

**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 + 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	2009-010668-40
Trial protocol	NL FI PT SI CZ DE HU DK EE IT
Global end of trial date	19 September 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	• Correction of full data set Data correction due to a system error in EudraCT- Results

Trial information**Trial identification**

Sponsor protocol code	1237.5
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01431274
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, +1 800 2430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 2430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	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	05 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 March 2013
Global end of trial reached?	Yes
Global end of trial date	19 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall 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	Slovenia: 105
Country: Number of subjects enrolled	Denmark: 150
Country: Number of subjects enrolled	Finland: 81
Country: Number of subjects enrolled	Italy: 49
Country: Number of subjects enrolled	Netherlands: 119
Country: Number of subjects enrolled	Portugal: 74
Country: Number of subjects enrolled	Bulgaria: 94
Country: Number of subjects enrolled	Czech Republic: 59
Country: Number of subjects enrolled	Estonia: 49
Country: Number of subjects enrolled	France: 80
Country: Number of subjects enrolled	Germany: 301
Country: Number of subjects enrolled	Hungary: 89

Country: Number of subjects enrolled	United States: 553
Country: Number of subjects enrolled	Australia: 22
Country: Number of subjects enrolled	Canada: 131
Country: Number of subjects enrolled	Guatemala: 110
Country: Number of subjects enrolled	India: 99
Country: Number of subjects enrolled	Japan: 279
Country: Number of subjects enrolled	Mexico: 45
Country: Number of subjects enrolled	New Zealand: 30
Country: Number of subjects enrolled	China: 316
Country: Number of subjects enrolled	Argentina: 206
Country: Number of subjects enrolled	Russian Federation: 56
Country: Number of subjects enrolled	Korea, Republic of: 175
Country: Number of subjects enrolled	Turkey: 97
Worldwide total number of subjects	3369
EEA total number of subjects	1250

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)	1703
From 65 to 84 years	1651
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

A "Missing" category is unavailable for the age group breakdown of enrolled patients. Hence, 8 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 one specialist site which would then ensure that they (the subjects) met all 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 orally 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.

Arm type	Active comparator
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Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details: 5 µg once daily with orally inhalation	
Arm title	Tio + Olo (T+O) 2.5 /5 µg

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	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 orally inhalation

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	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 orally 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 orally inhalation

Number of subjects in period 1^[1]	Olodaterol (Olo) 5 µg	Tiotropium (Tio) 2.5 µg	Tiotropium (Tio) 5 µg
Started	528	525	527
Completed	431	448	455
Not completed	97	77	72
Adverse event, serious fatal	4	6	4
Consent withdrawn by subject	29	20	17
Adverse event, non-fatal	47	31	39
Lost to follow-up	6	7	1
Protocol deviation	5	8	4
Reason other than specified above	6	5	7

Number of subjects in period 1^[1]	Tio + Olo (T+O) 2.5 /5 µg	Tio + Olo (T + O) 5/5 µg
Started	522	522
Completed	462	466
Not completed	60	56
Adverse event, serious fatal	7	7
Consent withdrawn by subject	20	11
Adverse event, non-fatal	23	30
Lost to follow-up	4	-
Protocol deviation	4	4
Reason other than specified above	2	4

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
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.	
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.	

Reporting group values	Olodaterol (Olo) 5 µg	Tiotropium (Tio) 2.5 µg	Tiotropium (Tio) 5 µg
Number of subjects	528	525	527
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	63.7	64.2	64.2
standard deviation	± 8	± 8.6	± 8.5
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	142	133	144
Male	386	392	383

Reporting group values	Tio + Olo (T+O) 2.5 /5 µg	Tio + Olo (T + O) 5/5 µg	Total
Number of subjects	522	522	2624
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	64.8	
standard deviation	± 8	± 8.2	-
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	133	138	690
Male	389	384	1934

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.	
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	525 ^[1]	524 ^[2]	526 ^[3]	521 ^[4]
Units: litre(s)				
least squares mean (standard error)	0.133 (± 0.008)	0.148 (± 0.008)	0.139 (± 0.008)	0.241 (± 0.008)

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	522 ^[5]			
Units: litre(s)				
least squares mean (standard error)	0.256 (± 0.008)			

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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.123
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.146
Variability estimate	Standard error of the mean
Dispersion value	0.012

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	1048
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.117
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.094
upper limit	0.14
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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.086
upper limit	0.132
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	1045
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	0.07
upper limit	0.116
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	1047
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	0.08
upper limit	0.125
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	1043
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2169
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.008
upper limit	0.037
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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.108
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.085
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.012

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	1051
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5849
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.017
upper limit	0.029
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	1049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1863
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.039
Variability estimate	Standard error of the mean
Dispersion value	0.012

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	1050
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4352
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.014
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:	
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 the number of patients used in the FAS analysis for different endpoint will	
End point type	Primary
End point timeframe:	
1 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	

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	519 ^[6]	519 ^[7]	520 ^[8]	518 ^[9]
Units: litre(s)				
least squares mean (standard error)	0.054 (± 0.009)	0.083 (± 0.008)	0.065 (± 0.008)	0.111 (± 0.008)

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			
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Subject group type	Reporting group			
Number of subjects analysed	521 ^[10]			
Units: litre(s)				
least squares mean (standard error)	0.136 (± 0.008)			

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 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	1040
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	0.059
upper limit	0.106
Variability estimate	Standard error of the mean
Dispersion value	0.012

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 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	1041
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	0.047
upper limit	0.094
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	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.081
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	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0174
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.029

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.005
upper limit	0.052
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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.046
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.07
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
Number of subjects included in analysis	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0407
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.024

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.048
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	1040
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	0.03
upper limit	0.077
Variability estimate	Standard error of the mean
Dispersion value	0.012

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
Number of subjects included in analysis	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3326
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.012

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.035
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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0151
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.006
upper limit	0.053
Variability estimate	Standard error of the mean
Dispersion value	0.012

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
Number of subjects included in analysis	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1421
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.018

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.041
upper limit	0.006
Variability estimate	Standard error of the mean
Dispersion value	0.012

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 the 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 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	525 ^[11]	524 ^[12]	526 ^[13]	521 ^[14]
Units: litre(s)				
least squares mean (standard error)				
Day 1	0.205 (± 0.009)	0.148 (± 0.009)	0.157 (± 0.009)	0.226 (± 0.009)
Day 85	0.161 (± 0.009)	0.176 (± 0.009)	0.162 (± 0.009)	0.271 (± 0.009)
Day 365	0.096 (± 0.009)	0.116 (± 0.009)	0.122 (± 0.009)	0.214 (± 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	522 ^[15]			
Units: litre(s)				

least squares mean (standard error)				
Day 1	0.237 (± 0.009)			
Day 85	0.289 (± 0.009)			
Day 365	0.237 (± 0.009)			

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
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0067
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.056
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 1
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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	1048
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	0.057
upper limit	0.104
Variability estimate	Standard error of the mean
Dispersion value	0.012

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 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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0746
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.045
Variability estimate	Standard error of the mean
Dispersion value	0.012

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 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	1045
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	0.054
upper limit	0.101
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 1
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.093
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 1
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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
Number of subjects included in analysis	1043
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3549
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.011

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.035
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 1
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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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.089
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.065
upper limit	0.113
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Olo 5 on Day 1
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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
Number of subjects included in analysis	1051
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.048

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.072
upper limit	-0.025
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 1
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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	1049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	-0.033
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 1
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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
Number of subjects included in analysis	1050
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5018
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.008

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.016
upper limit	0.032
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 85
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.104
upper limit	0.152
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 85
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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	1048
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.126

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.102
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 85
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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	1046
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	0.087
upper limit	0.135
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 85
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.109

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.085
upper limit	0.133
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on 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 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	1045
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.096
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.072
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on 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 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	1043
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1569
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.017

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.041
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 85
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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	1046
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	0.089
upper limit	0.137
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Olo 5 on Day 85
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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
Number of subjects included in analysis	1051
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8834
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.002

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.022
upper limit	0.026
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 85
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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	1049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2129
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.009
upper limit	0.039
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 85
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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
Number of subjects included in analysis	1050
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2702
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.013

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 365
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.141
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.117
upper limit	0.166
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 365
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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	1048
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	0.09
upper limit	0.139
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
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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	1046
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	0.143
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
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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	1045
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.099

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.074
upper limit	0.123
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
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.067
upper limit	0.117
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
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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
Number of subjects included in analysis	1043
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0717
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.023

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.047
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
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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	1046
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	0.097
upper limit	0.146
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Olo 5 on Day 365
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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
Number of subjects included in analysis	1051
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0344
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	0.051
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 365
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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	1049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1126
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.045
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 365
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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
Number of subjects included in analysis	1050
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6009
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	0.031
Variability estimate	Standard error of the mean
Dispersion value	0.013

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

End point title	Trough FEV1 response on Day 15, Day 43, Day 85, Day 169, and Day 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 the number of patients used in the FAS analysis for different endpoint 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	519 ^[16]	519 ^[17]	520 ^[18]	518 ^[19]
Units: litre(s)				
least squares mean (standard error)				
Day 15	0.085 (± 0.009)	0.101 (± 0.009)	0.094 (± 0.009)	0.132 (± 0.009)
Day 43	0.083 (± 0.009)	0.097 (± 0.009)	0.088 (± 0.009)	0.12 (± 0.009)
Day 85	0.057 (± 0.009)	0.077 (± 0.009)	0.07 (± 0.009)	0.128 (± 0.009)
Day 169	0.033 (± 0.009)	0.047 (± 0.009)	0.05 (± 0.009)	0.094 (± 0.009)
Day 365	0 (± 0.009)	0.028 (± 0.009)	0.036 (± 0.009)	0.075 (± 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			
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Subject group type	Reporting group			
Number of subjects analysed	521 ^[20]			
Units: litre(s)				
least squares mean (standard error)				
Day 15	0.157 (± 0.009)			
Day 43	0.163 (± 0.009)			
Day 85	0.146 (± 0.009)			
Day 169	0.112 (± 0.009)			
Day 365	0.099 (± 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
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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.072
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.049
upper limit	0.096
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 15
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	1041
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	0.039
upper limit	0.087
Variability estimate	Standard error of the mean
Dispersion value	0.012

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 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	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.012

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 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
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Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0122
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.007
upper limit	0.054
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 15
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.061
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on 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 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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0347
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.049
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 15
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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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.032
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.012

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

Tiotropium (Tio) 5 µg minus Olodaterol (Olo) 5µg. 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
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Number of subjects included in analysis	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4407
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.014
upper limit	0.033
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 15
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1777
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 15
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5641
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.017
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 43
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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	1040
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	0.057
upper limit	0.104
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 43
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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
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Number of subjects included in analysis	1041
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.099
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 43
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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	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.062
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on 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 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
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Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0517
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.047
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 43
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0072
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.056
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on 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 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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.066
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 43
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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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.042
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Olo 5 on Day 43
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6619
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.018
upper limit	0.029
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 43
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2401
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.038
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 43
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4601
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.033
upper limit	0.015
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 85
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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	1040
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	0.064
upper limit	0.112
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 85
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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
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Number of subjects included in analysis	1041
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	0.052
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 85
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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	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.046
upper limit	0.094
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on 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 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
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Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.051
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.027
upper limit	0.075
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 85
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	0.082
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on 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 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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1405
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.006
upper limit	0.042
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 85
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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	1040
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	0.045
upper limit	0.093
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Olo 5 on Day 85
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3118
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.036
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 85
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1171
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.019
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0.043
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 85
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5759
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.031
upper limit	0.017
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 169
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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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	0.103
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 169
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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
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Number of subjects included in analysis	1041
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	0.038
upper limit	0.086
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 169
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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	1037
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	0.037
upper limit	0.085
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on Day 169
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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
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Number of subjects included in analysis	1037
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	0.071
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 169
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.019
upper limit	0.068
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 169
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.136
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.018
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.006
upper limit	0.042
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 169
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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	1040
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	0.041
upper limit	0.089
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Olo 5 on Day 169
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1617
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.041
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 169
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2476
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.039
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 169
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8083
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.027
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 365
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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	1040
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	0.075
upper limit	0.124
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 365
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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
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Number of subjects included in analysis	1041
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	0.088
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 365
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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	1037
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	0.1
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
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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
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Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
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	0.072
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
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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	1038
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

