Online supplementary material

TABLE S1 Study methodology

Study design

These were multinational, replicate, phase III, multicentre, randomised, double-blind, active-controlled, 5-arm, parallel-group studies, registered with ClinicalTrials.gov (Study 1237.5: NCT01431274; Study 1237.6: NCT01431287) (fig. 1).

Following an initial screening visit and 2-week baseline period, eligible patients were randomised to receive tiotropium+olodaterol FDC (2.5/5 or 5/5 μg) or the individual components as monotherapy (tiotropium 2.5 or 5 μg, or olodaterol 5 μg) over 52 weeks. All study drugs were delivered QD in the morning via the Respimat® Soft Mist™ inhaler, with each administration comprising 2 actuations.

Treatment was assigned via an Interactive Voice Response System/Interactive Web Response System. Follow-up occurred 3 weeks after the last dose of study medication.

Study outcomes and assessments

3 primary end points were evaluated after 24 weeks of treatment: trough FEV_1 response in each individual study; FEV_1 $AUC_{0–3}$ response in each individual study (response defined as change from baseline; mean of the values of -1:00 h and -0:10 min prior to the first dose of study medication); and SGRQ total score in the combined data set. PFTs were performed on day 1 and at weeks 2, 6, 12, 18, 24, 32, 40 and 52. SGRQ was completed on day 1 and after 12, 24 and 52 weeks, prior to PFTs and all other procedures.

Spirometry was performed according to American Thoracic Society and European Respiratory Society recommendations [1] using a MasterScope® spirometer and centrally read by eResearch Technology, Germany. Qualifying PFTs were conducted at screening and included reversibility testing.

The key secondary end point was Mahler TDI focal score at 24 weeks, as a pre-

specified combined analysis [2, 3]. Mahler Baseline Dyspnoea Index was administered on day 1 and Mahler TDI at 6, 12, 18, 24 and 52 weeks following SGRQ assessment. Additional lung function secondary end points included: trough FVC, FVC $AUC_{0–3}$; FVC $AUC_{0–12}$ and FEV_1 $AUC_{0–12}$ response in a 12-h PFT sub-set of patients; FVC $peak_{0–3}$ and FEV_1 $peak_{0–3}$; FVC and FEV_1 at 5, 15 and 30 min, and 1, 2 and 3 h after inhalation of study medication.

Safety end points included AE reporting (recorded throughout the trial regardless of causality), vital signs, 12-lead electrocardiogram (pre-dose and repeated 40 min post-dose) and 24-h Holter monitoring in a sub-set of patients at selected sites.

Statistical analysis

Sample size calculation

A 2-sample t-test with equal numbers using Query Advisor 6.01 was performed to calculate sample sizes. Based on an estimate of standard deviation for FEV_1 $AUC_{0–3}$ of 226 mL, for trough FEV_1 of 225 mL and for SGRQ total score of 13 units, and a 2-sided alpha of 0.05, a sample size determination of 500 patients per group was made to provide 90% power to detect a difference of 46 mL for trough FEV_1 and for FEV_1 $AUC_{0–3}$, and a sample size of 1000 per group (combined data sets from Studies 1237.5 and 1237.6) to provide 90% power to detect a difference of 1.885 in SGRQ total score.

Primary end points

Analysis of the primary end points at 24 weeks was performed in all randomised patients who received ≥1 dose of treatment and had baseline and ≥1 post-baseline measurement at or before 24 weeks for any primary efficacy end point (full analysis set). The statistical analyses of lung function end points were performed for the individual studies. For SGRQ, a pre-specified combined analysis was conducted. Comparisons of the FDC with the component monotherapies were tested, each at 5% level of significance (2-sided), in hierarchical order, to protect the overall probability of type I error. Two different hierarchical testing strategies were employed to accommodate regional differences in regulatory requirements (USA *versus* EU; online

supplementary fig. S4).

The mean changes from baseline in FEV_1 $AUC_{0–3}$ response, trough FEV_1 response and SGRQ total score were analysed using an REML-based mixed-effect model repeated measures approach. Analyses included the fixed, categorical effects of treatment, test day and treatment-by-test-day interaction, as well as the continuous, fixed covariates of baseline and baseline-by-test day interaction. A spatial power covariance structure was used to model within-patient errors. The Kenward–Roger approximation was used to estimate denominator degrees of freedom. Analyses were implemented using SAS version 9.2.

Secondary end points

The key secondary end point (TDI focal score) was also analysed using an REML-based mixed-effect model repeated measures approach using the pre-specified combined data set from the replicate studies. As for the primary end points, a hierarchical testing model was used (online supplementary fig. S4).

Safety end points

All treated patients were included in the safety analysis, which was descriptive only. AEs were coded using MedDRA version 16.1. All AEs with an onset after the 1st dose of trial medication and up to a period of 21 days after the last dose were assigned to the treatment period for evaluation. An independent Data Monitoring Committee regularly reviewed unblinded safety data.

Additionally, aggregated safety end points reflecting cardiac safety (standard MedDRA queries and Boehringer Ingelheim-defined pharmacovigilance end points) as well as MACE were compared across all treatment groups and in a sub-group of patients with a history of cardiac disease.

FDC: fixed-dose combination; QD: once daily; MDI: metered dose inhaler; PFT: pulmonary function test; COPD: chronic obstructive pulmonary disease; GOLD: Global initiative for chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $AUC_{0–3}$: area under the curve

from 0–3 h; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index; AUC_{0-12}: area under the curve from 0–12 h; AE: adverse event; REML: restricted maximum likelihood; MedDRA: Medical Dictionary for Regulatory Activities; MACE: major adverse cardiac event.

References

1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.

2. Mahler DA. Mechanisms and measurement of dyspnea in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006; 3: 234–238.

3. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984; 85: 751–758.

TABLE S2 Demographic and baseline patient characteristics (treated population) in Studies 1237.5 (n=2624) and 1237.6 (n=2538)

	Study 1237.5					**Study 1237.6**				
	Olodaterol 5 µg (n=528)	**Tiotropium 2.5 µg (n=525)**	**Tiotropium 5 µg (n=527)**	**Tiotropium+ olodaterol 2.5/5 µg (n=522)**	**Tiotropium+ olodaterol 5/5 µg (n=522)**	**Olodaterol 5 µg (n=510)**	**Tiotropium 2.5 µg (n=507)**	**Tiotropium 5 µg (n=506)**	**Tiotropium+ olodaterol 2.5/5 µg (n=508)**	**Tiotropium+ olodaterol 5/5 µg (n=507)**
Male, n (%)	386 (73.1)	392 (74.7)	383 (72.7)	389 (74.5)	384 (73.6)	378 (74.1)	361 (71.2)	372 (73.5)	368 (72.4)	349 (68.8)
Mean (SD) age, years	63.7 (8.0)	64.2 (8.6)	64.2 (8.5)	64.1 (8.0)	64.8 (8.2)	64.7 (8.3)	63.9 (8.7)	63.5 (8.7)	64.1 (7.6)	62.7 (8.4)
Smoking status, n (%)										
Ex-smoker	332 (62.9)	310 (59.0)	339 (64.3)	326 (62.5)	333 (63.8)	328 (64.3)	334 (65.9)	324 (64.0)	332 (65.4)	296 (58.4)
Current smoker	196 (37.1)	215 (41.0)	188 (35.7)	196 (37.5)	189 (36.2)	182 (35.7)	173 (34.1)	182 (36.0)	176 (34.6)	211 (41.6)
Co-morbidities	447 (84.7)	445 (84.8)	456 (86.5)	447 (85.6)	455 (87.2)	450 (88.2)	439 (86.6)	446 (88.1)	442 (87.0)	435 (85.8)
Cardiac	96 (18.2)	93 (17.7)	111 (21.1)	110 (21.1)	106 (20.3)	138 (27.1)	119 (23.5)	108 (21.3)	119 (23.4)	107 (21.1)
Vascular	252 (47.7)	231 (44.0)	252 (47.8)	242 (46.4)	255 (48.9)	259 (50.8)	244 (48.1)	261 (51.6)	244 (48.0)	241 (47.5)
Pre-bronchodilator										

screening										
Mean (SD) FEV_1, L	1.20 (0.52)	1.26 (0.49)	1.20 (0.50)	1.22 (0.47)	1.17 (0.47)	1.22 (0.50)	1.18 (0.48)	1.20 (0.51)	1.20 (0.48)	1.19 (0.51)
Post-bronchodilator screening										
Mean (SD) FEV_1, L	1.37 (0.53)	1.43 (0.52)	1.36 (0.51)	1.40 (0.49)	1.33 (0.49)	1.38 (0.51)	1.35 (0.50)	1.38 (0.53)	1.37 (0.50)	1.36 (0.52)
Mean (SD) change from pre- to post-bronchodilator FEV_1, L	0.17 (0.14)	0.18 (0.16)	0.17 (0.15)	0.18 (0.14)	0.17 (0.15)	0.17 (0.14)	0.17 (0.15)	0.18 (0.15)	0.17 (0.13)	0.16 (0.15)
Mean (SD) FEV_1/FVC, %	44.4 (11.5)	45.5 (11.4)	44.7 (11.7)	44.3 (11.2)	44.2 (11.6)	45.7 (11.6)	44.7 (11.7)	45.3 (12.3)	44.9 (11.8)	46.1 (11.6)
Mean (SD) % of predicted normal FEV_1	49.9 (15.6)	50.9 (14.7)	49.7 (15.3)	50.5 (14.7)	49.5 (15.2)	50.7 (15.6)	49.7 (15.3)	49.7 (16.1)	50.0 (15.2)	49.1 (15.4)
GOLD, n (%)[#]										
1 (≥80%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
2 (50–<80%)	257 (48.7)	270 (51.4)	263 (49.9)	269 (51.5)	258 (49.4)	275 (53.9)	248 (48.9)	254 (50.2)	250 (49.2)	244 (48.1)
3 (30–<50%)	207 (39.2)	210 (40.0)	202 (38.3)	206 (39.5)	201 (38.5)	171 (33.5)	199 (39.3)	185 (36.6)	201 (39.6)	207 (40.8)
4 (<30%)	64 (12.1)	45 (8.6)	62 (11.8)	47 (9.0)	63 (12.1)	64 (12.5)	58 (11.4)	66 (13.0)	56 (11.0)	56 (11.0)

Baseline pulmonary medication										
SAMA[¶]	50 (9.5)	56 (10.7)	60 (11.4)	52 (10.0)	52 (10.0)	84 (16.5)	84 (16.6)	71 (14.0)	83 (16.3)	73 (14.4)
LAMA[+]	185 (35.0)	190 (36.2)	173 (32.8)	201 (38.5)	210 (40.2)	180 (35.3)	158 (31.2)	173 (34.2)	202 (39.8)	168 (33.1)
SABA[§]	223 (42.2)	233 (44.4)	208 (39.5)	224 (42.9)	223 (42.7)	201 (39.4)	200 (39.4)	193 (38.1)	197 (38.8)	177 (34.9)
LABA	249 (47.2)	252 (48.0)	234 (44.4)	265 (50.8)	261 (50.0)	242 (47.5)	223 (44.0)	216 (42.7)	226 (44.5)	225 (44.4)
ICS[f]	249 (47.2)	244 (46.5)	237 (45.0)	260 (49.8)	270 (51.7)	256 (50.2)	232 (45.8)	229 (45.3)	233 (45.9)	236 (46.5)
Xanthines[##]	45 (8.5)	45 (8.6)	46 (8.7)	57 (10.9)	51 (9.8)	51 (10.0)	49 (9.7)	63 (12.5)	52 (10.2)	57 (11.2)

SD: standard deviation; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global initiative for chronic Obstructive Lung Disease; SAMA: short-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting β-agonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid. [#]: Based on post-bronchodilator FEV_1 percentage predicted. In Study 1237.6, 1 patient on tiotropium 2.5 µg was not categorised; [¶]: ipratropium, ipratropium/fenoterol or ipratropium/salbutamol, oxitropium; [+]: tiotropium; [§]: all patients received SABAs as rescue medication; [f]: including beclomethasone, budesonide, ciclesonide, dulera, fluticasone, formoterol/beclomethasone, formoterol/budesonide, mometasone, mometasone furoate, salmeterol/fluticasone; [##]: including aminophylline, theophylline.

TABLE S3 Adjusted mean (SE) FEV_1 $AUC_{0–3}$ and trough FEV_1 responses (*i.e.* change from baseline) after 24 weeks of treatment (full analysis set): combined analysis

Treatment comparison	**Adjusted mean FEV_1 $AUC_{0–3}$[#], L (SE)**	**95% CI**	**Adjusted mean trough FEV_1[¶], L (SE)**	**95% CI**
Combined common study baseline	1.154 (0.007)		1.155 (0.007)	
Tiotropium+olodaterol 5/5 µg				
versus olodaterol 5 µg	0.128 (0.009)*	0.111, 0.144	0.085 (0.009)*	0.067, 0.102
versus tiotropium 5 µg	0.110 (0.009)*	0.093, 0.127	0.060 (0.009)*	0.043, 0.077
Tiotropium+olodaterol 2.5/5 µg				
versus olodaterol 5 µg	0.115 (0.009)*	0.098, 0.131	0.062 (0.009)*	0.045, 0.080
versus tiotropium 2.5 µg	0.111 (0.009)*	0.095, 0.128	0.045 (0.009)*	0.028, 0.062
versus tiotropium 5 µg	0.097 (0.009)*	0.080, 0.113	0.038 (0.009)*	0.021, 0.055
Tiotropium+olodaterol 5/5 µg				

versus tiotropium+olodaterol 2.5/5 µg	0.013 (0.009)	-0.004, 0.030	0.022 (0.009)**	0.005, 0.039

Adjusted mean (SE) obtained from fitting a mixed model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward−Roger approximation of denominator degrees of freedom. FEV_1: forced expiratory volume in 1 s; $AUC_{0–3}$: area under the curve from 0–3 h; SE: standard error; CI: confidence interval. [#]: Number of patients contributing to the mixed model for repeated measurements for adjusted mean FEV_1 $AUC_{0–3}$: tiotropium+olodaterol 5/5 µg n=1023; tiotropium+olodaterol 2.5/5 µg n=1027; tiotropium 5 µg n=1026; tiotropium 2.5 µg n=1028; olodaterol 5 µg n=1032; [¶]: number of patients contributing to the mixed model for repeated measurements for adjusted mean trough FEV_1: tiotropium+olodaterol 5/5 µg n=1017; tiotropium+olodaterol 2.5/5 µg n=1018; tiotropium 5 µg n=1018; tiotropium 2.5 µg n=1018; olodaterol 5 µg n=1022. *p<0.0001; **p=0.114.

TABLE S4 Adjusted mean (SE) FEV_1 $AUC_{0–3}$ and trough FEV_1 responses (*i.e.* change from baseline) after 24 weeks of treatment by baseline disease severity (full analysis set, combined data)

Treatment comparison	**GOLD 2**			**GOLD 3**			**GOLD 4**		
	Adjusted mean, L (SE)	**95% CI**	**p-value**	**Adjusted mean, L (SE)**	**95% CI**	**p-value**	**Adjusted mean, L (SE)**	**95% CI**	**p-value**
FEV_1 $AUC_{0–3}$									
Common study baseline	1.460 (0.009)			0.913 (0.006)			0.614 (0.007)		
Tiotropium+olodaterol 5/5 µg									
versus olodaterol	0.132	0.107,	<0.0001	0.127	0.101,	<0.0001	0.106	0.073,	<0.0001

5 µg	(0.013)	0.156		(0.013)	0.153		(0.017)	0.139	
versus tiotropium	0.119	0.094,	<0.0001	0.112	0.086,	<0.0001	0.063	0.030,	0.0002
5 µg	(0.013)	0.143		(0.013)	0.138		(0.017)	0.095	
Tiotropium+olodaterol 2.5/5 µg									
versus olodaterol	0.101	0.076,	<0.0001	0.136	0.110,	<0.0001	0.091	0.057,	<0.0001
5 µg	(0.013)	0.125		(0.013)	0.163		(0.017)	0.125	
versus tiotropium	0.111	0.087,	<0.0001	0.129	0.104,	<0.0001	0.041	0.005,	0.0245
2.5 µg	(0.013)	0.136		(0.013)	0.155		(0.018)	0.076	
versus tiotropium	0.088	0.063,	<0.0001	0.121	0.095,	<0.0001	0.048	0.014,	0.0052
5 µg	(0.013)	0.112		(0.013)	0.147		(0.017)	0.082	
Tiotropium+olodaterol 5/5 µg									
versus tiotropium + olodaterol	0.031	0.006,	0.0149	-0.009	-0.035,	0.4790	0.015	-0.019,	0.4015

