changed to 2-sided type I error rate of 0.05. Since tiotropium 5µg is a marketed product in several countries, a comparison of T+O 2.5/5 µg versus Tio 5 µg was added to the hierarchical testing sequences.</p>
29 August 2012	<p>Significant changes to the trial protocol introduced by this revision were the extension of procedures to be performed for early discontinuations (i.e. inclusion of all safety assessments as specified for the regular EOT visit), the expansion of event adjudication to include all SAEs (instead of fatal cases only), the addition of text regarding rescue treatment on days of Visit 7/7*, and the addition of a plausibility check between eDiary and RESPIMAT. FEV1 and FVC endpoints at individual time points were defined as further (instead of secondary) endpoints with actual values to be analysed instead of response. For the recording of SAEs a list of AEs that were defined as 'always serious AEs' was included to comply with a new BI internal procedure. The list was to come into effect for this trial once all countries and sites had received regulatory and ethics committee approval for the protocol revision. Since the trial was completed before all approvals were obtained, this SAE procedure was never implemented. Further specifications of the period during which contraception was required and a pregnancy test at the follow-up visit were added in response to an authority request. Instructions for clinical evaluation of liver injury were included to implement a new BI guideline to comply with the FDA guidance for industry 'Drug-Induced Liver Injury: Premarketing Clinical Evaluation'.</p>

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/or secondary endpoints are defined and analysed for trial 1237.5 and 1237.6, however due to the platform limitations those could not be provided. Results can be found on CT.gov study number: NCT01431287

Notes: