Online supplementary material

Methods

Patients

Patients were not permitted to take long-acting β_2-agonists or long-acting muscarinic antagonists (other than study medication) during the baseline, treatment and washout periods. Short-acting muscarinic antagonists were not allowed during the treatment periods but were permitted during baseline and washout periods (with an 8-h washout prior to assessments). Patients continued with inhaled corticosteroids if taken at baseline. Open-label salbutamol (albuterol) was provided as rescue medication throughout the study.

End points

The slope of breathing discomfort was used as a secondary end point instead of isotime due to the incomplete-crossover design of the study. Inspiratory capacity (IC) and intensity of breathing discomfort at isotime were originally planned to be determined for the primary (in addition to exercise endurance time [EET] during constant work-rate cycle ergometry [CWRCE] to symptom limitation at 75% of peak work rate) and key secondary end points but were subsequently moved to further end points prior to database lock.

Post hoc analyses

We performed the following *post hoc* analyses to identify a subgroup in which treatment responses to tiotropium/olodaterol were superior to tiotropium alone: IC and EET in subgroups defined by Global initiative for chronic Obstructive Lung Disease

stage (1/2 and 3/4); EET in subgroups by quartiles of percent predicted IC and IC (<80% predicted and ≥80% predicted); EET by locus of symptom limitation at baseline; IC and EET in subgroups defined by static hyperinflation and either static hyperinflation and/or dynamic hyperinflation. Static hyperinflation was defined as functional residual capacity (FRC) >120% predicted (comparisons of subgroups for FRC <120% predicted and FRC ≥120% predicted were performed). Dynamic hyperinflation was defined as end-exercise IC minus pre-exercise IC value of >100 mL. To be included in the analysis, patients were required to have an FRC ≥120% predicted or dynamic hyperinflation (or both).

Finally, we also compared demographics and baseline characteristics in patient subgroups defined according to whether EET treatment responses were superior to, or shorter than/equal to, tiotropium/olodaterol *versus* monotherapy. Due to the incomplete crossover design of the trial, these analyses were performed only for those patients who received both tiotropium/olodaterol 5/5 µg and tiotropium 5 µg.

These analyses did not identify any specific subgroup of patients exhibiting greater improvements in EET with tiotropium/olodaterol *versus* monotherapy.

Other assessments

Spirometry (forced expiratory volume in 1 s [FEV_1], forced vital capacity [FVC]) was conducted 30 min prior to dosing and 1 h post-dose at the randomisation visit and after 6 weeks of treatment. Safety was assessed via adverse events (AEs) recorded throughout the trial, and vital signs, blood chemistry and electrocardiogram were recorded at the end of each treatment period.

Statistical analysis

Standard deviation for within-patient treatment difference of log_{10} endurance time was ~0.181 s for patients with chronic obstructive pulmonary disease (COPD) in a similar crossover trial that assessed the effects of tiotropium 18 µg once daily and salmeterol 50 µg twice daily versus twice-daily fluticasone/salmeterol (500/50 µg) on static lung volumes and exercise tolerance (EudraCT 2006-004086-33). Using this standard deviation, it was estimated that a sample size of 203 patients would detect a treatment difference of 10% with 90% power at the 5% significance level for the primary end point of EET (log_{10} transformed) during CWRCE. This sample size would also detect a treatment difference of 0.1 L with ≥90% power at the 5% significance level for the primary end point of IC based on a standard deviation value of 0.42 from trial NCT01040130 for both studies [1].

Results

Spirometry

In both studies, FEV_1 and FVC (1 h post-dose) significantly increased after 6 weeks with both doses of tiotropium/olodaterol compared to placebo and monocomponents (tables S4 and S5). FEV_1 increased by 286–329 mL with tiotropium/olodaterol *versus* placebo and 77–135 mL *versus* monotherapies across both studies. FVC treatment differences were slightly larger in MORACTO® 2 than in MORACTO® 1: increases were >300 mL for both doses of tiotropium/olodaterol *versus* placebo in MORACTO® 1 and >450 mL in MORACTO® 2. Compared to monotherapies, tiotropium/olodaterol increased FVC by >100 mL in MORACTO® 1 and >140 mL in MORACTO® 2. Trough FEV_1 significantly increased by 167–208 mL with

tiotropium/olodaterol *versus* placebo and 28–93 mL *versus* monotherapies in MORACTO® 1, although differences for tiotropium/olodaterol *versus* tiotropium 5 µg were only significant at the tiotropium/olodaterol 5/5 µg dose. In MORACTO® 2, trough FEV_1 increased with tiotropium/olodaterol by 168–205 mL *versus* placebo and >70 mL *versus* olodaterol 5 µg (tables S4 and S5). Trough FVC significantly increased with tiotropium/olodaterol 2.5/5 and 5/5 µg compared to placebo (>250 mL) and olodaterol 5 µg (>100 mL) in both studies. In both studies, tiotropium/olodaterol 5/5 µg but not 2.5/5 µg significantly improved trough FVC compared to tiotropium 5 µg (tables S4 and S5).

AEs

The majority of AEs were mild to moderate in intensity, with severe AEs reported in 8.2% of patients overall (table S6). The most common AE was COPD worsening, with incidences of 6.3%, 9.3%, 9.2%, 9.4% and 10.3% of patients receiving tiotropium/olodaterol 2.5/5 and 5/5 µg, tiotropium 5 µg, olodaterol 5 µg and placebo, respectively. Severe AEs were recorded in 12 patients receiving tiotropium/olodaterol 2.5/5 µg, eight receiving tiotropium/olodaterol 5/5 µg, 16 receiving tiotropium 5 µg, eight receiving olodaterol 5 µg and seven patients in the placebo group. In MORACTO® 1, three serious AEs were considered to be related to the study drug by the investigator: one was reported in the tiotropium/olodaterol 2.5/5 µg group (cardiac pacemaker insertion), one in the tiotropium/olodaterol 5/5 µg group (angina unstable) and one in the placebo group (ventricular extrasystoles). In MORACTO® 2, two serious AEs were considered related by the investigator: one receiving tiotropium/olodaterol 5/5 µg (rash) and one with tiotropium 5 µg (atrial fibrillation).

TABLE S1 Baseline demographics and patient characteristics (treated set) for MORACTO® 1 and 2

	MORACTO® 1 (n=295)	**MORACTO® 2 (n=291)**
Male, n (%)	213 (72.2)	204 (70.1)
Race, n (%)		
Black/African American	7 (2.4)	5 (1.7)
Asian	1 (0.3)	1 (0.3)
White	287 (97.3)	285 (97.9)
Mean (SD) age, years	62.2 (7.5)	61.2 (7.9)
Mean (SD) body mass index, kg/m^2	27.3 (5.3)	26.7 (4.6)
Smoking status, n (%)		
Ex-smoker	181 (61.4)	176 (60.5)
Current smoker	114 (38.6)	115 (39.5)
Mean (SD) smoking history, pack-years	47.3 (22.9)	44.3 (23.3)

Mean (SD) pre-bronchodilator screening		
FEV_1, L	1.54 (0.49)	1.56 (0.50)
% predicted normal FEV_1[#]	52.64 (13.87)	52.05 (13.42)
Mean (SD) post-bronchodilator screening		
FEV_1, L	1.71 (0.48)	1.73 (0.51)
% predicted normal FEV_1[#]	58.59 (12.90)	57.70 (13.17)
Mean (SD) FEV_1 change from pre-bronchodilator, L	0.17 (0.16)	0.17 (0.16)
GOLD stage, n (%)		
1 (≥80% of predicted normal FEV_1)	0 (0.0)	1 (0.3)
2 (50–<80% of predicted normal FEV_1)	215 (72.9)	201 (69.1)
3 (30–<50% of predicted normal FEV_1)	78 (26.4)	86 (29.6)
4 (<30% of predicted normal FEV_1)	2 (0.7)	3 (1.0)
Mean (SD) IC pre-exercise, L	2.535 (0.713)	2.596 (0.737)
% predicted IC	70.0 (29.6)	70.4 (30.6)
Mean (SD) endurance time,[¶] s	520.4 (263.3)	502.8 (275.5)

Locus of symptom limitation at end-exercise, n (%)		
Breathing/leg discomfort	129 (43.7)	106 (36.4)
Breathing discomfort	99 (33.6)	108 (37.1)
Leg discomfort	54 (18.3)	68 (23.4)
Mean (SD) breathing discomfort at end-exercise, Borg scale	6.71 (2.56)	6.62 (2.27)
Mean (SD) leg discomfort at end-exercise, Borg units	6.61 (2.69)	6.28 (2.56)

SD: standard deviation; FEV_1: forced expiratory volume in 1 s; GOLD: Global initiative for chronic Obstructive Lung Disease; IC: inspiratory capacity. [#]: based on predicted values defined by the European Community for Steel and Coal [2]; [¶]: arithmetic mean (not log transformed).

TABLE S2 Adjusted mean[#] IC pre-exercise: treatment comparisons after 6 weeks of treatment for MORACTO® 1 and 2 (full analysis set)

Treatment comparison	**Adjusted mean (SE) IC, L**	**95% CI**	**p value**
MORACTO® 1			
Common baseline mean	2.533 (0.042)		
Tiotropium/olodaterol 2.5/5 µg			
versus placebo	0.218 (0.027)	0.164, 0.271	<0.0001[¶]
versus olodaterol 5 µg	0.092 (0.027)	0.038, 0.145	0.0008
versus tiotropium 5 µg	0.087 (0.027)	0.034, 0.141	0.0015[¶]
Tiotropium/olodaterol 5/5 µg			
versus placebo	0.244 (0.027)	0.191, 0.298	<0.0001
versus olodaterol 5 µg	0.119 (0.027)	0.065, 0.172	<0.0001
versus tiotropium 5 µg	0.114 (0.027)	0.061, 0.167	<0.0001

MORACTO® 2			
Common baseline mean	2.589 (0.044)		
Tiotropium/olodaterol 2.5/5 µg			
versus placebo	0.274 (0.025)	0.224, 0.324	<0.0001¶
versus olodaterol 5 µg	0.089 (0.025)	0.039, 0.138	0.0004¶
versus tiotropium 5 µg	0.097 (0.025)	0.047, 0.147	0.0001¶
Tiotropium/olodaterol 5/5 µg			
versus placebo	0.265 (0.025)	0.215, 0.315	<0.0001
versus olodaterol 5 µg	0.080 (0.025)	0.031, 0.129	0.0015
versus tiotropium 5 µg	0.088 (0.025)	0.039, 0.137	0.0005

IC: inspiratory capacity; SE: standard error; CI: confidence interval. #: adjusted mean difference obtained from mixed-effects model repeated measures approach with fixed effects of treatment and period, study baseline as covariate, patient as a random effect and compound symmetry as a covariance structure for within-patient variation; ¶: nominal p value.

TABLE S3 Adjusted mean[#] Borg-time slope of the intensity of breathing discomfort (modified Borg scale) during exercise and breathing discomfort (Borg scale) at isotime after 6 weeks of treatment (full analysis set)

	MORACTO® 1				**MORACTO® 2**			
	Patients, n	**Adjusted mean (SE) Borg-time slope, units/s**	**Patients, n**	**Adjusted mean (SE) Borg scale**	**Patients, n**	**Adjusted mean (SE) Borg-time slope, units/s**	**Patients, n**	**Adjusted mean (SE) Borg scale**
Placebo	209	0.018 (0.001)	209	5.19 (0.14)	205	0.018 (0.001)	206	5.08 (0.14)
O 5 µg	208	0.016 (0.001)	208	4.35 (0.14)	207	0.017 (0.001)	207	4.94 (0.14)
T 5 µg	209	0.016 (0.001)	209	4.49 (0.14)	208	0.015 (0.001)	209	4.56 (0.13)
T/O 2.5/5 µg	212	0.015 (0.001)	212	4.33 (0.14)	212	0.014 (0.001)	213	4.47 (0.13)
T/O 5/5 µg	212	0.016 (0.001)	212	4.50 (0.14)	216	0.015 (0.001)	216	4.39 (0.13)

SE: standard error; O: olodaterol; T: tiotropium. [#]: adjusted mean obtained from mixed-effects model repeated measures approach with fixed effects of treatment and period, study baseline as covariate, patient as a random effect and compound symmetry as a covariance structure for within-patient variation.

TABLE S4 Adjusted mean[#] FEV_1 and FVC 1 h post-dose, trough FEV_1 and FVC[¶] after 6 weeks of treatment for MORACTO® 1 and 2 (full analysis set)

	Patients, n	**Adjusted mean (SE) FEV_1, L**	**Patients, n**	**Adjusted mean (SE) FVC, L**	**Patients, n**	**Adjusted mean (SE) trough FEV_1, L**	**Patients, n**	**Adjusted mean (SE) trough FVC, L**
MORACTO® 1								
Placebo	216	1.497 (0.013)	220	3.009 (0.023)	216	1.461 (0.012)	216	2.926 (0.020)
O 5 µg	214	1.689 (0.013)	216	3.240 (0.023)	213	1.575 (0.012)	213	3.063 (0.020)
T 5 µg	218	1.706 (0.013)	223	3.275 (0.023)	217	1.600 (0.012)	217	3.144 (0.020)
T/O 2.5/5 µg	216	1.783 (0.013)	221	3.390 (0.023)	216	1.628 (0.012)	216	3.180 (0.020)
T/O 5/5 µg	224	1.820 (0.013)	225	3.420 (0.023)	224	1.669 (0.012)	224	3.233 (0.020)
MORACTO® 2								
Placebo	210	1.548 (0.016)	210	3.115 (0.026)	210	1.516 (0.014)	210	3.079 (0.024)
O 5 µg	215	1.742 (0.016)	215	3.397 (0.026)	214	1.611 (0.014)	214	3.243 (0.024)

T 5 µg	211	1.741 (0.016)	211	3.427 (0.026)	211	1.640 (0.014)	211	3.296 (0.024)
T/O 2.5/5 µg	215	1.852 (0.016)	215	3.567 (0.026)	215	1.684 (0.014)	215	3.349 (0.024)
T/O 5/5 µg	219	1.876 (0.016)	219	3.589 (0.025)	218	1.721 (0.014)	218	3.386 (0.023)

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SE: standard error; O: olodaterol; T: tiotropium. [#]: adjusted mean difference obtained from mixed-effects model repeated measures approach with fixed effects of treatment and period, period baseline and patient baseline as covariates, patient as a random effect, compound symmetry as a covariance structure for within-patient variation and Kenward–Roger approximation of denominator degrees of freedom; [¶]: 30 min pre-dose.

TABLE S5 Adjusted mean FEV_1 and FVC 1 h post-dose, trough FEV_1 and FVC[#] after 6 weeks of treatment for MORACTO® 1 and 2: treatment differences (full analysis set)

Treatment comparison	**Adjusted mean (SE) FEV_1, mL**	**95% CI**	**Adjusted mean (SE) FVC, mL**	**95% CI**	**Adjusted mean (SE) trough FEV_1, mL**	**95% CI**	**Adjusted mean (SE) trough FVC, mL**	**95% CI**
MORACTO® 1								
Common baseline mean	1497 (29)		2985 (46)					
T/O 2.5/5 µg								
versus placebo	286 (15)***	256, 315	381 (26)***	331, 431	167 (15)***	139, 196	254 (25)***	205, 304
versus O 5 µg	93 (15)***	63, 123	149 (26)***	99, 200	52 (15)**	24, 81	117 (25)***	67, 167
versus T 5 µg	77 (15)***	47, 106	115 (26)***	65, 165	28 (15)	-1, 56	36 (25)	-13, 86
T/O 5/5 µg								
versus placebo	323 (15)***	293, 352	411 (25)***	361, 461	208 (14)***	180, 236	307 (25)***	258, 356
versus O 5 µg	130 (15)***	101, 160	179 (26)***	129, 230	93 (14)***	65, 122	170 (25)***	120, 219

versus T 5 µg	114 (15)***	84, 143	145 (25)***	95, 195	68 (14)***	40, 97	89 (25)**	40, 138
MORACTO® 2								
Common baseline mean	1528 (31)		3130 (51)					
T/O 2.5/5 µg								
versus placebo	305 (18)***	269, 340	452 (30)***	394, 510	168 (18)***	133, 202	271 (29)***	214, 327
versus O 5 µg	110 (18)***	75, 145	170 (30)***	112, 227	73 (18)***	38, 107	107 (29)**	50, 163
versus T 5 µg	111 (18)***	76, 146	140 (30)***	82, 198	44 (18)*	10, 79	53 (29)	-3, 110
T/O 5/5 µg								
versus placebo	329 (18)***	294, 364	475 (29)***	417, 532	205 (18)***	170, 239	307 (29)***	251, 364
versus O 5 µg	134 (18)***	99, 169	192 (29)***	135, 250	110 (17)***	75, 144	143 (29)***	87, 199
versus T 5 µg	135 (18)***	100, 170	163 (29)***	105, 221	81 (18)***	47, 115	90 (29)**	34, 146

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; SE: standard error; CI: confidence interval; T: tiotropium; O: olodaterol. [#]: 30 min pre-dose. ***p<0.0001; **p<0.001; *p<0.05.

TABLE S6 Combined data: summary of AEs (treated set)

	Placebo, n (%) (n=436)	**Olodaterol 5 µg, n (%) (n=435)**	**Tiotropium 5 µg, n (%) (n=444)**	**Tiotropium/ olodaterol 2.5/5 µg, n (%) (n=441)**	**Tiotropium/ olodaterol 5/5 µg, n (%) (n=450)**
Any AE	178 (40.8)	175 (40.2)	170 (38.3)	160 (36.3)	180 (40.0)
Severe AEs	7 (1.6)	8 (1.8)	16 (3.6)	8 (1.8)	12 (2.7)
Drug related[#]	21 (4.8)	8 (1.8)	14 (3.2)	13 (2.9)	17 (3.8)
AEs leading to discontinuation	10 (2.3)	6 (1.4)	6 (1.4)	4 (0.9)	7 (1.6)
AEs with an incidence >3%					
COPD	45 (10.3)	41 (9.4)	41 (9.2)	28 (6.3)	42 (9.3)
Nasopharyngitis	20 (4.6)	23 (5.3)	16 (3.6)	24 (5.4)	24 (5.3)
Dyspnoea	19 (4.4)	12 (2.8)	14 (3.2)	14 (3.2)	11 (2.4)
Cough	17 (3.9)	11 (2.5)	16 (3.6)	7 (1.6)	7 (1.6)
Headache	6 (1.4)	7 (1.6)	5 (1.1)	9 (2.0)	10 (2.2)

Back pain	6 (1.4)	10 (2.3)	4 (0.9)	9 (2.0)	5 (1.1)
Influenza	4 (0.9)	4 (0.9)	6 (1.4)	5 (1.1)	5 (1.1)

AE: adverse event; COPD: chronic obstructive pulmonary disease. [#]: investigator determined.

TABLE S7 Adjusted arithmetic mean exercise endurance time during constant work-rate cycle ergometry after 6 weeks of treatment for MORACTO® 1 and 2 (full analysis set)

Treatment	**MORACTO® 1**	**MORACTO® 2**	**Combined studies**
	Mean (SE)	**Mean (SE)**	**Mean (SE)**
Placebo	448.4 (17.6)	493.2 (17.8)	470.6 (12.6)
Olodaterol 5 µg	531.6 (17.6)	510.2 (17.7)	521.1 (12.6)
Tiotropium 5 µg	532.7 (17.6)	539.9 (17.7)	536.2 (12.6)
Tiotropium/olodaterol 2.5/5 µg	557.0 (17.5)	546.8 (17.6)	552.1 (12.5)
Tiotropium/olodaterol 5/5 µg	540.0 (17.5)	567.9 (17.5)	554.5 (12.5)

SE: standard error.

References

1. Maltais F, Kirsten A-M, Hamilton A, De Sousa D, Voß F, Decramer M. Evaluation of the effects of olodaterol on exercise endurance in patients with chronic obstructive pulmonary disease: results from two 6-week crossover studies. *Respir Res* 2016; 17: 77.

2. Quanjer PhH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. *Eur Respir J* 1993; 6 (Suppl 16): 5–40.

FIGURE S1 Hierarchical testing sequence for the primary end points for MORACTO® 1 and 2. IC: inspiratory capacity; EET: exercise endurance time; CWRCE: constant work-rate cycle ergometry.

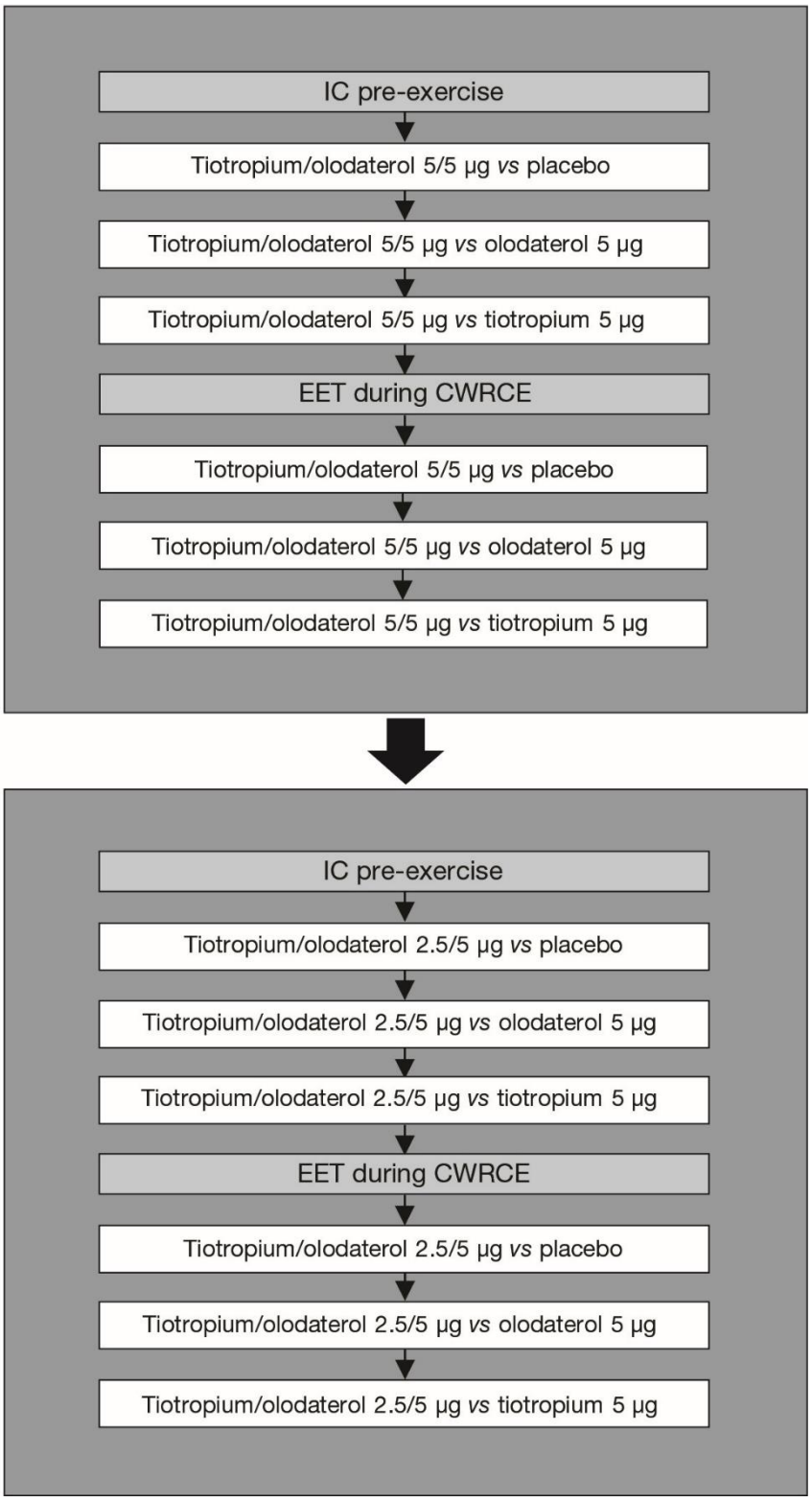
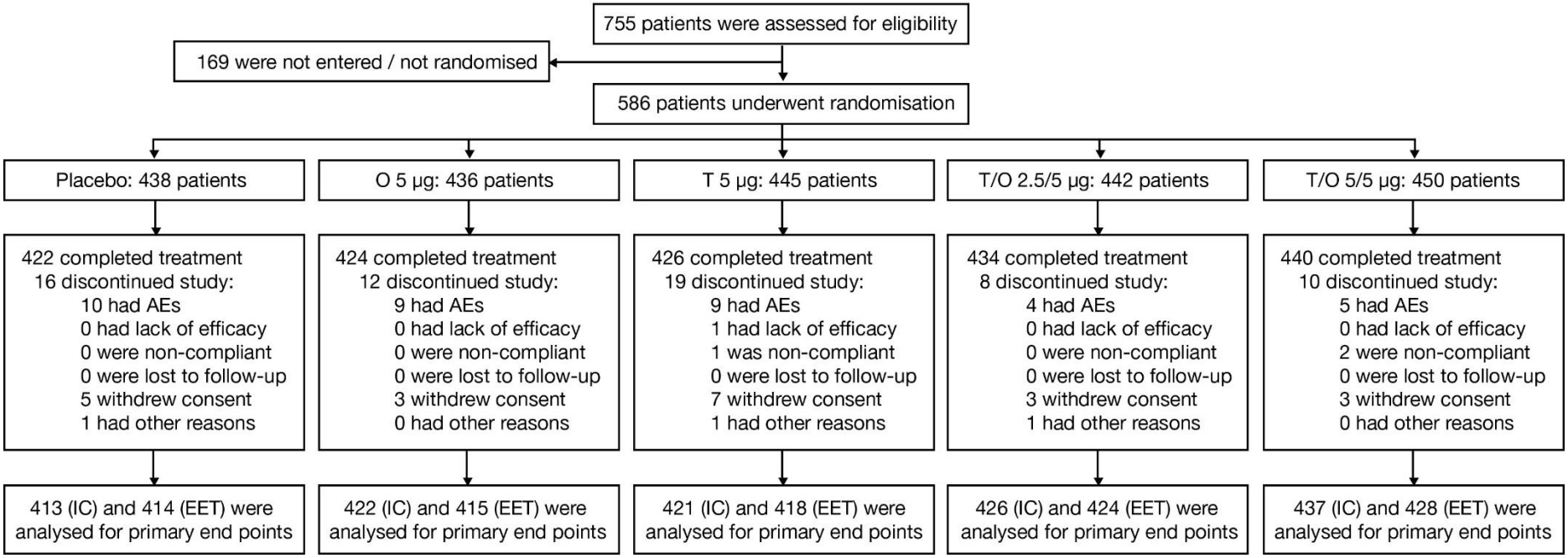
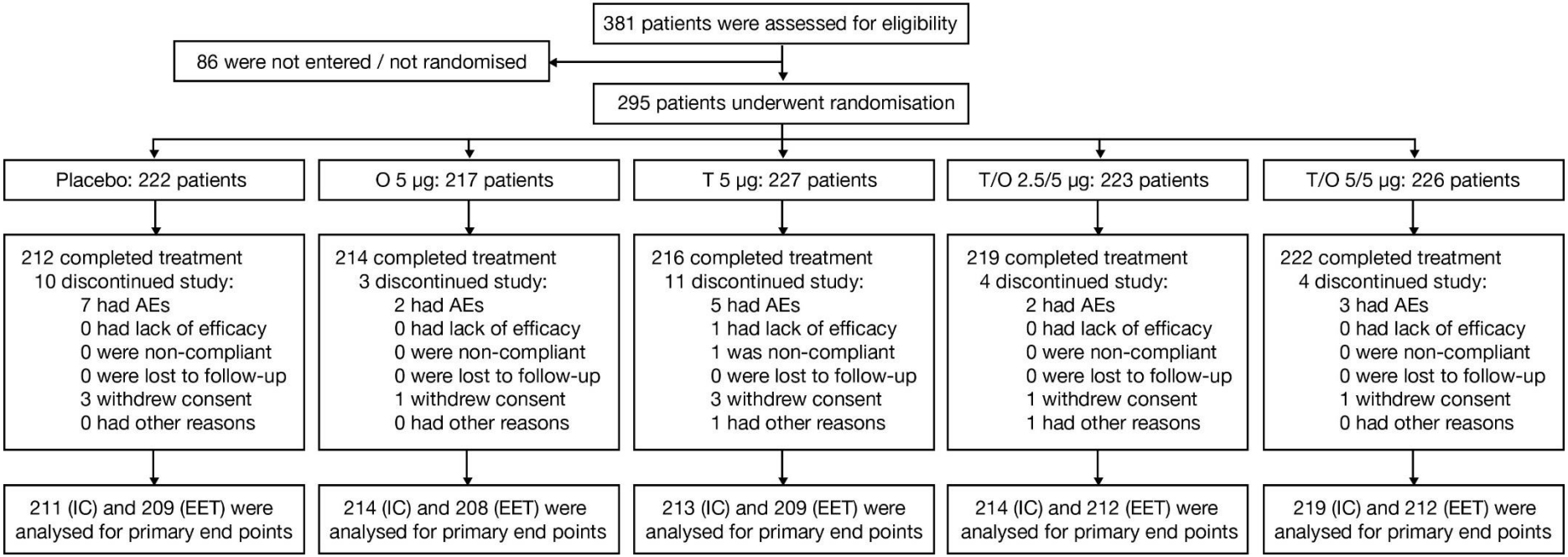


FIGURE S2 Participant flow for (a) combined studies, (b) MORACTO® 1 and (c) MORACTO® 2. O: olodaterol; T: tiotropium; AE: adverse event; IC: inspiratory capacity; EET: exercise endurance time.

a)



b)


381 patients were assessed for eligibility
86 were not entered / not randomised
295 patients underwent randomisation
Placebo: 222 patients
O 5 µg: 217 patients
T 5 µg: 227 patients
T/O 2.5/5 µg: 223 patients
T/O 5/5 µg: 226 patients
212 completed treatment
10 discontinued study:
7 had AEs
0 had lack of efficacy
0 were non-compliant
0 were lost to follow-up
3 withdrew consent
0 had other reasons
214 completed treatment
3 discontinued study:
2 had AEs
0 had lack of efficacy
0 were non-compliant
0 were lost to follow-up
1 withdrew consent
0 had other reasons
216 completed treatment
11 discontinued study:
5 had AEs
1 had lack of efficacy
1 was non-compliant
0 were lost to follow-up
3 withdrew consent
1 had other reasons
219 completed treatment
4 discontinued study:
2 had AEs
0 had lack of efficacy
0 were non-compliant
0 were lost to follow-up
1 withdrew consent
1 had other reasons
222 completed treatment
4 discontinued study:
3 had AEs
0 had lack of efficacy
0 were non-compliant
0 were lost to follow-up
1 withdrew consent
0 had other reasons
211 (IC) and 209 (EET) were analysed for primary end points
214 (IC) and 208 (EET) were analysed for primary end points
213 (IC) and 209 (EET) were analysed for primary end points
214 (IC) and 212 (EET) were analysed for primary end points
219 (IC) and 212 (EET) were analysed for primary end points

c)

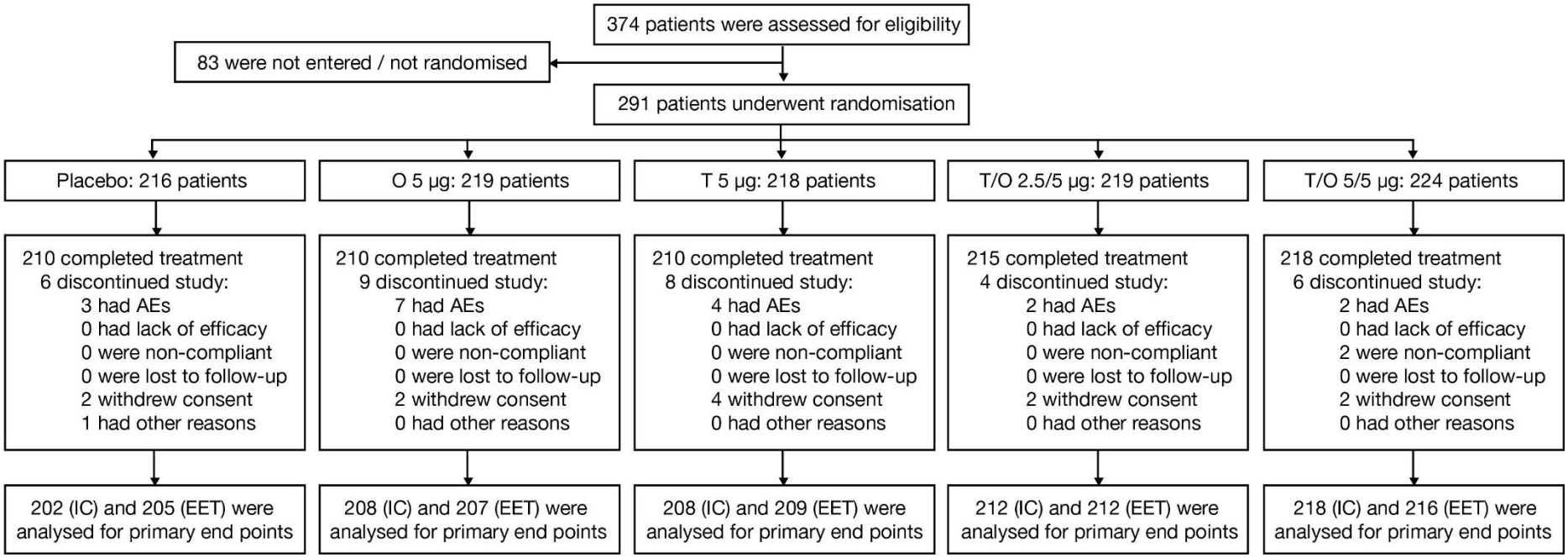
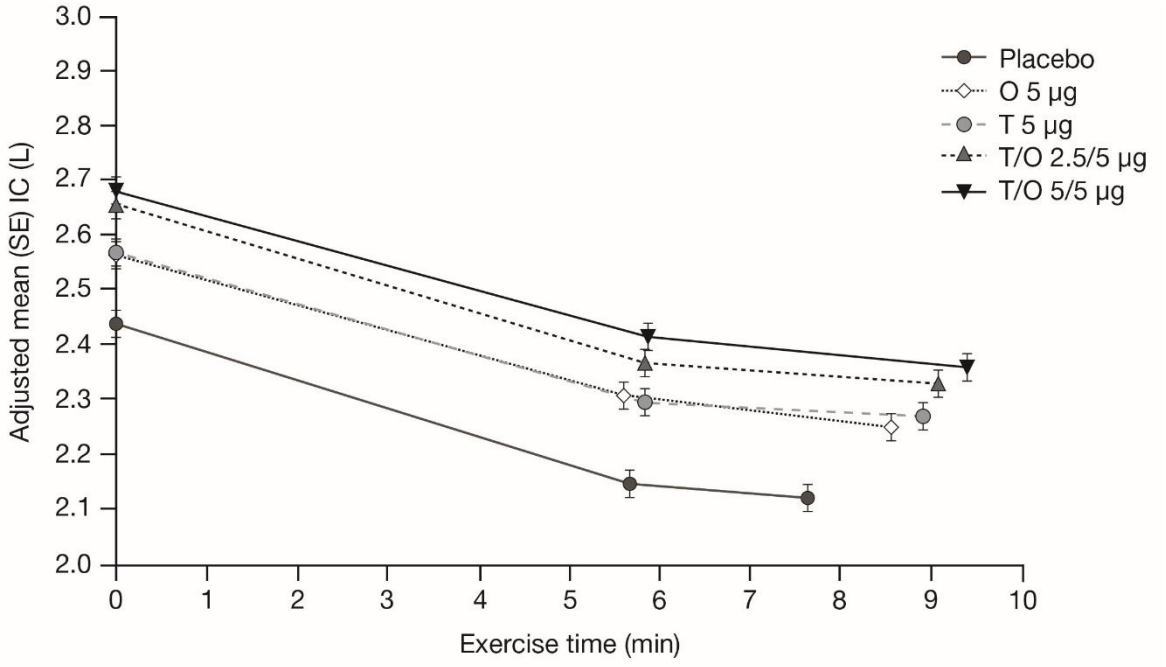

374 patients were assessed for eligibility
83 were not entered / not randomised
291 patients underwent randomisation
Placebo: 216 patients
O 5 µg: 219 patients
T 5 µg: 218 patients
T/O 2.5/5 µg: 219 patients
T/O 5/5 µg: 224 patients
210 completed treatment
6 discontinued study:
3 had AEs
0 had lack of efficacy
0 were non-compliant
0 were lost to follow-up
2 withdrew consent
1 had other reasons
210 completed treatment
9 discontinued study:
7 had AEs
0 had lack of efficacy
0 were non-compliant
0 were lost to follow-up
2 withdrew consent
0 had other reasons
210 completed treatment
8 discontinued study:
4 had AEs
0 had lack of efficacy
0 were non-compliant
0 were lost to follow-up
4 withdrew consent
0 had other reasons
215 completed treatment
4 discontinued study:
2 had AEs
0 had lack of efficacy
0 were non-compliant
0 were lost to follow-up
2 withdrew consent
0 had other reasons
218 completed treatment
6 discontinued study:
2 had AEs
0 had lack of efficacy
2 were non-compliant
0 were lost to follow-up
2 withdrew consent
0 had other reasons
202 (IC) and 205 (EET) were analysed for primary end points
208 (IC) and 207 (EET) were analysed for primary end points
208 (IC) and 209 (EET) were analysed for primary end points
212 (IC) and 212 (EET) were analysed for primary end points
218 (IC) and 216 (EET) were analysed for primary end points

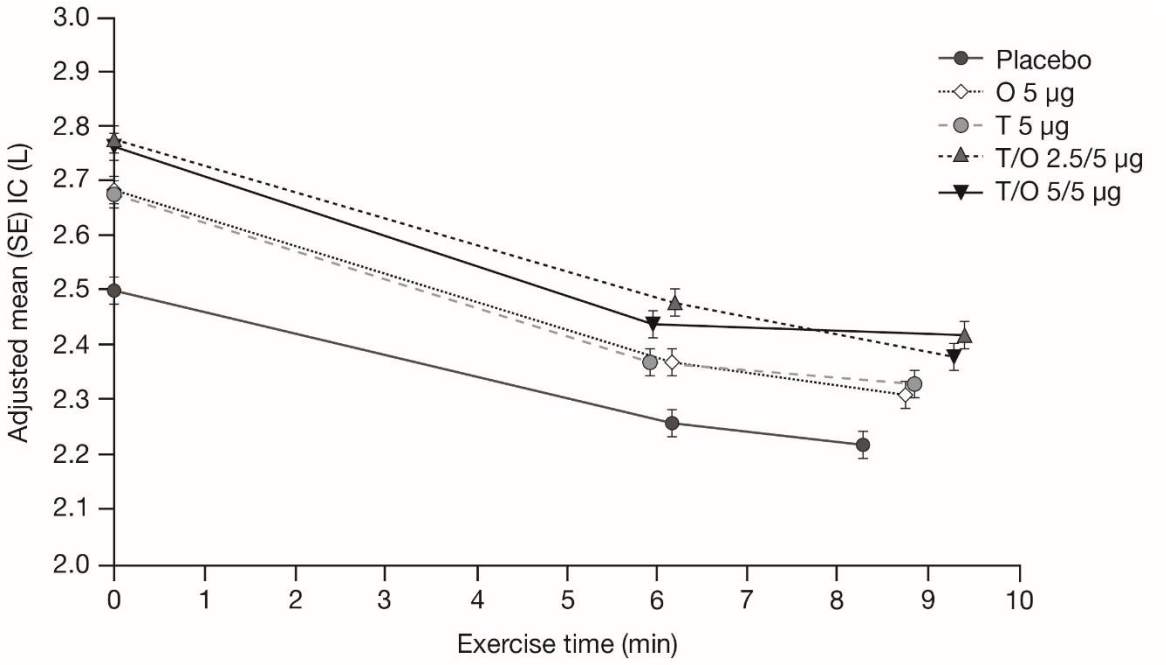
FIGURE S3 Adjusted mean IC pre-exercise, isotime and end-exercise after 6 weeks of treatment for (a) MORACTO® 1 and (b) MORACTO® 2. O: olodaterol; T: tiotropium; SE: standard error; IC: inspiratory capacity.

a)



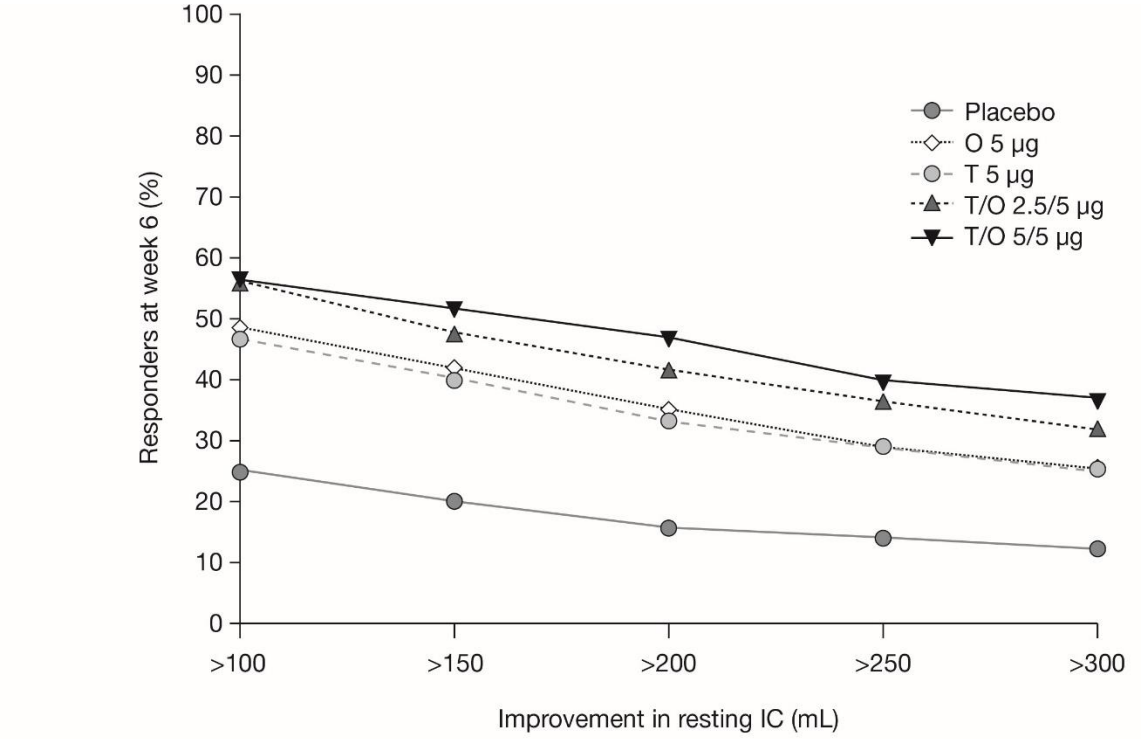
	Pre-exercise	Isotime	End-exercise
T/O 5/5 µg	p<0.0001 *vs* placebo; *vs* T 5 µg; *vs* O 5 µg	p<0.0001 *vs* placebo; *vs* T 5 µg; *vs* O 5 µg	p<0.0001 *vs* placebo; p<0.001 *vs* T 5 µg; *vs* O 5 µg
T/O 2.5/5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* T 5 µg; *vs* O 5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* T 5 µg; *vs* O 5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* T 5 µg; *vs* O 5 µg

b)



	Pre-exercise	Isotime	End-exercise
T/O 5/5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* T 5 µg; *vs* O 5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* T 5 µg; *vs* O 5 µg	p<0.0001 *vs* placebo; p<0.01 *vs* O 5 µg
T/O 2.5/5 µg	p<0.0001 *vs* placebo; p<0.001 *vs* T 5 µg; *vs* O 5 µg	p<0.0001 *vs* placebo; p<0.001 *vs* T 5 µg; *vs* O 5 µg	p<0.0001 *vs* placebo; p<0.001 *vs* T 5 µg; *vs* O 5 µg

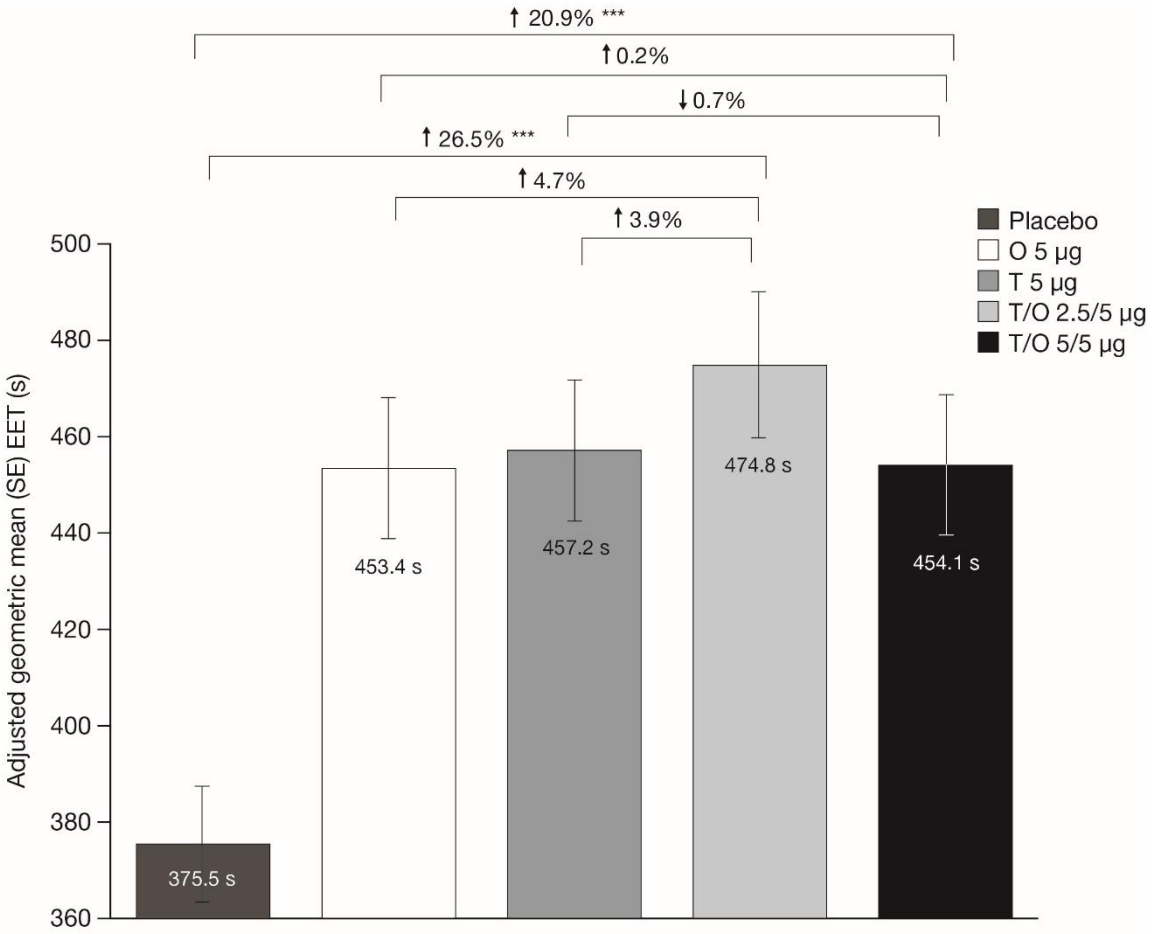
FIGURE S4 Cumulative proportion of responders for improvements in pre-exercise IC after 6 weeks of treatment (combined data). O: olodaterol; T: tiotropium; IC: inspiratory capacity.



	>100 mL IC improvement	>150 mL IC improvement	>200 mL IC improvement	>250 mL IC improvement	>300 mL IC improvement
T/O 5/5 µg	p<0.0001 *vs* placebo; p<0.01 *vs* O 5 µg; p<0.001 *vs* T 5 µg	p<0.0001 *vs* placebo, *vs* T 5 µg; p<0.001 *vs* O 5 µg	p<0.0001 *vs* placebo; *vs* O 5 µg; *vs* T 5 µg	p<0.0001 *vs* placebo; *vs* O 5 µg; *vs* T 5 µg	p<0.0001 *vs* placebo; *vs* O 5 µg; *vs* T 5 µg
T/O 2.5/5 µg	p<0.0001 *vs* placebo; p<0.01 *vs* O 5 µg; p<0.001 *vs* T 5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* O 5 µg; p<0.01 *vs* T 5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* O 5 µg; p<0.01 *vs* T 5 µg	p<0.0001 *vs* placebo; p<0.01 *vs* O 5 µg; *vs* T 5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* O 5 µg; p<0.01 *vs* T 5 µg

FIGURE S5 Adjusted geometric mean EET during constant work-rate cycle ergometry after 6 weeks of treatment for (a) MORACTO® 1 and (b) MORACTO® 2. Data were log_{10} transformed followed by reverse transformation. *p<0.01; **p<0.001; ***p<0.0001. O: olodaterol; T: tiotropium; SE: standard error; EET: exercise endurance time.

a)



b)

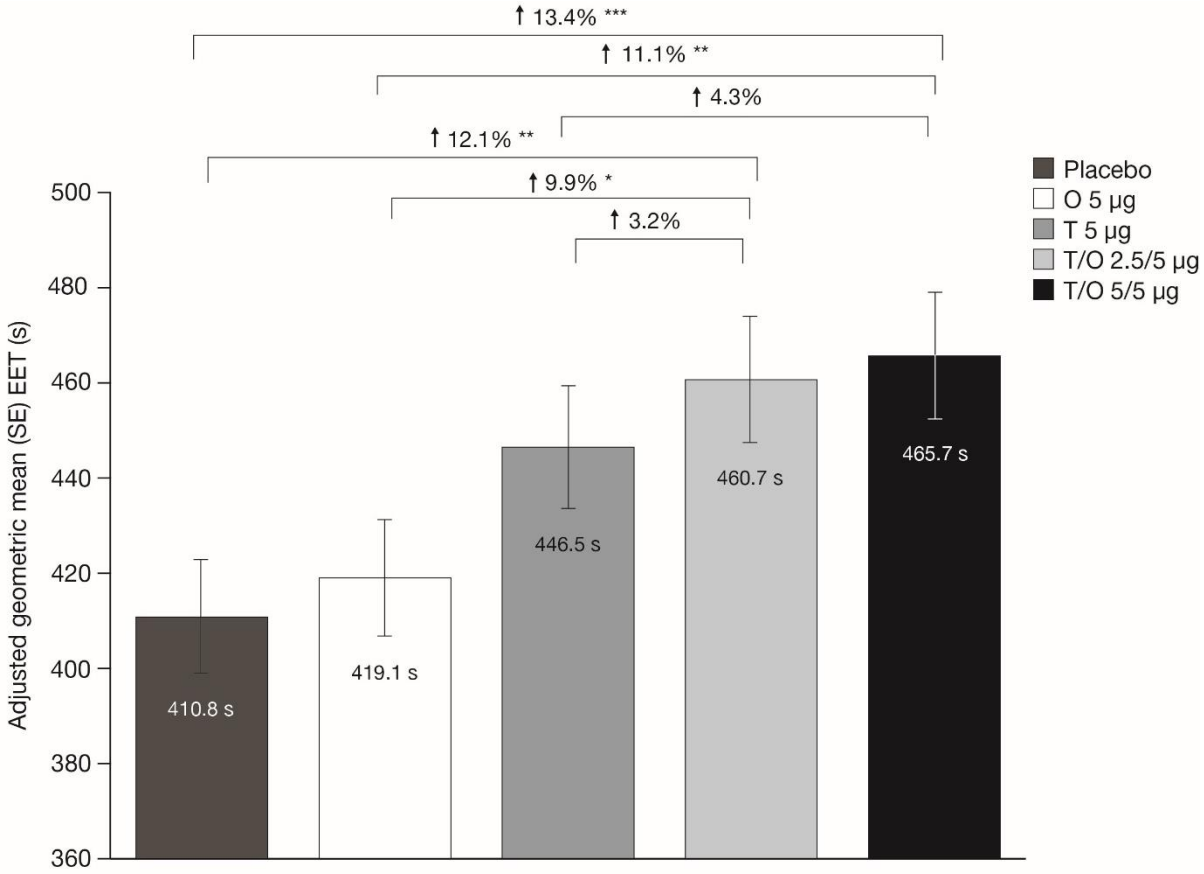
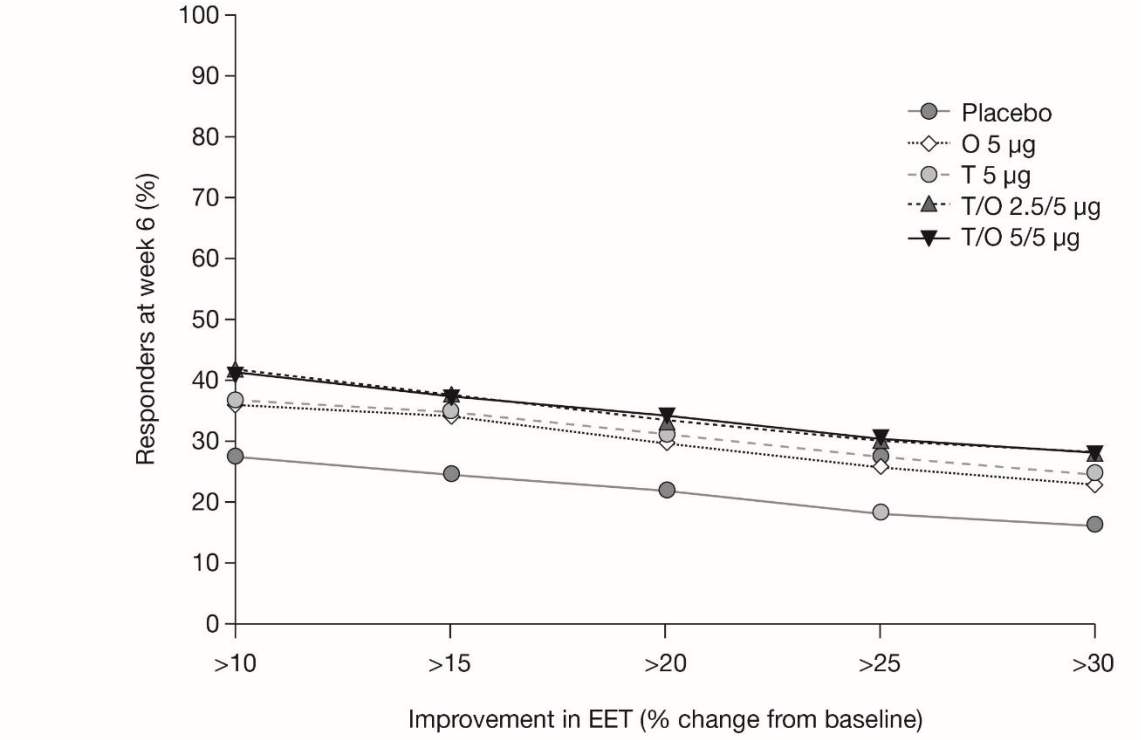

↑ 13.4% ***
↑ 11.1% **
↑ 4.3%
↑ 12.1% **
↑ 9.9% *
↑ 3.2%
Placebo
O 5 µg
T 5 µg
T/O 2.5/5 µg
T/O 5/5 µg
Adjusted geometric mean (SE) EET (s)
500
480
460
440
420
400
380
360
410.8 s
419.1 s
446.5 s
460.7 s
465.7 s

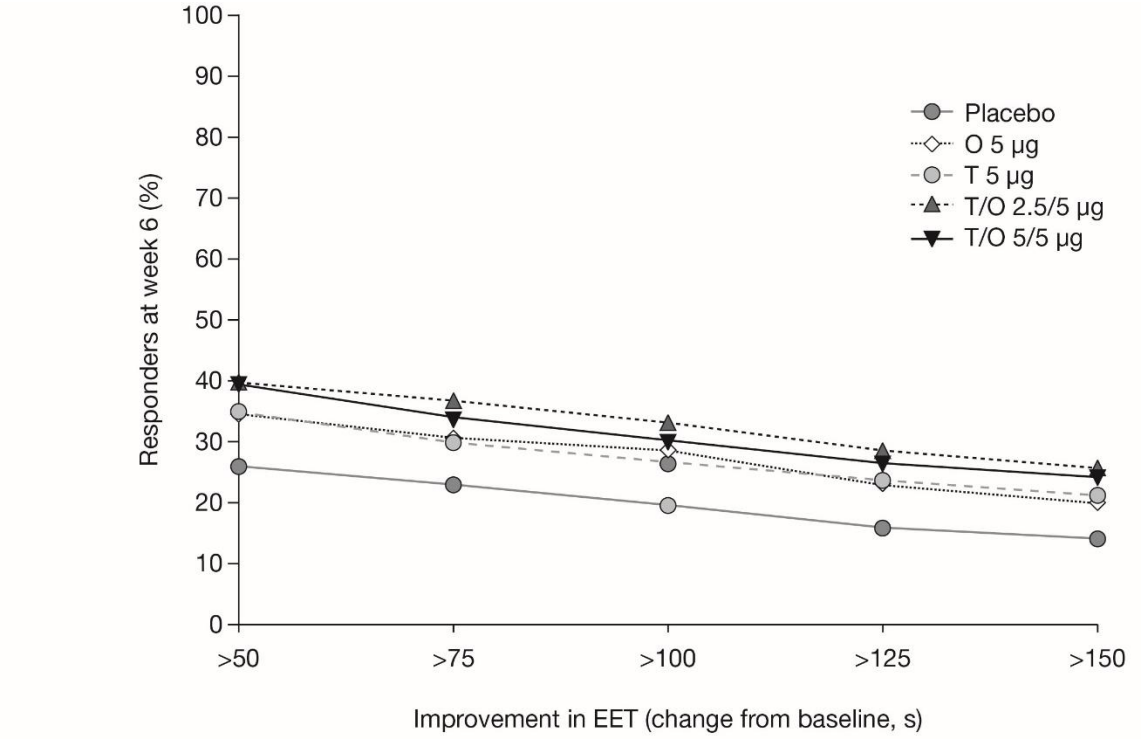
FIGURE S6 Cumulative proportion of responders for improvements in EET during constant work-rate cycle ergometry (percent change from baseline) after 6 weeks of treatment (combined data). O: olodaterol; T: tiotropium; EET: exercise endurance time.



	>10% EET improvement	>15% EET improvement	>20% EET improvement	>25% EET improvement	>30% EET improvement
T/O 5/5 µg	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo; p<0.05 *vs* O 5 µg
T/O 2.5/5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* O 5 µg	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo; p<0.05 *vs* O 5 µg

FIGURE S7 Cumulative proportion of responders for improvements in EET during constant work-rate cycle ergometry after 6 weeks of treatment (combined data).

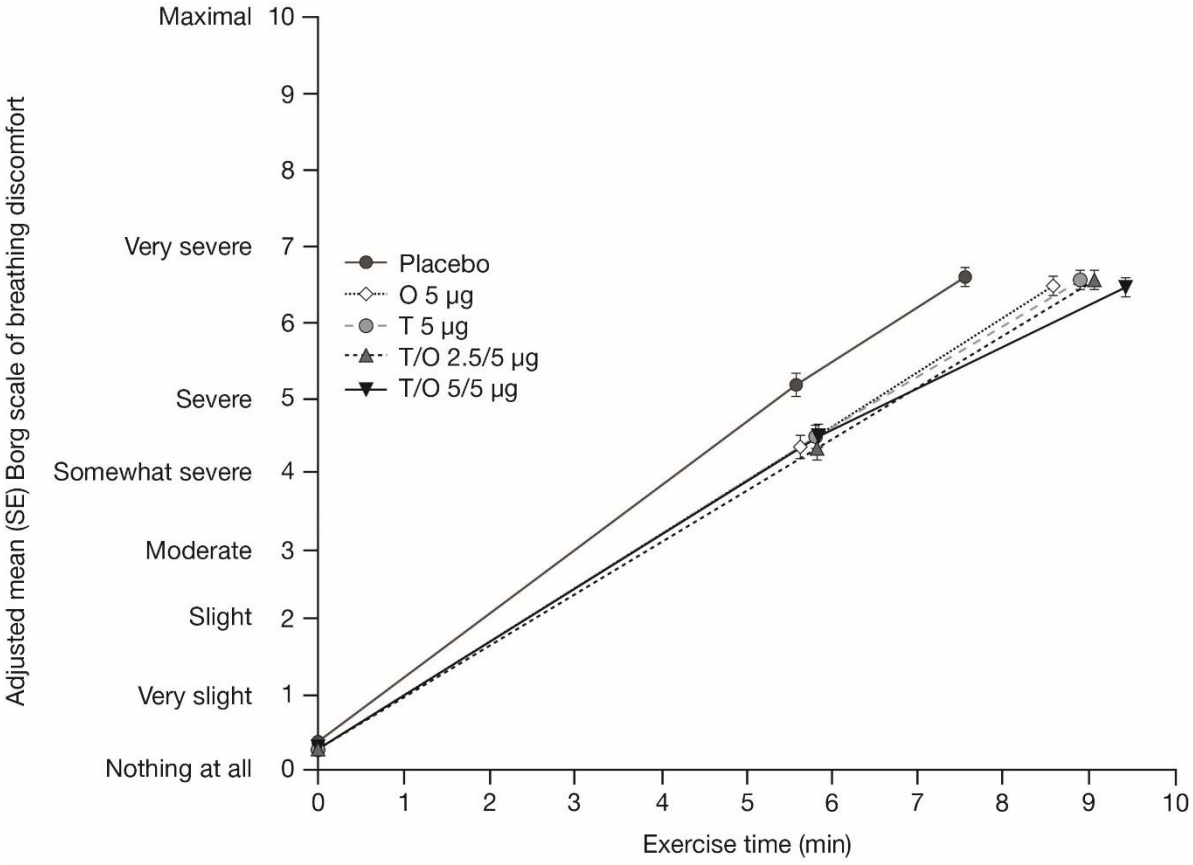
O: olodaterol; T: tiotropium; EET: exercise endurance time.



	>50 s EET improvement	>75 s EET improvement	>100 s EET improvement	>125 s EET improvement	>150 s EET improvement
T/O 5/5 µg	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo
T/O 2.5/5 µg	p<0.0001 *vs* placebo	p<0.0001 *vs* placebo; p<0.05 *vs* O 5 µg, *vs* T 5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* T 5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* O 5 µg	p<0.0001 *vs* placebo; p<0.05 *vs* O 5 µg

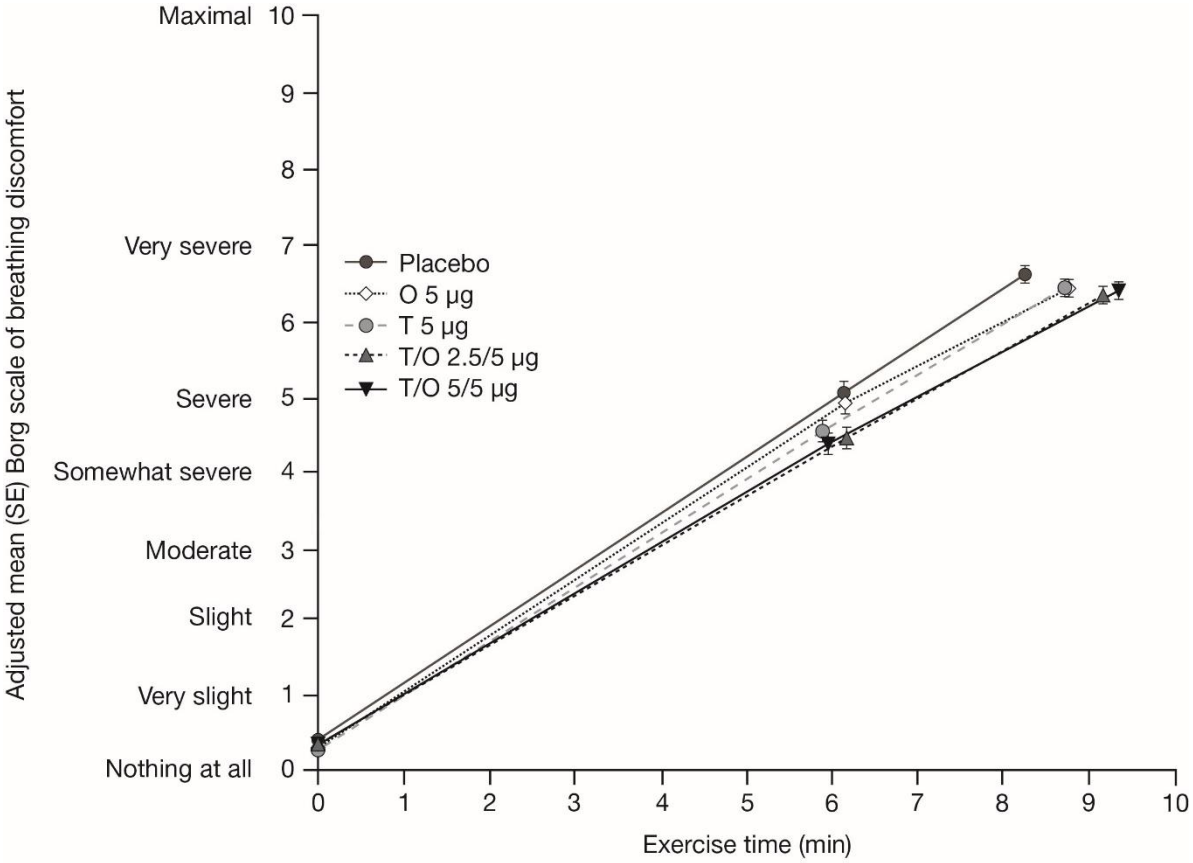
FIGURE S8 Adjusted mean intensity of breathing discomfort (Borg scale) after 6 weeks at pre-exercise, isotime and end-exercise for (a) MORACTO® 1 and (b) MORACTO® 2. O: olodaterol; T: tiotropium; SE: standard error; NS: not significant.

a)



	Pre-exercise	Isotime	End-exercise
T/O 5/5 µg	NS for all comparisons	p<0.0001 *vs* placebo	NS for all comparisons
T/O 2.5/5 µg	p<0.05 *vs* placebo		

b)



	Pre-exercise	Isotime	End-exercise
T/O 5/5 µg	NS for all comparisons	p<0.0001 *vs* placebo; p<0.001 *vs* O 5 µg	NS for all comparisons
T/O 2.5/5 µg		p=0.0001 *vs* placebo; p<0.01 *vs* O 5 µg	p<0.05 *vs* placebo