2.5/5 µg	(0.013)	0.056		(0.013)	0.016		(0.017)	0.048	
Trough FEV_1									
Common study	1.461			0.913			0.614		
baseline	(0.009)			(0.006)			(0.007)		
Tiotropium+olodaterol									
5/5 µg									
versus olodaterol	0.083	0.057,	<0.0001	0.089	0.062,	<0.0001	0.070	0.037,	<0.0001
5 µg	(0.013)	0.109		(0.014)	0.115		(0.016)	0.102	
versus tiotropium	0.069	0.042,	<0.0001	0.059	0.033,	<0.0001	0.021	-0.011,	0.2022
5 µg	(0.013)	0.095		(0.013)	0.086		(0.016)	0.052	
Tiotropium+olodaterol									
2.5/5 µg									

versus olodaterol 5 µg	0.052 (0.013)	0.026, 0.078	<0.0001	0.073 (0.014)	0.047, 0.100	<0.0001	0.060 (0.017)	0.026, 0.093	0.0005
versus tiotropium 2.5 µg	0.045 (0.013)	0.019, 0.071	0.0008	0.058 (0.013)	0.032, 0.084	<0.0001	-0.007 (0.018)	-0.042, 0.028	0.6904
versus tiotropium 5 µg	0.038 (0.013)	0.012, 0.064	0.0044	0.044 (0.013)	0.018, 0.070	0.0010	0.010 (0.017)	-0.023, 0.044	0.5337
Tiotropium+olodaterol 5/5 µg									
versus tiotropium + olodaterol 2.5/5 µg	0.031 (0.013)	0.005, 0.057	0.0203	0.015 (0.013)	-0.011, 0.041	0.2506	0.010 (0.017)	-0.023, 0.044	0.5495

SE: standard error; FEV_1: forced expiratory volume in 1 s; $AUC_{0–3}$: area under the curve from 0–3 h; GOLD: Global initiative for chronic Obstructive Lung Disease; CI: confidence interval.

TABLE S5 Secondary lung function end points after 24 weeks of treatment (full analysis set): combined analysis

Treatment comparison	**Adjusted mean FVC $AUC_{0–3}$[#], L (SE)**	**95% CI**	**Adjusted mean trough FVC[¶], L (SE)**	**95% CI**
Combined common baseline mean	2.713 (0.012)		2.715 (0.012)	
Tiotropium+olodaterol 5/5 µg				
versus olodaterol 5 µg	0.196 (0.017)*	0.162, 0.230	0.155 (0.018)*	0.121, 0.190
versus tiotropium 5 µg	0.149 (0.017)*	0.116, 0.182	0.074 (0.018)*	0.039, 0.108
Tiotropium+olodaterol 2.5/5 µg				
versus olodaterol 5 µg	0.190 (0.017)*	0.157, 0.224	0.141 (0.018)*	0.107, 0.176
versus tiotropium 2.5 µg	0.148 (0.017)*	0.115, 0.182	0.071 (0.018)*	0.037, 0.106
versus tiotropium 5 µg	0.143 (0.017)*	0.110, 0.177	0.060 (0.018)**	0.025, 0.094

The adjusted mean (SE) is obtained from fitting a mixed model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward−Roger approximation of denominator degrees of freedom. FVC: forced vital capacity; $AUC_{0–3}$: area under

the curve from 0–3 h; SE: standard error; CI: confidence interval. [#]: Number of patients contributing to the mixed model for repeated measurements in each treatment group for FVC $AUC_{0–3}$: tiotropium+olodaterol 5/5 µg n=1023; tiotropium+olodaterol 2.5/5 µg n=1027; tiotropium 5 µg n=1026; tiotropium 2.5 µg n=1028; olodaterol 5 µg n=1032; [¶]: number of patients contributing to the mixed model for repeated measurements in each treatment group for trough FVC: tiotropium+olodaterol 5/5 µg n=1017; tiotropium+olodaterol 2.5/5 µg n=1018; tiotropium 5 µg n=1018; tiotropium 2.5 µg n=1018; olodaterol 5 µg n=1022. *p<0.0001; **p<0.001

TABLE S6 Adjusted mean Mahler TDI focal score at 24 weeks and treatment comparisons (full analysis set): combined analysis

Adjusted mean Mahler TDI focal score	**Adjusted mean (SE)[#]**	
Combined common baseline mean	6.544 (0.031)	
Olodaterol 5 µg	1.564 (0.096)	
Tiotropium 2.5 µg	1.690 (0.095)	
Tiotropium 5 µg	1.627 (0.096)	
Tiotropium+olodaterol 2.5/5 µg	1.980 (0.095)	
Tiotropium+olodaterol 5/5 µg	1.983 (0.095)	
Adjusted mean Mahler TDI focal score	**Treatment difference**	**Treatment difference**
Treatment comparisons	**Adjusted mean (SE)[#]**	**95% CI**
Tiotropium+olodaterol 5/5 µg		
versus olodaterol 5 µg	0.420 (0.135)*	0.155, 0.684
versus tiotropium 5 µg	0.356 (0.135)**	0.092, 0.619

Tiotropium+olodaterol 2.5/5 µg		
versus olodaterol 5 µg	0.416 (0.135)*	0.152, 0.681
versus tiotropium 2.5 µg	0.290 (0.134)**	0.027, 0.554
versus tiotropium 5 µg	0.352 (0.135)**	0.089, 0.616
Tiotropium+olodaterol 5/5 µg		
versus tiotropium + olodaterol 2.5/5 µg	0.003 (0.134)	-0.259, 0.266

The adjusted mean (SE) are obtained from fitting a mixed model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward−Roger approximation of denominator degrees of freedom. TDI: Transition Dyspnoea Index; SE: standard error; CI: confidence interval. [#]: Number of patients contributing to the mixed model for repeated measurements for adjusted mean TDI focal score: olodaterol 5 µg n=984; tiotropium 2.5 µg n= 982; tiotropium 5 µg n=978; tiotropium+olodaterol 2.5/5 µg n=992; tiotropium+olodaterol 5/5 µg n=992. *p<0.005; **p<0.05.

TABLE S7 Summary of AEs in Studies 1237.5 and 1237.6 (treated set)

	Olodaterol 5 µg, n (%)	**Tiotropium 2.5 µg, n (%)**	**Tiotropium 5 µg, n (%)**	**Tiotropium+ olodaterol 2.5/5 µg, n (%)**	**Tiotropium+ olodaterol 5/5 µg, n (%)**
Study 1237.5					
Total number of patients	528 (100.0)	525 (100.0)	527 (100.0)	522 (100.0)	522 (100.0)
All AEs	390 (73.9)	374 (71.2)	381 (72.3)	395 (75.7)	387 (74.1)
Treatment-related AEs	32 (6.1)	24 (4.6)	25 (4.7)	30 (5.7)	36 (6.9)
AEs leading to discontinuation	49 (9.3)	37 (7.0)	42 (8.0)	29 (5.6)	37 (7.1)
Serious AEs	75 (14.2)	66 (12.6)	79 (15.0)	81 (15.5)	87 (16.7)
Fatal	4 (0.8)	8 (1.5)	9 (1.7)	8 (1.5)	9 (1.7)
Life-threatening	2 (0.4)	2 (0.4)	1 (0.2)	2 (0.4)	2 (0.4)

Disabling/incapacitating	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	2 (0.4)
Requiring hospitalisation	69 (13.1)	59 (11.2)	71 (13.5)	71 (13.6)	80 (15.3)
Prolonging hospitalisation	4 (0.8)	4 (0.8)	2 (0.4)	3 (0.6)	3 (0.6)
Other	7 (1.3)	6 (1.1)	7 (1.3)	13 (2.5)	6 (1.1)
Specific AEs with an incidence >2%					
Infections and infestations	184 (34.8)	176 (33.5)	179 (34.0)	205 (39.3)	182 (34.9)
Nasopharyngitis	65 (12.3)	64 (12.2)	67 (12.7)	64 (12.3)	67 (12.8)
Upper respiratory tract infection	24 (4.5)	30 (5.7)	30 (5.7)	40 (7.7)	25 (4.8)
Pneumonia	22 (4.2)	11 (2.1)	19 (3.6)	20 (3.8)	19 (3.6)
Bronchitis	11 (2.1)	11 (2.1)	14 (2.7)	14 (2.7)	17 (3.3)
Influenza	12 (2.3)	14 (2.7)	10 (1.9)	13 (2.5)	15 (2.9)
Urinary tract infection	10 (1.9)	10 (1.9)	14 (2.7)	13 (2.5)	9 (1.7)
Nervous system disorders	41 (7.8)	48 (9.1)	48 (9.1)	43 (8.2)	41 (7.9)
Headache	16 (3.0)	12 (2.3)	16 (3.0)	15 (2.9)	14 (2.7)

Respiratory, thoracic and mediastinal disorders	230 (43.6)	215 (41.0)	215 (40.8)	190 (36.4)	202 (38.7)
COPD exacerbation	182 (34.5)	169 (32.2)	175 (33.2)	153 (29.3)	170 (32.6)
Dyspnoea	18 (3.4)	20 (3.8)	22 (4.2)	15 (2.9)	17 (3.3)
Cough	14 (2.7)	19 (3.6)	20 (3.8)	14 (2.7)	16 (3.1)
Gastrointestinal disorders	82 (15.5)	73 (13.9)	73 (13.9)	72 (13.8)	69 (13.2)
Diarrhoea	18 (3.4)	11 (2.1)	13 (2.5)	16 (3.1)	12 (2.3)
Musculoskeletal and connective tissue disorders	63 (11.9)	48 (9.1)	63 (12.0)	69 (13.2)	79 (15.1)
Back pain	20 (3.8)	10 (1.9)	11 (2.1)	20 (3.8)	13 (2.5)
General disorders and administration site conditions	45 (8.5)	25 (4.8)	45 (8.5)	40 (7.7)	33 (6.3)
Chest pain	7 (1.3)	4 (0.8)	12 (2.3)	7 (1.3)	5 (1.0)
Study 1237.6					
Total number of patients	510 (100.0)	507 (100.0)	506 (100.0)	508 (100.0)	507 (100.0)
All AEs	405 (79.4)	384 (75.7)	376 (74.3)	374 (73.6)	374 (73.8)
Treatment-related AEs	37 (7.3)	38 (7.5)	38 (7.5)	32 (6.3)	37 (7.3)

AEs leading to discontinuation	54 (10.6)	53 (10.5)	51 (10.1)	28 (5.5)	39 (7.7)
Serious AEs	106 (20.8)	90 (17.8)	93 (18.4)	87 (17.1)	82 (16.2)
Fatal	10 (2.0)	4 (0.8)	8 (1.6)	6 (1.2)	9 (1.8)
Life-threatening	1 (0.2)	3 (0.6)	1 (0.2)	3 (0.6)	3 (0.6)
Disabling/incapacitating	1 (0.2)	2 (0.4)	1 (0.2)	0 (0.0)	1 (0.2)
Requiring hospitalisation	93 (18.2)	85 (16.8)	84 (16.6)	78 (15.4)	73 (14.4)
Prolonging hospitalisation	8 (1.6)	6 (1.2)	1 (0.2)	4 (0.8)	3 (0.6)
Other	13 (2.5)	10 (2.0)	11 (2.2)	5 (1.0)	6 (1.2)
Specific AEs with an incidence >2%					
Infections and infestations	209 (41.0)	187 (36.9)	169 (33.4)	189 (37.2)	192 (37.9)
Nasopharyngitis	66 (12.9)	59 (11.6)	54 (10.7)	70 (13.8)	61 (12.0)
Upper respiratory tract infection	32 (6.3)	31 (6.1)	27 (5.3)	29 (5.7)	29 (5.7)
Pneumonia	14 (2.7)	13 (2.6)	7 (1.4)	11 (2.2)	15 (3.0)
Bronchitis	22 (4.3)	12 (2.4)	9 (1.8)	14 (2.8)	14 (2.8)

Influenza	13 (2.5)	11 (2.2)	12 (2.4)	15 (3.0)	16 (3.2)
Urinary tract infection	3 (0.6)	8 (1.6)	16 (3.2)	10 (2.0)	13 (2.6)
Nervous system disorders	46 (9.0)	45 (8.9)	53 (10.5)	57 (11.2)	43 (8.5)
Headache	15 (2.9)	11 (2.2)	25 (4.9)	15 (3.0)	13 (2.6)
Respiratory, thoracic and mediastinal disorders	240 (47.1)	238 (46.9)	226 (44.7)	203 (40.0)	203 (40.0)
COPD exacerbation	188 (36.9)	183 (36.1)	165 (32.6)	148 (29.1)	162 (32.0)
Dyspnoea	20 (3.9)	24 (4.7)	29 (5.7)	22 (4.3)	22 (4.3)
Cough	17 (3.3)	27 (5.3)	25 (4.9)	29 (5.7)	24 (4.7)
Gastrointestinal disorders	83 (16.3)	79 (15.6)	81 (16.0)	74 (14.6)	74 (14.6)
Diarrhoea	15 (2.9)	12 (2.4)	14 (2.8)	13 (2.6)	12 (2.4)
Musculoskeletal and connective tissue disorders	61 (12.0)	71 (14.0)	54 (10.7)	86 (16.9)	77 (15.2)
Back pain	15 (2.9)	13 (2.6)	8 (1.6)	20 (3.9)	24 (4.7)
General disorders and administration site conditions	42 (8.2)	39 (7.7)	53 (10.5)	42 (8.3)	40 (7.9)
Chest pain	10 (2.0)	13 (2.6)	10 (2.0)	8 (1.6)	9 (1.8)

A patient may be counted in >1 preferred term. AE: adverse event; COPD: chronic obstructive pulmonary disease.

TABLE S8 Summary of rate ratios (95% confidence interval) of MACE and cardiac AEs

	Tiotropium+olodaterol 2.5/5 µg *versus* olodaterol 5 µg	**Tiotropium+olodaterol 2.5/5 µg *versus* tiotropium 2.5 µg**	**Tiotropium+olodaterol 5/5 µg *versus* olodaterol 5 µg**	**Tiotropium+olodaterol 5/5 µg *versus* tiotropium 5 µg**
Any MACE	0.87 (0.53, 1.44)	1.00 (0.60, 1.68)	1.07 (0.66, 1.73)	1.11 (0.68, 1.80)
Any cardiac event	0.98 (0.68, 1.40)	0.97 (0.68, 1.38)	0.75 (0.51, 1.10)	0.81 (0.55, 1.20)

MACE: major adverse cardiac event; AE: adverse event.

Supplementary figure legends

FIGURE S1 Adjusted mean trough FEV_1 in (a) Study 1237.5 and (b) Study 1237.6, and FEV_1 $AUC_{0–3}$ in (c) Study 1237.5 and (d) Study 1237.6 over 52 weeks: full analysis set. Tio: tiotropium; Olo: olodaterol; FEV_1: forced expiratory volume in 1 s; $AUC_{0–3}$: area under the curve from 0–3 h.

FIGURE S2 Adjusted weekly mean daily (24-h) rescue medication use (actuations/day) over 52 weeks: full analysis set. Combined analysis. Tio: tiotropium; Olo: olodaterol.

FIGURE S3 Kaplan-Meier estimates of probability of moderate/severe COPD exacerbations: combined analysis. COPD: chronic obstructive pulmonary disease; Tio: tiotropium; Olo: olodaterol; CI: confidence interval.

FIGURE S4 Hierarchical testing model. Tio: tiotropium; Olo: olodaterol; FDC: fixed-dose combination; FEV_1: forced expiratory volume in 1 s; $AUC_{0–3}$: area under the curve from 0–3 h; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index.