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on 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 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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0554
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.048
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 365
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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	1040
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	0.047
upper limit	0.096
Variability estimate	Standard error of the mean
Dispersion value	0.012

Statistical analysis title	Tio 5 vs Olo 5 on Day 365
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0041
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	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 365
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0248
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.004
upper limit	0.053
Variability estimate	Standard error of the mean
Dispersion value	0.013

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 365
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5338
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	0.032
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 169, and Day 365

End point title	Forced vital capacity (FVC) AUC (0-3h) response on Day 1, Day 85, Day 169, and Day 365
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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

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	525 ^[21]	524 ^[22]	526 ^[23]	521 ^[24]
Units: litre(s)				
least squares mean (standard error)				
Day 1	0.35 (± 0.017)	0.277 (± 0.017)	0.289 (± 0.017)	0.4 (± 0.017)
Day 85	0.247 (± 0.017)	0.318 (± 0.017)	0.275 (± 0.017)	0.432 (± 0.017)
Day 169	0.212 (± 0.017)	0.279 (± 0.017)	0.254 (± 0.017)	0.386 (± 0.017)
Day 365	0.172 (± 0.018)	0.241 (± 0.018)	0.221 (± 0.018)	0.364 (± 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	522 ^[25]			
Units: litre(s)				
least squares mean (standard error)				
Day 1	0.427 (± 0.017)			
Day 85	0.469 (± 0.017)			
Day 169	0.407 (± 0.017)			
Day 365	0.377 (± 0.018)			

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 on 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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 1
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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	1048
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.138
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.186
Variability estimate	Standard error of the mean
Dispersion value	0.024

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 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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0426
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.002
upper limit	0.098
Variability estimate	Standard error of the mean
Dispersion value	0.024

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 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	1045
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	0.074
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 1
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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	1047
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	0.063
upper limit	0.159
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 1
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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	1043
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2661
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.021
upper limit	0.075
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 1
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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	1046
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	0.102
upper limit	0.198
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	Tio 5 vs Olo 5 on Day 1
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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	1051
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0119
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.109
upper limit	-0.014
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 1
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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	1049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.121
upper limit	-0.025
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 1
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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	1050
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6408
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.036
upper limit	0.059
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 85
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.221
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.173
upper limit	0.27
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 85
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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
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Number of subjects included in analysis	1048
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	0.145
upper limit	0.242
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 85
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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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.185
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.136
upper limit	0.233
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on 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 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
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Number of subjects included in analysis	1045
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.065
upper limit	0.162
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 85
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.157
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.108
upper limit	0.205
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on 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 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	1043
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1355
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.085
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 85
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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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.151
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.102
upper limit	0.199
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Olo 5 on Day 85
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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	1051
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2562
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.076
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 85
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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	1049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0041
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.119
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 85
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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	1050
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0815
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.043
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.091
upper limit	0.005
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 169
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.195
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.149
upper limit	0.242
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 169
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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
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Number of subjects included in analysis	1048
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	0.107
upper limit	0.199
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 169
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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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.174
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.128
upper limit	0.221
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on Day 169
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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
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Number of subjects included in analysis	1045
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.107
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.061
upper limit	0.154
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 169
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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	1047
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	0.086
upper limit	0.178
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on Day 169
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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	1043
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3727
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.067
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 169
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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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.082
upper limit	0.175
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	Tio 5 vs Olo 5 on Day 169
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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	1051
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0744
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.089
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 169
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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	1049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0047
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.067
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.021
upper limit	0.114
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 169
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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	1050
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2945
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.025
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.071
upper limit	0.022
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 365
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.205
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.155
upper limit	0.255
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 365
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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
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Number of subjects included in analysis	1048
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	0.107
upper limit	0.206
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 365
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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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.192
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.142
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 2.5 on 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 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
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Number of subjects included in analysis	1045
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.074
upper limit	0.174
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 365
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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	1047
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.144
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 5/5 vs T+O 2.5/5 on 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 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	1043
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6103
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.037
upper limit	0.062
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 365
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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	1046
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.137
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.087
upper limit	0.186
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Olo 5 on Day 365
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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	1051
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0559
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.098
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 365
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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	1049
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0073
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.118
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 365
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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	1050
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4368
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.03
Variability estimate	Standard error of the mean
Dispersion value	0.025

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 response defined as trough FVC minus baseline FVC. Baseline was defined as mean of 2 pre-dose measurements performed 1h&at 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 and 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	519 ^[26]	519 ^[27]	520 ^[28]	518 ^[29]
Units: litre(s)				
least squares mean (standard error)				
Day 15	0.149 (± 0.018)	0.222 (± 0.018)	0.22 (± 0.018)	0.27 (± 0.018)
Day 43	0.15 (± 0.018)	0.206 (± 0.018)	0.213 (± 0.018)	0.254 (± 0.018)
Day 85	0.077 (± 0.018)	0.168 (± 0.018)	0.144 (± 0.018)	0.23 (± 0.018)
Day 170	0.093 (± 0.017)	0.184 (± 0.017)	0.169 (± 0.017)	0.225 (± 0.017)
Day 365	0.014 (± 0.018)	0.114 (± 0.018)	0.108 (± 0.018)	0.155 (± 0.018)

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	521 ^[30]			
Units: litre(s)				
least squares mean (standard error)				
Day 15	0.296 (± 0.018)			
Day 43	0.318 (± 0.018)			
Day 85	0.265 (± 0.018)			
Day 170	0.246 (± 0.017)			
Day 365	0.191 (± 0.018)			

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 on Day 15
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	1040
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 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 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	1041
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.027
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title

T+O 2.5/5 vs Olo 5 on Day 15

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	1037
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	0.072
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title

T+O 2.5/5 vs Tio 2.5 on Day 15

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	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0545
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.097
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 15
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0456
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.099
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on 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 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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2949
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.023
upper limit	0.075
Variability estimate	Standard error of the mean
Dispersion value	0.025

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 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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.074
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.123
Variability estimate	Standard error of the mean
Dispersion value	0.025

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 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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0045
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.022
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 15
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0035
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.024
upper limit	0.122
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 15
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9369
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.051
upper limit	0.047
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 43
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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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.168
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.119
upper limit	0.217
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 43
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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
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Number of subjects included in analysis	1041
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.105
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.056
upper limit	0.154
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 43
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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	1037
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	0.054
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 2.5 on 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 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
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Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0585
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.096
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 43
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1042
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.008
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on 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 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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0097
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.016
upper limit	0.114
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 43
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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	1040
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	0.063
upper limit	0.161
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Olo 5 on Day 43
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.063
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.014
upper limit	0.112
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 43
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
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	Tio 5 vs Tio 2.5 on Day 43
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7889
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.042
upper limit	0.056
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 85
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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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.187
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.138
upper limit	0.237
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 85
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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
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Number of subjects included in analysis	1041
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	0.072
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day85
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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	1037
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	0.103
upper limit	0.202
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on 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 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
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Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0134
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.013
upper limit	0.111
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 85
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
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	T+O 5/5 vs T+O 2.5/5 on 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 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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.167
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.015
upper limit	0.084
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 85
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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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.048
upper limit	0.146
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Olo 5 on Day 85
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0085
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.017
upper limit	0.115
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 85
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.041
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 85
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3332
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.074
upper limit	0.025
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 170
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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	1040
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	0.105
upper limit	0.201
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 170
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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
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Number of subjects included in analysis	1041
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.029
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 2.5/5 vs Olo 5 on Day 170
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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	1037
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	0.084
upper limit	0.18
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on 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 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
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Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0926
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.007
upper limit	0.089
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 170
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0231
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.008
upper limit	0.103
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on 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 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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3802
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.069
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs Tio 2.5 on Day 170
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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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0105
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.062
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.015
upper limit	0.11
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	Tio 5 vs Olo 5 on Day 170
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.076
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.028
upper limit	0.125
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 170
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.043
upper limit	0.139
Variability estimate	Standard error of the mean
Dispersion value	0.025

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 170
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5554
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.062
upper limit	0.034
Variability estimate	Standard error of the mean
Dispersion value	0.024

Statistical analysis title	T+O 5/5 vs Olo 5 on Day 365
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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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.178
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.127
upper limit	0.228
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs Tio 5 on Day 365
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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
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Number of subjects included in analysis	1041
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011
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 Olo 5 on Day 365
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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	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.142
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.091
upper limit	0.192
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Tio 2.5 on 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 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
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Number of subjects included in analysis	1037
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1112
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.041
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.009
upper limit	0.091
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 2.5/5 vs Tio 5 on Day 365
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0632
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.098
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	T+O 5/5 vs T+O 2.5/5 on 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 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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1615
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 Tio 2.5 on Day 365
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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	1040
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0027
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.027
upper limit	0.127
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Olo 5 on Day 365
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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	1039
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	0.044
upper limit	0.144
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 2.5 vs Olo 5 on Day 365
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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	1038
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.101
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.151
Variability estimate	Standard error of the mean
Dispersion value	0.026

Statistical analysis title	Tio 5 vs Tio 2.5 on Day 365
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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	1039
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7925
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.007
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.057
upper limit	0.044
Variability estimate	Standard error of the mean
Dispersion value	0.026

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 447 days)

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	75 / 528 (14.20%)	66 / 525 (12.57%)	79 / 527 (14.99%)
number of deaths (all causes)	5	11	12
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Basal cell carcinoma			

subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm of bladder			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Benign ovarian tumour			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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 cancer			
subjects affected / exposed	1 / 528 (0.19%)	1 / 525 (0.19%)	0 / 527 (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
Bladder neoplasm			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Bladder papilloma			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Brain neoplasm			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 / 528 (0.00%)	1 / 525 (0.19%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chronic lymphocytic leukaemia			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
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 cancer			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Enchondroma			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric neoplasm			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Glioblastoma multiforme			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Hepatic cancer			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Lipoma			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 adenocarcinoma			

subjects affected / exposed	1 / 528 (0.19%)	1 / 525 (0.19%)	2 / 527 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma metastatic			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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 cancer metastatic			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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 / 528 (0.19%)	1 / 525 (0.19%)	5 / 527 (0.95%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Malignant melanoma			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	2 / 527 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Metastases to bone			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
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 central nervous system			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 carcinoma			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Prostate cancer			
subjects affected / exposed	2 / 528 (0.38%)	1 / 525 (0.19%)	2 / 527 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal cell carcinoma			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Squamous cell carcinoma of skin			

subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Ureteric cancer			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Arteriosclerosis			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Circulatory collapse			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Hypertension			
subjects affected / exposed	2 / 528 (0.38%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypotension			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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 vascular disorder			
subjects affected / exposed	2 / 528 (0.38%)	0 / 525 (0.00%)	0 / 527 (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
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
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 septal operation			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Electrocution			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Hernia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Local swelling			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Malaise			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Multi-organ failure			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	2 / 527 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Non-cardiac chest pain			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 528 (0.38%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic adhesions			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Prostatitis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Prostatomegaly			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Uterine prolapse			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal			

disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 528 (0.38%)	0 / 525 (0.00%)	0 / 527 (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
Asthma			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Bronchospasm			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
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	27 / 528 (5.11%)	25 / 525 (4.76%)	24 / 527 (4.55%)
occurrences causally related to treatment / all	3 / 35	0 / 28	0 / 29
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Dyspnoea			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	2 / 528 (0.38%)	0 / 525 (0.00%)	0 / 527 (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
Hypercapnia			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Hypoxia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung infiltration			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising pneumonia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Pleural effusion			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 congestion			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 embolism			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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 hypertension			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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 oedema			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Respiratory distress			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bipolar disorder			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Confusional state			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			

subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Major depression			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 decompensation			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Psychotic disorder			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Suicidal ideation			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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			
Arteriogram coronary			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac murmur			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic specific antigen increased			

subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Ankle fracture			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Bone fissure			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Brain contusion			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Cervical vertebral fracture			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Clavicle fracture			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Facial bones fracture			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Femur fracture			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Fractured coccyx			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Humerus fracture			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Limb injury			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Meniscus injury			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Periprosthetic fracture			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post laminectomy syndrome			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Procedural pain			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Radius fracture			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Road traffic accident			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Skull fractured base			

subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Subdural haematoma			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Subdural haemorrhage			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Tendon rupture			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Thermal burn			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Thoracic vertebral fracture			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Wound			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	1 / 528 (0.19%)	1 / 525 (0.19%)	0 / 527 (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
Angina pectoris			
subjects affected / exposed	1 / 528 (0.19%)	1 / 525 (0.19%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Atrial fibrillation			
subjects affected / exposed	2 / 528 (0.38%)	1 / 525 (0.19%)	2 / 527 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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	0 / 528 (0.00%)	2 / 525 (0.38%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure chronic			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 congestive			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Cardiomyopathy			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Coronary artery disease			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	2 / 527 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve stenosis			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Myocardial infarction			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	2 / 527 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral infarction			
subjects affected / exposed	1 / 528 (0.19%)	1 / 525 (0.19%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	2 / 528 (0.38%)	2 / 525 (0.38%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Convulsion			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Critical illness polyneuropathy			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Cubital tunnel syndrome			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Dementia			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Dizziness			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Epilepsy			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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 stroke			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Intracranial aneurysm			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 stroke			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
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 radiculopathy			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Multiple sclerosis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Post herpetic neuralgia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Sciatica			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Syncope			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 528 (0.00%)	2 / 525 (0.38%)	0 / 527 (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
Vocal cord paralysis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal adhesions			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Abdominal hernia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Abdominal pain			
subjects affected / exposed	2 / 528 (0.38%)	0 / 525 (0.00%)	0 / 527 (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
Abdominal pain upper			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Anal fistula			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Coeliac disease			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Crohn's disease			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Diarrhoea			

subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Diverticular perforation			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Duodenitis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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 polyps			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Gastric ulcer			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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 haemorrhage			
subjects affected / exposed	2 / 528 (0.38%)	0 / 525 (0.00%)	0 / 527 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Haematemesis			

subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Inguinal hernia			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Intestinal obstruction			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Large intestine polyp			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 cyst			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 duct dilatation			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Pancreatitis acute			

subjects affected / exposed	0 / 528 (0.00%)	2 / 525 (0.38%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Rectal ulcer			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Umbilical hernia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Vomiting			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Bile duct stone			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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 dilatation			

subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Cholangitis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Cholecystitis acute			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cyst			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Jaundice cholestatic			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 and urinary disorders			
Calculus ureteric			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Haematuria			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Nephrolithiasis			

subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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 colic			
subjects affected / exposed	2 / 528 (0.38%)	0 / 525 (0.00%)	0 / 527 (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
Renal failure acute			
subjects affected / exposed	2 / 528 (0.38%)	0 / 525 (0.00%)	2 / 527 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure chronic			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Urethral stenosis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperparathyroidism primary			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Arthritis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Bone pain			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Fascial hernia			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
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 spinal stenosis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
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 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			

subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Spinal column stenosis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Bronchitis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
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	1 / 528 (0.19%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Extradural abscess			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Gastroenteritis			
subjects affected / exposed	3 / 528 (0.57%)	0 / 525 (0.00%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Infected bites			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Klebsiella sepsis			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Lobar pneumonia			

subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (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
Localised infection			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media chronic			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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			
subjects affected / exposed	8 / 528 (1.52%)	5 / 525 (0.95%)	5 / 527 (0.95%)
occurrences causally related to treatment / all	0 / 8	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia bacterial			
subjects affected / exposed	0 / 528 (0.00%)	1 / 525 (0.19%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Pyelonephritis			

subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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	0 / 528 (0.00%)	2 / 525 (0.38%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinusitis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Staphylococcal sepsis			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			

subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (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
Fluid overload			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	1 / 527 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Hypoglycaemia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Hyponatraemia			
subjects affected / exposed	0 / 528 (0.00%)	0 / 525 (0.00%)	0 / 527 (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
Hypovolaemia			
subjects affected / exposed	1 / 528 (0.19%)	0 / 525 (0.00%)	0 / 527 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Tio+Olo FDC (2.5/5 µg)	Tio+Olo FDC (5/5 µg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 522 (15.52%)	87 / 522 (16.67%)	
number of deaths (all causes)	10	10	
number of deaths resulting from adverse events	0	0	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of bladder			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign ovarian tumour			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder papilloma			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Bronchial carcinoma			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enchondroma			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	2 / 522 (0.38%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric neoplasm			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma multiforme			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic cancer			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			

subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	3 / 522 (0.57%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma of the skin			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (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 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 522 (0.38%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer metastatic			

subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septal operation			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Electrocution			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Local swelling			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic adhesions			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	20 / 522 (3.83%)	36 / 522 (6.90%)	
occurrences causally related to treatment / all	0 / 21	2 / 40	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 522 (0.00%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary oedema			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	0 / 522 (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 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric decompensation			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Arteriogram coronary			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac murmur			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic specific antigen increased			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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			
Alcohol poisoning			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fissure			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.19%)	0 / 522 (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 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	2 / 522 (0.38%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 522 (0.38%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured coccyx			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			

subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post laminectomy syndrome			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 522 (0.19%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 522 (0.00%)	4 / 522 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	2 / 522 (0.38%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiomyopathy			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			

subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve stenosis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 522 (0.19%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (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 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Critical illness polyneuropathy			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cubital tunnel syndrome			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intracranial aneurysm			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			

subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (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 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 adhesions			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coeliac disease			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	2 / 522 (0.38%)	3 / 522 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cyst			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic duct dilatation			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal ulcer			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (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	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			

subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cyst			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism primary			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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			
Arthritis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 522 (0.38%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fascial hernia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural abscess			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bites			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	3 / 522 (0.57%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 522 (1.92%)	9 / 522 (1.72%)	
occurrences causally related to treatment / all	0 / 11	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			

subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
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 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 522 (0.00%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 522 (0.00%)	2 / 522 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 522 (0.19%)	0 / 522 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 522 (0.19%)	1 / 522 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 522 (0.00%)	0 / 522 (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	221 / 528 (41.86%)	207 / 525 (39.43%)	210 / 527 (39.85%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	155 / 528 (29.36%)	144 / 525 (27.43%)	151 / 527 (28.65%)
occurrences (all)	242	207	239
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	65 / 528 (12.31%)	64 / 525 (12.19%)	67 / 527 (12.71%)
occurrences (all)	82	83	85
Upper respiratory tract infection			
subjects affected / exposed	24 / 528 (4.55%)	30 / 525 (5.71%)	30 / 527 (5.69%)
occurrences (all)	32	44	36

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	211 / 522 (40.42%)	193 / 522 (36.97%)	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	133 / 522 (25.48%)	134 / 522 (25.67%)	
occurrences (all)	193	200	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	64 / 522 (12.26%)	67 / 522 (12.84%)	
occurrences (all)	78	84	
Upper respiratory tract infection			
subjects affected / exposed	40 / 522 (7.66%)	25 / 522 (4.79%)	
occurrences (all)	61	35	

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: NCT01431274.

Notes: