Clinical trial results:
Randomised, double-blind, placebo-controlled, 6 treatment, 4 period, incomplete cross-over trial to characterise the 24-hour lung function profiles of tiotropium + olodaterol fixed dose combination (2.5/5 µg, 5/5 µg), tiotropium (2.5 µg, 5 µg) and olodaterol (5 µg) (oral inhalation, delivered by the Respimat® Inhaler) after 6 weeks once daily treatment in patients with Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2011-004710-42
Trial protocol	DE NL DK BE HU
Global end of trial date	12 August 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	16 July 2015

Trial information

Trial identification

Sponsor protocol code	1237.20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01559116
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173 , 55216 Ingelheim am Rhein , Germany,
Public contact	Clinical Trial Information Disclosure , QRPE Processes and Systems Coordination , +1 800 243 0127 , clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Clinical Trial Information Disclosure , QRPE Processes and Systems Coordination , +1 800 243 0127 , clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 July 2013
Global end of trial reached?	Yes
Global end of trial date	12 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to determine the 24-hour FEV1-time profile of tiotropium + olodaterol FDC (2.5/5 µg, 5/5 µg), administered once daily by the RESPIMAT Inhaler, after 6 weeks of treatment.

Protection of trial subjects:

An independent DMC was formed to ensure patient safety and was to make recommendations to the sponsor with regard to the continuation and potential modification or termination of the trial.
All patients were informed that they were free to withdraw their consent at any time during the study without penalty or prejudice. The patients were informed that their personal trial related data would be considered confidential and used by BI in accordance with the local data protection laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 2012
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	Netherlands: 40
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	Germany: 94
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	United States: 47
Worldwide total number of subjects	259
EEA total number of subjects	205

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)	172
From 65 to 84 years	87
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

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

Period 1

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

Arms

Arm title	All subjects

Arm description:

All enrolled subject were included.

Arm type	all treatments combined subjects
Investigational medicinal product name	Tiotropium (Tio), Olodaterol (Olo), Tio+Olo, placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Randomised, double-blind, placebo-controlled, 6 treatment, 4 period, incomplete cross-over trial to characterise the 24-hour lung function profiles of tiotropium + olodaterol fixed dose combination (2.5/5 µg, 5/5 µg), tiotropium (2.5 µg, 5 µg) and olodaterol (5 µg) (oral inhalation, delivered by the Respimat® Inhaler) after 6 weeks once daily treatment in patients with Chronic Obstructive Pulmonary Disease (COPD)

Number of subjects in period 1[1]	All subjects
Started	219
Completed	193
Not completed	26
Consent withdrawn by subject	4
Adverse event, non-fatal	10
'Other than stated above '	9
Lost to follow-up	1
Lack of efficacy	1
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication. Thus, even though 259 subjects were enrolled in the trail, 40 subjects were not treated. Therefore only 219 subjects were reported in the baseline period.

Period 2

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

2 inhalations once daily (a.m. dosing) for 6 weeks

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

Dosage and administration details:

2 placebo inhalations once daily (a.m. dosing) for 6 weeks

Arm title	Olo 5 µg

Arm description:

2 inhalations once daily (a.m. dosing) for 6 weeks. Olodaterol (Olo): one dose (5 µg) only

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:

2 inhalations once daily (a.m. dosing) for 6 weeks. Olodaterol: one dose only

Arm title	Tio 2.5 µg

Arm description:

2 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium (Tio): low dose

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 inhalations once daily (a.m. dosing) for 6 weeks.
Tiotropium: low dose

Arm title	Tio 5 µg

Arm description:	
2 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium (Tio): high dose	
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 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium: high dose	
Arm title	T+O 2.5/5 µg
Arm description:	
2 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium + Olodaterol (T+O) fixed dose combination (FDC) low dose: low dose + one dose only	
Arm type	Experimental
Investigational medicinal product name	Tiotropium, Olodaterol FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
2 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium + Olodaterol (T+O) fixed dose combination (FDC) low dose: low dose + one dose only.	
Arm title	T+O 5/5 µg
Arm description:	
2 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium+Olodaterol (T+O) fixed dose combination (FDC) high dose: high dose + one dose only	
Arm type	Experimental
Investigational medicinal product name	Tio, Olo FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details:	
2 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium+Olodaterol fixed dose combination (FDC) high dose: high dose + one dose only	

Number of subjects in period 2	Placebo	Olo 5 µg	Tio 2.5 µg
Started	138	138	137
Completed	130	136	135
Not completed	8	2	2
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	6	2	1
'Other than stated above '	-	-	1
Lost to follow-up	1	-	-

Lack of efficacy	1	-	-

Number of subjects in period 2	Tio 5 µg	T+O 2.5/5 µg	T+O 5/5 µg
Started	138	136	139
Completed	135	135	138
Not completed	3	1	1
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	1	-	-
'Other than stated above '	2	-	1
Lost to follow-up	-	-	-
Lack of efficacy	-	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description:

Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication. Therefore 219 subjects were in baseline characteristic reporting group.

Reporting group values	Overall trial	Total	
Number of subjects	219	219	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 61.1 ± 7.7	 -	
Gender categorical Units: Subjects			
Female	90	90	
Male	129	129	

End points

End points reporting groups

Reporting group title	All subjects
Reporting group description:	
All enrolled subject were included.	
Reporting group title	Placebo
Reporting group description:	
2 inhalations once daily (a.m. dosing) for 6 weeks	
Reporting group title	Olo 5 µg
Reporting group description:	
2 inhalations once daily (a.m. dosing) for 6 weeks. Olodaterol (Olo): one dose (5 µg) only	
Reporting group title	Tio 2.5 µg
Reporting group description:	
2 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium (Tio): low dose	
Reporting group title	Tio 5 µg
Reporting group description:	
2 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium (Tio): high dose	
Reporting group title	T+O 2.5/5 µg
Reporting group description:	
2 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium + Olodaterol (T+O) fixed dose combination (FDC) low dose: low dose + one dose only	
Reporting group title	T+O 5/5 µg
Reporting group description:	
2 inhalations once daily (a.m. dosing) for 6 weeks. Tiotropium+Olodaterol (T+O) fixed dose combination (FDC) high dose: high dose + one dose only	

Primary: Forced Expiratory Volume in 1 Second (FEV1) AUC0-24h Response [L] After 6 Weeks Treatment.

End point title	Forced Expiratory Volume in 1 Second (FEV1) AUC0-24h Response [L] After 6 Weeks Treatment.

End point description:

Area under the Forced Expiratory Volume in 1 second (FEV1) after 6 weeks treatement-time curve from 0 to 24 h post-dose, using the trapezoidal rule, divided by the duration (24 h) to report in litres.
Response was defined as the change from patient baseline.
Full Analysis Set (FAS): included all randomised patients who received at least 1 dose of study medication, had a period baseline measurement, and at least 1 evaluable postbaseline measurement for the primary endpoint at any Week 6 visit.
Pulmonary function test (PFT) time schedule:
At Visits 2, 4, 6, 8: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2 and 3 h post-dose.
At Visits 3, 5, 7, 9: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose.

End point type	Primary

End point timeframe:

Day 1 and week 6 (details in description)

End point values	Placebo	Olo 5 µg	Tio 2.5 µg	Tio 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	132[1]	136[2]	136[3]	135[4]
Units: litre(s)				
least squares mean (standard error)	-0.037 (± 0.014)	0.129 (± 0.013)	0.117 (± 0.013)	0.133 (± 0.014)

Notes:

[1] - Full analysis set (FAS): definition in description

[2] - FAS

[3] - FAS

[4] - FAS

End point values	T+O 2.5/5 µg	T+O 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[5]	138[6]		
Units: litre(s)				
least squares mean (standard error)	0.241 (± 0.014)	0.244 (± 0.013)		

Notes:

[5] - FAS

[6] - FAS

Statistical analyses

Statistical analysis title	T+O 5/5 vs placebo

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 5/5 minus Placebo.

Comparison groups	Placebo v T+O 5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.252
upper limit	0.309
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[7] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 5/5 µg
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[8]
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	0.087
upper limit	0.143
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[8] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (274) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.082
upper limit	0.139
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[9] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 2.5/5 minus Placebo.

Comparison groups	Placebo v T+O 2.5/5 µg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.277
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.249
upper limit	0.306
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[10] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (267) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 2.5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[11]
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	0.083
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[11] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[12]
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	0.096
upper limit	0.152
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[12] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

Comparison groups	Tio 5 µg v T+O 2.5/5 µg

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[13]
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	0.079
upper limit	0.136
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[13] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 5/5 minus T+O 2.5/5.

Comparison groups	T+O 2.5/5 µg v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.8238
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.031
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[14] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and

Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 5/5 µg
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.127
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.099
upper limit	0.155
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[15] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (274) does not reflect the actual number.

Statistical analysis title	Tio 5 vs Olo 5

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as Tio 5 minus Olo 5.

Comparison groups	Olo 5 µg v Tio 5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.7722
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.024
upper limit	0.032
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[16] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

Statistical analysis title	Tio 2.5 vs Olo 5

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as Tio 2.5 minus Olo 5.

Comparison groups	Olo 5 µg v Tio 2.5 µg
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.3842
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.041
upper limit	0.016
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[17] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (272) does not reflect the actual number.

Statistical analysis title	Tio 5 vs Tio 2.5

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as Tio 5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v Tio 5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.2487
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.017
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.012
upper limit	0.045
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[18] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

Statistical analysis title	Olo 5 vs placebo

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as Olo 5 minus Placebo.

Comparison groups	Placebo v Olo 5 µg
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.137
upper limit	0.194
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[19] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (268) does not reflect the actual number.

Statistical analysis title	Tio 2.5 vs placebo

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as Tio 2.5 minus Placebo.

Comparison groups	Tio 2.5 µg v Placebo
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority[20]
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	0.125
upper limit	0.182
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[20] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (268) does not reflect the actual number.

Statistical analysis title	Tio 5 vs placebo

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures
(MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient
as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger
approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as Tio 5 minus Placebo.

Comparison groups	Placebo v Tio 5 µg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.141
upper limit	0.198
Variability estimate	Standard error of the mean
Dispersion value	0.014

Notes:

[21] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (267) does not reflect the actual number.

Secondary: FEV1 AUC0-12h Response [L] After 6 Weeks Treatment

End point title	FEV1 AUC0-12h Response [L] After 6 Weeks Treatment

End point description:

This is a key secondary endpoint.
Area under the Forced Expiratory Volume in 1 second (FEV1) after 6 weeks treatement-time curve from 0 to 12 h post-dose, using the trapezoidal rule, divided by the duration (12h) to report in litres.
Response was defined as the change from patient baseline.
PFT time schedule:
At Visits 2, 4, 6, 8: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2 and 3 h post-dose
At Visits 3, 5, 7, 9: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose.

End point type	Secondary

End point timeframe:

baseline and after 6 weeks (details in description)

End point values	Placebo	Olo 5 µg	Tio 2.5 µg	Tio 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	132[22]	136[23]	136[24]	135[25]
Units: litre(s)				
least squares mean (standard error)	-0.013 (± 0.015)	0.179 (± 0.015)	0.171 (± 0.015)	0.186 (± 0.015)

Notes:

[22] - FAS

[23] - FAS

[24] - FAS

[25] - FAS

End point values	T+O 2.5/5 µg	T+O 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[26]	138[27]		
Units: litre(s)				
least squares mean (standard error)	0.31 (± 0.015)	0.305 (± 0.015)		

Notes:

[26] - FAS

[27] - FAS

Statistical analyses

Statistical analysis title	T+O 5/5 vs placebo

Statistical analysis description:

The adjusted mean and standard error (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect; compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 5/5 minus Placebo.

Comparison groups	Placebo v T+O 5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.319
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.289
upper limit	0.349
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[28] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 5/5 minus Olo 5

Comparison groups	Olo 5 µg v T+O 5/5 µg
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[29]
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	0.096
upper limit	0.156
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[29] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (274) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[30]
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	0.089
upper limit	0.149
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[30] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Placebo.

Comparison groups	Placebo v T+O 2.5/5 µg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.323
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.293
upper limit	0.354
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[31] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (267) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 2.5/5 µg

Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[32]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.101
upper limit	0.161
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[32] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.139
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.109
upper limit	0.169
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[33] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of

denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[34]
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	0.093
upper limit	0.154
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[34] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

Secondary: FEV1 AUC12-24h Response [L] After 6 Weeks Treatment

End point title	FEV1 AUC12-24h Response [L] After 6 Weeks Treatment

End point description:

This is a key secondary endpoint.
Area under the Forced Expiratory Volume in 1 second (FEV1) after 6 weeks treatement-time curve from 12 to 24 h post-dose using the trapezoidal rule, divided by the duration (12 h) to report in litres.
Response was defined as the change from patient baseline.
PFT time schedule:
At Visits 2, 4, 6, 8: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2 and 3 h post-dose.
At Visits 3, 5, 7, 9: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose.

End point type	Secondary

End point timeframe:

baseline and after 6 weeks (details in description)

End point values	Placebo	Olo 5 µg	Tio 2.5 µg	Tio 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	132[35]	136[36]	136[37]	135[38]
Units: litre(s)				
least squares mean (standard error)	-0.06 (± 0.014)	0.079 (± 0.013)	0.062 (± 0.013)	0.081 (± 0.014)

Notes:

[35] - FAS

[36] - FAS

[37] - FAS

[38] - FAS

End point values	T+O 2.5/5 µg	T+O 5/5 µg		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[39]	138[40]		
Units: litre(s)				
least squares mean (standard error)	0.172 (± 0.014)	0.182 (± 0.013)		

Notes:

[39] - FAS

[40] - FAS

Statistical analyses

Statistical analysis title	T+O 5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 5/5 minus Placebo.

Comparison groups	Placebo v T+O 5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[41]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.243
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.212
upper limit	0.273
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[41] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 5/5 µg

Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[42]
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	0.074
upper limit	0.133
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[42] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (274) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[43]
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	0.072
upper limit	0.132
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[43] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of

denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus placebo.

Comparison groups	Placebo v T+O 2.5/5 µg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.232
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.201
upper limit	0.262
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[44] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (267) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[45]
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	0.063
upper limit	0.123
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[45] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed

effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[46] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[47]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.091
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.061
upper limit	0.121
Variability estimate	Standard error of the mean
Dispersion value	0.015

Notes:

[47] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

Secondary: Trough FEV1 Response [L] After 6 Weeks Treatment

End point title	Trough FEV1 Response [L] After 6 Weeks Treatment

End point description:

The trough was defined as the mean of the 23 h and 23 h50 min measurements at Visits 3, 5, 7, 9 and Response was defined as the change from patient baseline.
PFT time schedule:
At Visits 2, 4, 6, 8: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2 and 3 h post-dose.
At Visits 3, 5, 7, 9: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose.

End point type	Secondary

End point timeframe:

baseline and after 6 weeks (details in description)

End point values	Placebo	Olo 5 µg	Tio 2.5 µg	Tio 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	132[48]	136[49]	136[50]	135[51]
Units: litre(s)				
least squares mean (standard error)	-0.006 (± 0.015)	0.109 (± 0.015)	0.095 (± 0.015)	0.122 (± 0.015)

Notes:

[48] - FAS

[49] - FAS

[50] - FAS

[51] - FAS

End point values	T+O 2.5/5 µg	T+O 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[52]	138[53]		
Units: litre(s)				
least squares mean (standard error)	0.196 (± 0.015)	0.201 (± 0.015)		

Notes:

[52] - FAS

[53] - FAS

Statistical analyses

Statistical analysis title	T+O 5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Placebo.

Comparison groups	Placebo v T+O 5/5 µg

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.207
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.173
upper limit	0.241
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[54] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 5/5 µg
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[55]
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	0.059
upper limit	0.126
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[55] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (274) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of

denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[56]
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	0.045
upper limit	0.113
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[56] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus placebo.

Comparison groups	Placebo v T+O 2.5/5 µg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.201
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.167
upper limit	0.235
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[57] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (267) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed

effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[58]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.052
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[58] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[59]
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	0.067
upper limit	0.135
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[59] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[60]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.039
upper limit	0.107
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[60] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

Secondary: Peak(0-3h) FEV1 Response [L] After 6 Weeks Treatment

End point title	Peak(0-3h) FEV1 Response [L] After 6 Weeks Treatment

End point description:

The peak was defined as the maximum value measured within the first 3 h post dosing and response was defined as the change from patient baseline.
PFT time schedule:
At Visits 2, 4, 6, 8: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2 and 3 h post-dose.
At Visits 3, 5, 7, 9: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose.

End point type	Secondary

End point timeframe:

baseline and after 6 weeks (details in description)

End point values	Placebo	Olo 5 µg	Tio 2.5 µg	Tio 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	135[61]	138[62]	136[63]	137[64]
Units: litre(s)				
least squares mean (standard error)	0.072 (± 0.017)	0.291 (± 0.016)	0.29 (± 0.016)	0.3 (± 0.016)

Notes:

[61] - FAS

[62] - FAS

[63] - FAS

[64] - FAS

End point values	T+O 2.5/5 µg	T+O 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[65]	138[66]		
Units: litre(s)				
least squares mean (standard error)	0.422 (± 0.016)	0.411 (± 0.016)		

Notes:

[65] - FAS

[66] - FAS

Statistical analyses

Statistical analysis title	T+O 5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Placebo.

Comparison groups	Placebo v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[67]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.338
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.305
upper limit	0.371
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[67] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 5/5 µg

Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.087
upper limit	0.153
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[68] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (276) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 5/5 µg
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority[69]
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	0.078
upper limit	0.143
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[69] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (275) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of

denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus placebo.

Comparison groups	Placebo v T+O 2.5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[70]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.317
upper limit	0.383
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[70] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[71]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.098
upper limit	0.164
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[71] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed

effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[72]
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	0.099
upper limit	0.165
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[72] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[73]
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	0.089
upper limit	0.155
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[73] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (272) does not reflect the actual number.

Secondary: FVC AUC0-24h Response [L] After 6 Weeks Treatment

End point title	FVC AUC0-24h Response [L] After 6 Weeks Treatment

End point description:

Area under the Forced Vital Capacity (FVC) after 6 weeks treatment period-time curve from 0 to 24 h post-dose using the trapezoidal rule, divided by the duration (24 h) to report in litres. Response was defined as the change from patient baseline.
PFT time schedule:
At Visits 2, 4, 6, 8: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2 and 3 h post-dose.
At Visits 3, 5, 7, 9: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose.

End point type	Secondary

End point timeframe:

baseline and after 6 weeks (details in description)

End point values	Placebo	Olo 5 µg	Tio 2.5 µg	Tio 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	132[74]	136[75]	136[76]	135[77]
Units: litre(s)				
least squares mean (standard error)	-0.065 (± 0.023)	0.158 (± 0.022)	0.172 (± 0.022)	0.191 (± 0.022)

Notes:

[74] - FAS

[75] - FAS

[76] - FAS

[77] - FAS

End point values	T+O 2.5/5 µg	T+O 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[78]	138[79]		
Units: litre(s)				
least squares mean (standard error)	0.331 (± 0.022)	0.368 (± 0.022)		

Notes:

[78] - FAS

[79] - FAS

Statistical analyses

Statistical analysis title	T+O 5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Placebo.

Comparison groups	Placebo v T+O 5/5 µg

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[80]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.433
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.389
upper limit	0.477
Variability estimate	Standard error of the mean
Dispersion value	0.022

Notes:

[80] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 5/5 µg
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[81]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.166
upper limit	0.253
Variability estimate	Standard error of the mean
Dispersion value	0.022

Notes:

[81] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (274) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of

denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[82]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.177
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.133
upper limit	0.221
Variability estimate	Standard error of the mean
Dispersion value	0.022

Notes:

[82] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus placebo.

Comparison groups	Placebo v T+O 2.5/5 µg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority[83]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.396
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.352
upper limit	0.441
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[83] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (267) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed

effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[84]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.173
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.129
upper limit	0.217
Variability estimate	Standard error of the mean
Dispersion value	0.022

Notes:

[84] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[85]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.115
upper limit	0.203
Variability estimate	Standard error of the mean
Dispersion value	0.022

Notes:

[85] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[86]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.096
upper limit	0.184
Variability estimate	Standard error of the mean
Dispersion value	0.022

Notes:

[86] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

Secondary: FVC AUC0-12h Response [L] After 6 Weeks Treatment

End point title	FVC AUC0-12h Response [L] After 6 Weeks Treatment

End point description:

Area under the Forced Vital Capacity (FVC) after 6 weeks treatment period-time curve from 0 to 12 h post-dose using the trapezoidal rule, divided by the duration (12 h) to report in litres. Response was defined as the change from patient baseline.
PFT time schedule:
At Visits 2, 4, 6, 8: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2 and 3 h post-dose.
At Visits 3, 5, 7, 9: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose.

End point type	Secondary

End point timeframe:

baseline and after 6 weeks (details in description)

End point values	Placebo	Olo 5 µg	Tio 2.5 µg	Tio 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	132[87]	136[88]	136[89]	135[90]
Units: litre(s)				
least squares mean (standard error)	-0.023 (± 0.024)	0.24 (± 0.024)	0.249 (± 0.024)	0.261 (± 0.024)

Notes:
[87] - FAS
[88] - FAS
[89] - FAS
[90] - FAS

End point values	T+O 2.5/5 µg	T+O 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[91]	138[92]		
Units: litre(s)				
least squares mean (standard error)	0.42 (± 0.024)	0.44 (± 0.024)		

Notes:
[91] - FAS
[92] - FAS

Statistical analyses

Statistical analysis title	T+O 5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Placebo.

Comparison groups	Placebo v T+O 5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[93]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.463
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.417
upper limit	0.509
Variability estimate	Standard error of the mean
Dispersion value	0.024

Notes:
[93] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.

The adjusted mean difference is calculated as T+O 5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 5/5 µg
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[94]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.154
upper limit	0.246
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[94] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (274) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[95]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.179
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.133
upper limit	0.225
Variability estimate	Standard error of the mean
Dispersion value	0.023

Notes:

[95] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random

effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus placebo.

Comparison groups	Placebo v T+O 2.5/5 µg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority[96]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.443
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.396
upper limit	0.49
Variability estimate	Standard error of the mean
Dispersion value	0.024

Notes:

[96] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (267) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[97]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.181
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.134
upper limit	0.227
Variability estimate	Standard error of the mean
Dispersion value	0.024

Notes:

[97] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[98]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.171
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.125
upper limit	0.218
Variability estimate	Standard error of the mean
Dispersion value	0.024

Notes:

[98] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[99]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.113
upper limit	0.206
Variability estimate	Standard error of the mean
Dispersion value	0.024

Notes:

[99] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

Secondary: FVC AUC12-24h Response [L] After 6 Weeks Treatment

End point title	FVC AUC12-24h Response [L] After 6 Weeks Treatment

End point description:

Area under the Forced Vital Capacity (FVC) after 6 weeks treatment period-time curve from 12 to 24 h post-dose
using the trapezoidal rule, divided by the duration (12 h) to report in litres. Response was defined as the change from patient baseline.
PFT time schedule:
At Visits 2, 4, 6, 8: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2 and 3 h post-dose.
At Visits 3, 5, 7, 9: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose.

End point type	Secondary

End point timeframe:

baseline and after 6 weeks (details in description)

End point values	Placebo	Olo 5 µg	Tio 2.5 µg	Tio 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	132[100]	136[101]	136[102]	135[103]
Units: litre(s)				
least squares mean (standard error)	-0.108 (± 0.023)	0.077 (± 0.023)	0.095 (± 0.023)	0.122 (± 0.023)

Notes:

[100] - FAS

[101] - FAS

[102] - FAS

[103] - FAS

End point values	T+O 2.5/5 µg	T+O 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[104]	138[105]		
Units: litre(s)				
least squares mean (standard error)	0.243 (± 0.023)	0.296 (± 0.023)		

Notes:

[104] - FAS

[105] - FAS

Statistical analyses

Statistical analysis title	T+O 5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of

denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Placebo.

Comparison groups	Placebo v T+O 5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[106]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.404
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.355
upper limit	0.453
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[106] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 5/5 µg
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[107]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.219
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.267
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[107] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (274) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed

effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[108]
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	0.126
upper limit	0.223
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[108] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus placebo.

Comparison groups	Placebo v T+O 2.5/5 µg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority[109]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.351
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.301
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[109] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (267) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[110]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.117
upper limit	0.214
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[110] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[111]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.148
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.099
upper limit	0.197
Variability estimate	Standard error of the mean
Dispersion value	0.025

Notes:

[111] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[112]
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

Notes:

[112] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

Secondary: Trough FVC Response [L] After 6 Weeks Treatment

End point title	Trough FVC Response [L] After 6 Weeks Treatment

End point description:

The trough was defined as the mean of the 23 h and 23 h50 min measurements at visits 3, 5, 7, 9 and response was defined as the
change from patient baseline.
PFT time schedule:
At Visits 2, 4, 6, 8: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2 and 3 h post-dose.
At Visits 3, 5, 7, 9: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose.

End point type	Secondary

End point timeframe:

baseline and after 6 weeks (details in description)

End point values	Placebo	Olo 5 µg	Tio 2.5 µg	Tio 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	132[113]	136[114]	136[115]	135[116]
Units: litre(s)				
least squares mean (standard error)	-0.025 (± 0.026)	0.134 (± 0.026)	0.115 (± 0.026)	0.183 (± 0.026)

Notes:

[113] - FAS

[114] - FAS

[115] - FAS

[116] - FAS

End point values	T+O 2.5/5 µg	T+O 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[117]	138[118]		
Units: litre(s)				
least squares mean (standard error)	0.282 (± 0.026)	0.304 (± 0.026)		

Notes:

[117] - FAS

[118] - FAS

Statistical analyses

Statistical analysis title	T+O 5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Placebo.

Comparison groups	Placebo v T+O 5/5 µg
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[119]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.329
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.274
upper limit	0.385
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[119] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 5/5 µg
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority[120]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.115
upper limit	0.225
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[120] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (274) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[121]
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	0.066
upper limit	0.176
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[121] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus placebo.

Comparison groups	Placebo v T+O 2.5/5 µg
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority[122]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.307
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.251
upper limit	0.363
Variability estimate	Standard error of the mean
Dispersion value	0.029

Notes:

[122] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (267) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[123]
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	0.092
upper limit	0.203
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[123] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[124]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.166
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.111
upper limit	0.222
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[124] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 2.5/5 µg

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[125]
P-value	= 0.0005
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.043
upper limit	0.154
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[125] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

Secondary: Peak (0-3h) FVC Response [L] After 6 Weeks Treatment

End point title	Peak (0-3h) FVC Response [L] After 6 Weeks Treatment

End point description:

Peak (0-3h) Forced Vital Capacity (FVC) responses.
Peak was defined as the maximum value measured within the first 3 h post dosing and response was defined as the change from patient baseline.
PFT time schedule:
At Visits 2, 4, 6, 8: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2 and 3 h post-dose.
At Visits 3, 5, 7, 9: pre-dose PFT: 30 mins prior to inhalation of dose of study medication; post-dose PFT: 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 h and 23h 50 min post-dose.

End point type	Secondary

End point timeframe:

baseline and after 6 weeks (details in description)

End point values	Placebo	Olo 5 µg	Tio 2.5 µg	Tio 5 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	135[126]	138[127]	136[128]	137[129]
Units: litre(s)				
least squares mean (standard error)	0.159 (± 0.029)	0.463 (± 0.029)	0.45 (± 0.029)	0.47 (± 0.029)

Notes:

[126] - FAS

[127] - FAS

[128] - FAS

[129] - FAS

End point values	T+O 2.5/5 µg	T+O 5/5 µg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135[130]	138[131]		
Units: litre(s)				
least squares mean (standard error)	0.612 (±	0.621 (±		

	0.029)	0.028)

Notes:

[130] - FAS

[131] - FAS

Statistical analyses

Statistical analysis title	T+O 5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Placebo.

Comparison groups	Placebo v T+O 5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[132]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.462
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.408
upper limit	0.516
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[132] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 5/5 µg
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority[133]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.159

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.105
upper limit	0.212
Variability estimate	Standard error of the mean
Dispersion value	0.027

Notes:

[133] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (276) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 5/5 µg
Number of subjects included in analysis	275
Analysis specification	Pre-specified
Analysis type	superiority[134]
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	0.098
upper limit	0.205
Variability estimate	Standard error of the mean
Dispersion value	0.027

Notes:

[134] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (275) does not reflect the actual number.

Statistical analysis title	T+O 2.5/5 vs placebo

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus placebo.

Comparison groups	Placebo v T+O 2.5/5 µg

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[135]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.452
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.398
upper limit	0.507
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[135] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (270) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Olo 5.

Comparison groups	Olo 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	superiority[136]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.149
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.095
upper limit	0.203
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[136] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (273) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of

denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 2.5.

Comparison groups	Tio 2.5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority[137]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.161
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.107
upper limit	0.216
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[137] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (271) does not reflect the actual number.

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

Statistical analysis description:

The adjusted mean (SE) are obtained from fitting a mixed effect model repeated measures (MMRM) including fixed
effects of treatment and period; period baseline and patient baseline as covariates; patient as a random effect;
compound symmetry covariance structure for within−patient variation and Kenward−Roger approximation of
denominator degrees of freedom.
The adjusted mean difference is calculated as T+O 2.5/5 minus Tio 5.

Comparison groups	Tio 5 µg v T+O 2.5/5 µg
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[138]
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	0.087
upper limit	0.196
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[138] - The actual number of subjects analyzed is 219. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (272) does not reflect the actual number.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From drug administration until 21 days after the last administration, up to 92 days.	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo matching Tiotropium+Olodaterol fixed dose combination (FDC) solution for inhalation - RESPIMAT: 2 Oral inhalations once daily in the morning for 6 weeks.	
Reporting group title	Olodaterol (5 µg)
Reporting group description:	
Olodaterol solution for inhalation - RESPIMAT: 2 oral inhalations once daily in the morning for 6 weeks.	
Reporting group title	Tiotropium (2.5 µg)
Reporting group description:	
Tiotropium solution for inhalation - RESPIMAT : 2 oral inhalations once daily in the morning for 6 weeks.	
Reporting group title	Tiotropium (5 µg)
Reporting group description:	
Tiotropium solution for inhalation - RESPIMAT : 2 oral inhalations once daily in the morning for 6 weeks.	
Reporting group title	Tiotropium+Olodaterol FDC (2.5/5 µg)
Reporting group description:	
Tiotropium + Olodaterol fixed dose combination (FDC) solution for inhalation - RESPIMAT: 2 oral inhalations once daily in the morning for 6 weeks.	
Reporting group title	Tiotropium+Olodaterol FDC (5/5 µg)
Reporting group description:	
Tiotropium + Olodaterol fixed dose combination (FDC) solution for inhalation - RESPIMAT: 2 oral inhalations once daily in the morning for 6 weeks.	

Serious adverse events	Placebo	Olodaterol (5 µg)	Tiotropium (2.5 µg)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 138 (2.90%)	8 / 138 (5.80%)	5 / 137 (3.65%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rectal cancer			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (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 disorder			
subjects affected / exposed	0 / 138 (0.00%)	1 / 138 (0.72%)	0 / 137 (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
Arterial occlusive disease			
subjects affected / exposed	0 / 138 (0.00%)	2 / 138 (1.45%)	0 / 137 (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
Peripheral artery aneurysm			
subjects affected / exposed	0 / 138 (0.00%)	1 / 138 (0.72%)	0 / 137 (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 artery thrombosis			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	0 / 138 (0.00%)	1 / 138 (0.72%)	0 / 137 (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
Inflammation			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (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

Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 138 (0.00%)	1 / 138 (0.72%)	0 / 137 (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
Food allergy			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (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
Hypersensitivity			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (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, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 138 (1.45%)	2 / 138 (1.45%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 138 (0.00%)	1 / 138 (0.72%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			

subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (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
Comminuted fracture			
subjects affected / exposed	0 / 138 (0.00%)	1 / 138 (0.72%)	0 / 137 (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			
Atrial tachycardia			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 138 (0.00%)	1 / 138 (0.72%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 138 (0.72%)	0 / 138 (0.00%)	0 / 137 (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			
Cerebrovascular accident			
subjects affected / exposed	1 / 138 (0.72%)	1 / 138 (0.72%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Transient ischaemic attack			
subjects affected / exposed	1 / 138 (0.72%)	0 / 138 (0.00%)	0 / 137 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (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			
Renal infarct			
subjects affected / exposed	0 / 138 (0.00%)	1 / 138 (0.72%)	0 / 137 (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			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 138 (0.00%)	1 / 138 (0.72%)	0 / 137 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 138 (1.45%)	0 / 138 (0.00%)	1 / 137 (0.73%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingitis			
subjects affected / exposed	0 / 138 (0.00%)	0 / 138 (0.00%)	0 / 137 (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

Serious adverse events	Tiotropium (5 µg)	Tiotropium+Olodaterol FDC (2.5/5 µg)	Tiotropium+Olodaterol FDC (5/5 µg)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 138 (2.17%)	4 / 136 (2.94%)	1 / 139 (0.72%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	0 / 138 (0.00%)	1 / 136 (0.74%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial disorder			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (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
Arterial occlusive disease			
subjects affected / exposed	0 / 138 (0.00%)	1 / 136 (0.74%)	0 / 139 (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 artery aneurysm			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (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			
Impaired healing			

subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (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
Inflammation			
subjects affected / exposed	0 / 138 (0.00%)	1 / 136 (0.74%)	0 / 139 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 138 (0.72%)	0 / 136 (0.00%)	0 / 139 (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
Food allergy			
subjects affected / exposed	1 / 138 (0.72%)	0 / 136 (0.00%)	0 / 139 (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
Hypersensitivity			
subjects affected / exposed	1 / 138 (0.72%)	0 / 136 (0.00%)	0 / 139 (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			
Ovarian cyst			
subjects affected / exposed	0 / 138 (0.00%)	1 / 136 (0.74%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 138 (0.72%)	0 / 136 (0.00%)	0 / 139 (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
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	1 / 139 (0.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (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	1 / 138 (0.72%)	0 / 136 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 138 (0.72%)	0 / 136 (0.00%)	0 / 139 (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			
Arthropod bite			
subjects affected / exposed	1 / 138 (0.72%)	0 / 136 (0.00%)	0 / 139 (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
Comminuted fracture			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (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 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myocardial ischaemia			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (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			
Dermatitis allergic			
subjects affected / exposed	1 / 138 (0.72%)	0 / 136 (0.00%)	0 / 139 (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 and urinary disorders			
Renal infarct			
subjects affected / exposed	0 / 138 (0.00%)	0 / 136 (0.00%)	0 / 139 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 138 (0.72%)	0 / 136 (0.00%)	0 / 139 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 138 (0.72%)	0 / 136 (0.00%)	0 / 139 (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
Salpingitis			

subjects affected / exposed	0 / 138 (0.00%)	1 / 136 (0.74%)	0 / 139 (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

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

Non-serious adverse events	Placebo	Olodaterol (5 µg)	Tiotropium (2.5 µg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 138 (30.43%)	21 / 138 (15.22%)	30 / 137 (21.90%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	15 / 138 (10.87%)	5 / 138 (3.62%)	13 / 137 (9.49%)
occurrences (all)	16	5	14
Cough			
subjects affected / exposed	7 / 138 (5.07%)	2 / 138 (1.45%)	3 / 137 (2.19%)
occurrences (all)	7	3	3
Dyspnoea			
subjects affected / exposed	9 / 138 (6.52%)	3 / 138 (2.17%)	4 / 137 (2.92%)
occurrences (all)	9	3	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 138 (10.14%)	12 / 138 (8.70%)	12 / 137 (8.76%)
occurrences (all)	14	12	12

Non-serious adverse events	Tiotropium (5 µg)	Tiotropium+Olodaterol FDC (2.5/5 µg)	Tiotropium+Olodaterol FDC (5/5 µg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 138 (21.01%)	23 / 136 (16.91%)	25 / 139 (17.99%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	12 / 138 (8.70%)	8 / 136 (5.88%)	9 / 139 (6.47%)
occurrences (all)	12	8	9
Cough			
subjects affected / exposed	6 / 138 (4.35%)	2 / 136 (1.47%)	7 / 139 (5.04%)
occurrences (all)	6	2	7
Dyspnoea			

subjects affected / exposed occurrences (all)	3 / 138 (2.17%) 3	1 / 136 (0.74%) 1	2 / 139 (1.44%) 2
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	12 / 138 (8.70%) 12	12 / 136 (8.82%) 12	9 / 139 (6.47%) 10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 March 2012	Additional guidance was provided regarding individual withdrawal criteria, and regarding medication restrictions. It was specified that adjudication was to be carried out for all SAEs (rather than only fatal events), and that clinically significant laboratory values were to be entered as AEs. Modifications were introduced regarding the time points of vital sign acquisition and regarding the pre-dose time window for PFT measurements. Administrative changes, corrections, and further clarifications were introduced.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported