Tiotropium and olodaterol fixed-dose combination *versus* mono-components in COPD (GOLD 2–4)

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ABSTRACT Efficacy and safety of tiotropium+olodaterol fixed-dose combination (FDC) compared with the mono-components was evaluated in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) in two replicate, randomised, double-blind, parallel-group, multicentre, phase III trials.

Patients received tiotropium+olodaterol FDC 2.5/5 µg or 5/5 µg, tiotropium 2.5 µg or 5 µg, or olodaterol 5 µg delivered once-daily *via* Respimat inhaler over 52 weeks. Primary end points were forced expiratory volume in 1 s (FEV_1) area under the curve from 0 to 3 h (AUC_{0-3}) response, trough FEV_1 response and St George's Respiratory Questionnaire (SGRQ) total score at 24 weeks.

In total, 5162 patients (2624 in Study 1237.5 and 2538 in Study 1237.6) received treatment. Both FDCs significantly improved FEV_1 AUC_{0-3} and trough FEV_1 response *versus* the mono-components in both studies. Statistically significant improvements in SGRQ total score *versus* the mono-components were only seen for tiotropium+olodaterol FDC 5/5 µg. Incidence of adverse events was comparable between the FDCs and the mono-components.

These studies demonstrated significant improvements in lung function and health-related quality of life with once-daily tiotropium+olodaterol FDC *versus* mono-components over 1 year in patients with moderate to very severe COPD.

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Introduction

Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMAs), are the cornerstone of maintenance therapy for patients with moderate to very severe chronic obstructive pulmonary disease (COPD) whose symptoms are not adequately controlled by short-acting bronchodilators alone [1, 2].

Tiotropium is an established once-daily LAMA that improves the main functional and patient-orientated outcomes of COPD [3–8]. Tiotropium has also been demonstrated to moderate disease progression, even in the early stages of COPD (*e.g.* patients not receiving maintenance therapy [9] or those with Global initiative for chronic Obstructive Lung Disease (GOLD) stage 2 disease [10]).

The novel once-daily long-acting β_2-agonist (LABA) olodaterol is a highly selective and nearly full β_2 agonist [11, 12] that provides 24-h bronchodilation in patients with COPD [13–16]. Olodaterol is also associated with symptomatic benefit [17] and enhanced exercise capacity [18].

An option recommended by GOLD for patients not adequately controlled on a single long-acting bronchodilator is to combine a LAMA with a LABA [2]. This has prompted the development of combining LAMA+LABA as fixed-dose combinations (FDCs) [1]. The complementary modes of action of tiotropium and olodaterol have previously been demonstrated in animal models and phase II clinical trials [19–22].

We hypothesised that combination therapy with tiotropium+olodaterol FDC would provide improvements in lung function, health-related quality of life and other COPD disease parameters compared to monotherapy with either component alone, with a comparable safety profile. These two replicate, global, phase III trials (TOnado 1 and 2) aimed to assess the efficacy and safety of once-daily treatment with orally inhaled tiotropium+olodaterol FDC 5/5 µg or 2.5/5 µg delivered *via* the Respimat Soft Mist Inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) compared with their individual mono-components in patients with moderate to very severe COPD (GOLD stage 2–4) over 52 weeks.

Methods

Study design

These were multinational, replicate, phase III, multicentre, randomised, double-blind, active-controlled, five-arm, parallel-group studies, registered with ClinicalTrials.gov (Study 1237.5: NCT01431274; Study 1237.6: NCT01431287) (fig. 1). Three primary end points were evaluated after 24 weeks of treatment: forced expiratory volume in 1 s (FEV_1) area under the curve from 0 to 3 h ($AUC_{0–3}$) response (in each individual trial), trough FEV_1 response in each individual trial (response defined as change from baseline; mean of the values of 1 h and 10 min prior to the first dose of study medication); and St George's Respiratory Questionnaire (SGRQ) total score (SGRQ was analysed in a pre-specified combined analysis of data from both studies). Pulmonary function tests (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. Details of the study design, assessments performed and statistical methodology are provided in table S1 of the online supplementary material.

Patients continued to receive treatment with inhaled corticosteroids as required and were provided with salbutamol/albuterol metered-dose inhaler (100 µg per actuation) as rescue medication to be used as necessary at any point during the trial. Temporary increases in the dose or addition of oral steroids or theophylline preparations were allowed during the treatment portion of the study; PFTs were not performed within 7 days of the last administered dose.

Patients

Patients were randomised if they met the following main inclusion criteria: outpatients aged ⩾40 years with a history of moderate to very severe COPD (GOLD stage 2–4) [23]; post-bronchodilator FEV_1 <80% of predicted normal; post-bronchodilator FEV_1/forced vital capacity (FVC) <70%; current or ex-smokers with a smoking history of >10 pack–years.

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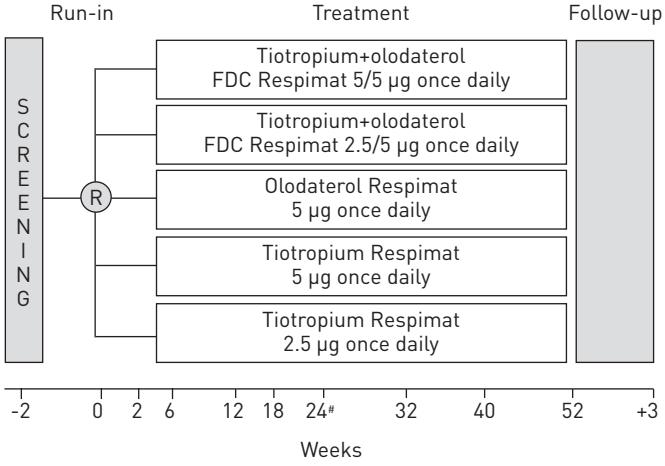


FIGURE 1 Study design (Study 1237.5: NCT01431274; Study 1237.6: NCT01431287). R: randomisation; FDC: fixed-dose combination. #: primary end-point assessment.

Patients with a significant disease other than COPD were excluded from the trials. Other exclusion criteria included: clinically relevant abnormal baseline laboratory parameters or a history of asthma; myocardial infarction within 1 year of screening; unstable or life-threatening cardiac arrhythmia; known active tuberculosis; clinically evident bronchiectasis; cystic fibrosis or life-threatening pulmonary obstruction; hospitalised for heart failure within the past year; diagnosed thyrotoxicosis or paroxysmal tachycardia; previous thoracotomy with pulmonary resection; regular use of daytime oxygen if patients were unable to abstain during clinic visits; or currently enrolled in a pulmonary rehabilitation programme (or completed in the 6 weeks before screening).

Patients with moderate or severe renal impairment (creatinine clearance $\leqslant$50 mL·min^{-1}) were not excluded from the study but were closely monitored by the investigator.

Both studies were performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and local regulations. The protocols were approved by the authorities and the ethics committees of the respective institutions, and signed informed consent was obtained from all patients.

Results

Patient disposition and baseline characteristics

A total of 5163 patients (2624 Study 1237.5; 2539 Study 1237.6) were randomised to receive treatment in 25 countries; 5162 patients were treated (2624 Study 1237.5; 2538 Study 1237.6). Overall, 84.6% of patients (86.2% Study 1237.5; 83.0% Study 1237.6) completed the studies. The discontinuation rate was higher in the monotherapy than the combination treatment groups in both studies (fig. 2). The data for the individual studies are presented in the online supplementary material.

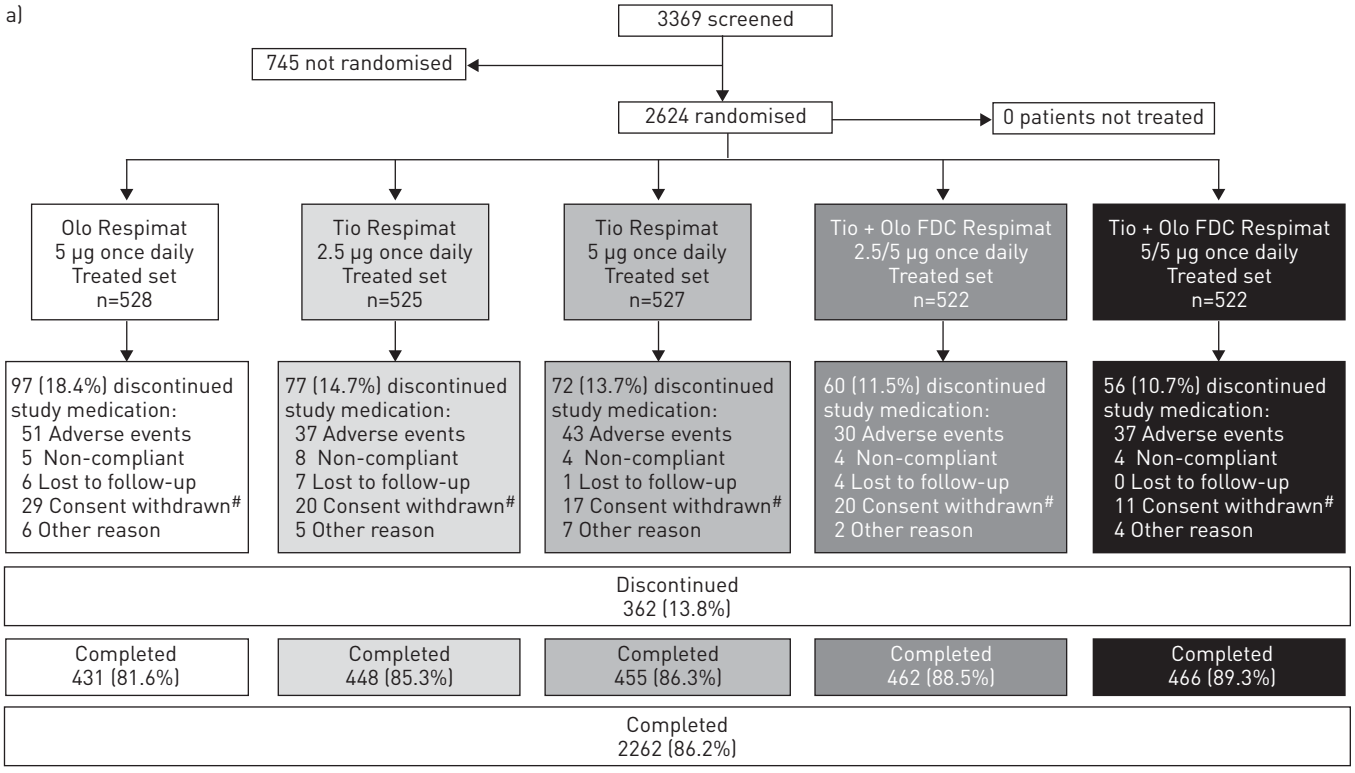
Baseline demographics were generally similar across treatment groups. The majority of patients were male (72.9% total) and approximately one-third were current smokers. Most patients were classified as GOLD stage 2/3 (88.6%); the remaining patients (11.3%) were classified as GOLD stage 4. Overall, 86.4% of patients had diagnosed co-morbidities at baseline; 1107 (21.4%) had cardiac disorders and 2481 (48.1%) had vascular disorders including hypertension (table 1, and table S2 in the online supplementary material for individual study data).

Efficacy

Lung function

FEV_1 AUC_{0-3} responses for tiotropium+olodaterol FDC 2.5/5 µg, 5/5 µg, tiotropium 2.5 µg, 5 µg and olodaterol 5 µg were 241, 256, 148, 139 and 133 mL, respectively, in Study 1237.5, and 256, 268, 125, 165 and 136 mL, respectively, in Study 1237.6. Improvements in adjusted mean FEV_1 AUC_{0-3} with tiotropium +olodaterol FDC 5/5 µg and 2.5/5 µg over the corresponding individual components in the individual studies and the combined analysis were statistically significant ($p<0.0001$ for all comparisons) (table 2, and table S3 in the online supplementary material). The comparison of tiotropium+olodaterol FDC 2.5/5 µg with tiotropium 5 µg (performed to compare the combination with the licensed tiotropium dose) was $p<0.0001$ for all analyses.

Trough FEV_1 responses after 24 weeks for tiotropium+olodaterol FDC 2.5/5 µg, 5/5 µg, tiotropium 2.5 µg, 5 µg and olodaterol 5 µg were 111, 136, 83, 65 and 54 mL, respectively, in Study 1237.5, and 125, 145, 62, 96 and 57 mL, respectively, in Study 1237.6. Improvements in the adjusted mean trough FEV_1 with



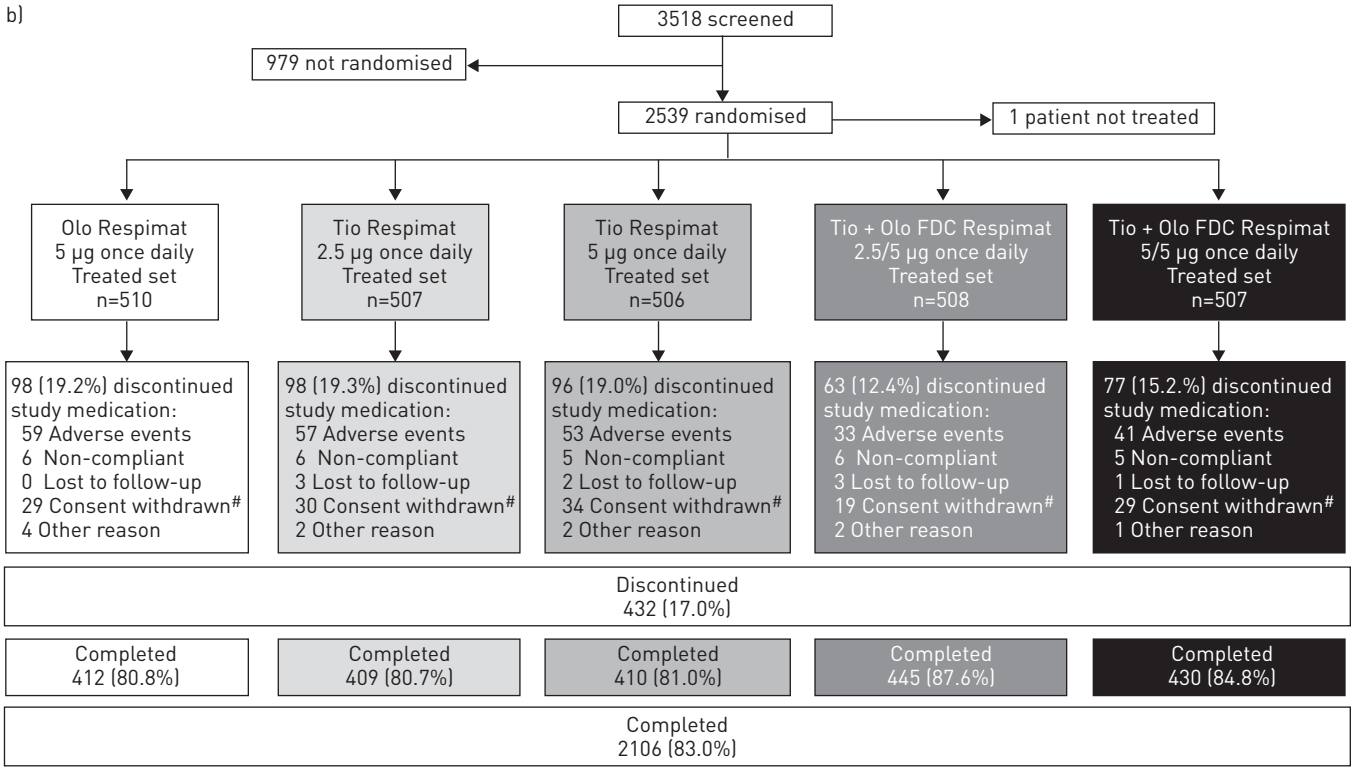


FIGURE 2 Patient disposition and flow in (a) Study 1237.5 and (b) Study 1237.6. Tio: tiotropium; Olo: olodaterol; FDC: fixed-dose combination. #: not due to adverse event.

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TABLE 1 Demographic and baseline patient characteristics (treated population): combined data (n=5162)

	Olodaterol 5 µg	Tiotropium 2.5 µg	Tiotropium 5 µg	Tiotropium+olodaterol 2.5/5 µg	Tiotropium+olodaterol 5/5 µg
Participants n	1038	1032	1033	1030	1029
Male	764 (73.6)	753 (73.0)	755 (73.1)	757 (73.5)	733 (71.2)
Age years	64.2±8.2	64.0±8.7	63.9±8.6	64.1±7.8	63.8±8.3
Smoking status					
Ex-smoker	660 (63.6)	644 (62.4)	663 (64.2)	658 (63.9)	629 (61.1)
Current smoker	378 (36.4)	388 (37.6)	370 (35.8)	372 (36.1)	400 (38.9)
Co-morbidities	897 (86.4)	884 (85.7)	902 (87.3)	889 (86.3)	890 (86.5)
Cardiac	234 (22.5)	212 (20.5)	219 (21.2)	229 (22.2)	213 (20.7)
Vascular	511 (49.2)	475 (46.0)	513 (49.7)	486 (47.2)	496 (48.2)
Pre-bronchodilator screening FEV_1 mL	1209±505	1218±489	1200±504	1208±473	1180±493
Post-bronchodilator screening FEV_1 mL	1377±520	1393±511	1370±521	1385±496	1344±505
Change from pre- to post-bronchodilator FEV_1 mL	168±143	174±150	171±146	177±138	164±148
FEV_1/FVC %	45.0±11.6	45.1±11.6	45.0±12.0	44.6±11.5	45.1±11.6
FEV_1 % pred	50.3±15.6	50.3±15.0	49.7±15.7	50.2±14.9	49.3±15.3
GOLD stage[#]					
1 (FEV_1 ⩾80% pred)	0 (0.0)	1 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)
2 (FEV_1 50–<80% pred)	532 (51.3)	518 (50.2)	517 (50.0)	519 (50.4)	502 (48.8)
3 (FEV_1 30–<50% pred)	378 (36.4)	409 (39.6)	387 (37.5)	407 (39.5)	408 (39.7)
4 (FEV_1 <30% pred)	128 (12.3)	103 (10.0)	128 (12.4)	103 (10.0)	119 (11.6)
Baseline pulmonary medication					
SAMA[¶]	134 (12.9)	140 (13.6)	131 (12.7)	135 (13.1)	125 (12.1)
LAMA[+]	365 (35.2)	348 (33.7)	346 (33.5)	403 (39.1)	378 (36.7)
SABA[§]	424 (40.8)	433 (42.0)	401 (38.8)	421 (40.9)	400 (38.9)
LABA[f]	491 (47.3)	475 (46.0)	450 (43.6)	491 (47.7)	486 (47.2)
ICS[##]	505 (48.7)	476 (46.1)	466 (45.1)	493 (47.9)	506 (49.2)
Xanthines[¶¶]	96 (9.2)	94 (9.1)	109 (10.6)	109 (10.6)	108 (10.5)
Baseline cardiovascular medication	620 (59.7)	580 (56.2)	596 (57.7)	599 (58.2)	581 (56.5)
β-blockers	102 (9.8)	119 (11.5)	109 (10.6)	117 (11.4)	110 (10.8)

Data are presented as n (%) or mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; % pred: % predicted; 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, oxitropin; [+]: tiotropium; [§]: all patients received SABAs as rescue medication; [f]: including arformoterol, formoterol, indacaterol, fenoterol and salmeterol; [##]: including beclomethasone, budesonide, ciclesonide, mometasone furoate/formoterol fumarate hihydrate, fluticasone, formoterol/beclomethasone, formoterol/budesonide, mometasone, mometasone furoate, salmeterol/fluticasone; [¶¶]: including aminophylline, theophylline.

tiotropium+olodaterol FDC 5/5 µg and 2.5/5 µg over the corresponding individual components in both the individual studies and the combined data were statistically significant ($p<0.05$ for all comparisons) (table 2, and table S3 in the online supplementary material).

There was no influence of sex on either FEV_1 $AUC_{0–3}$ or trough FEV_1 response. An analysis of FEV_1 $AUC_{0–3}$ and trough FEV_1 response according to baseline disease severity showed that responses were lower in patients with more severe disease (table S4 in the online supplementary material).

An analysis of FEV_1 $AUC_{0–3}$ and trough FEV_1 according to inhaled corticosteroid use is presented in table 3. This confirms that tiotropium+olodaterol improves lung function whether patients were receiving inhaled corticosteroid or not.

Improvements were observed for FEV_1 values on all test days over each of the 52-week studies (fig. 3a and b, and fig. S1 in the online supplementary material). Responses in trough FVC and FVC $AUC_{0–3}$ over 24 weeks of treatment were in line with the primary end points (table S5 in the online supplementary material).

Health status and symptomatic benefit

After 24 weeks, the pre-specified analysis of the adjusted mean SGRQ total score (table 4) revealed statistically significant improvements for tiotropium+olodaterol FDC 5/5 µg over corresponding individual components (*versus* olodaterol 5 µg: −1.693 (0.553), $p<0.01$; *versus* tiotropium 5 µg: −1.233 (0.551), $p<0.05$) but not for tiotropium+olodaterol FDC 2.5/5 µg *versus* the individual components (table 5).

TABLE 2 FEV_1 AUC_{0-3} and trough FEV_1 responses (*i.e.* change from baseline) after 24 weeks of treatment (full analysis set) in Studies 1237.5 and 1237.6 separately

Treatment comparison	FEV_1 AUC_{0-3}[#] L	p-value	Trough FEV_1[¶] L	p-value
Study 1237.5 common study baseline	1.158±0.010		1.161±0.010	
Tiotropium+olodaterol 5/5 μg				
versus olodaterol 5 μg	0.123±0.012 (0.100–0.146)	<0.0001	0.082±0.012 (0.059–0.106)	<0.0001
versus tiotropium 5 μg	0.117±0.012 (0.094–0.140)	<0.0001	0.071±0.012 (0.047–0.094)	<0.0001
Tiotropium+olodaterol 2.5/5 μg				
versus olodaterol 5 μg	0.109±0.012 (0.086–0.132)	<0.0001	0.058±0.012 (0.034–0.081)	<0.0001
versus tiotropium 2.5 μg	0.093±0.012 (0.070–0.116)	<0.0001	0.029±0.012 (0.005–0.052)	0.0174
versus tiotropium 5 μg	0.102±0.012 (0.080–0.125)	<0.0001	0.046±0.012 (0.023–0.070)	0.0001
Tiotropium+olodaterol 5/5 μg				
versus tiotropium+olodaterol 2.5/5 μg	0.014±0.012 (-0.008–0.037)	0.2169	0.024±0.012 (0.001–0.048)	0.0407
Study 1237.6 common study baseline	1.150±0.010		1.150±0.010	
Tiotropium+olodaterol 5/5 μg				
versus olodaterol 5 μg	0.132±0.013 (0.108–0.157)	<0.0001	0.088±0.013 (0.063–0.113)	<0.0001
versus tiotropium 5 μg	0.103±0.012 (0.078–0.127)	<0.0001	0.050±0.013 (0.024–0.075)	0.0001
Tiotropium+olodaterol 2.5/5 μg				
versus olodaterol 5 μg	0.121±0.012 (0.096–0.145)	<0.0001	0.067±0.013 (0.042–0.092)	<0.0001
versus tiotropium 2.5 μg	0.131±0.012 (0.106–0.155)	<0.0001	0.062±0.013 (0.037–0.087)	<0.0001
versus tiotropium 5 μg	0.091±0.012 (0.066–0.115)	<0.0001	0.029±0.013 (0.004–0.054)	0.0231
Tiotropium+olodaterol 5/5 μg				
versus tiotropium+olodaterol 2.5/5 μg	0.012±0.012 (-0.013–0.036)	0.3394	0.021±0.013 (-0.004–0.046)	0.1073

Data are presented as adjusted mean±SE (95% CI), unless otherwise stated. Adjusted means were 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 to 3 h. [#]: number of patients contributing to the mixed model for repeated measurements for adjusted mean FEV_1 AUC_{0-3} Study 1237.5: tiotropium +olodaterol 5/5 μg n=522, tiotropium+olodaterol 2.5/5 μg n=521, tiotropium 5 μg n=526, tiotropium 2.5 μg n=524, olodaterol 5 μg n=525; Study 1237.6: tiotropium+olodaterol 5/5 μg n=502, tiotropium+olodaterol 2.5/5 μg n=506, tiotropium 5 μg n=500, tiotropium 2.5 μg n=504, olodaterol 5 μg n=507. [¶]: number of patients contributing to the mixed model for repeated measurements for adjusted mean trough FEV_1 Study 1237.5: tiotropium+olodaterol 5/5 μg n=521, tiotropium+olodaterol 2.5/5 μg n=518, tiotropium 5 μg n=520, tiotropium 2.5 μg n=519, olodaterol 5 μg n=519; Study 1237.6: tiotropium+olodaterol 5/5 μg n=497, tiotropium+olodaterol 2.5/5 μg n=500, tiotropium 5 μg n=498, tiotropium 2.5 μg n=499, olodaterol 5 μg n=503.

Responder rates for SGRQ total scores after 24 weeks for the combined data set (responders defined as decrease in SGRQ total score ⩾4.0 units, minimum clinically important difference) were: tiotropium +olodaterol FDC 5/5 μg, 57.5%; tiotropium+olodaterol FDC 2.5/5 μg, 53.2%, and responder rates of 49.6%, 48.7% and 44.8% for tiotropium 2.5 μg, 5 μg and olodaterol 5 μg, respectively. The increases in responder rate for tiotropium+olodaterol FDC 5/5 μg over its individual components were statistically significant (nominal p<0.05), and for tiotropium+olodaterol FDC 2.5/5 μg there was a significant improvement in responder rate *versus* olodaterol 5 μg and tiotropium 5 μg but not tiotropium 2.5 μg (table 5).

The pre-specified analysis of the key secondary end point (Mahler Transition Dyspnoea Index focal score at 24 weeks (combined data set)) showed statistically significant improvements for both tiotropium+olodaterol FDCs *versus* their mono-components (nominal p<0.05) (table S6 in the online supplementary material).

Rescue medication

Both tiotropium+olodaterol FDC 5/5 μg and 2.5/5 μg provided reductions in adjusted weekly mean daily (24-h) rescue medication use compared to the monotherapy components throughout the 52-week treatment period (fig. S2 in the online supplementary material).

Exacerbations

Figure S3 in the online supplementary material shows Kaplan–Meier estimates of probability of moderate/ severe COPD exacerbation. There was a trend for improvement in exacerbations with both FDCs *versus* the monotherapy components.

Safety

Table 6 shows a summary of adverse events for the combined data set (for Studies 1237.5 and 1237.6, see table S7 in the online supplementary material). Adverse event incidence was generally balanced across all

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TABLE 3 FEV_1 AUC_{0-3} and trough FEV_1 responses (*i.e.* change from baseline) after 24 weeks of treatment by ICS usage (full analysis set, combined data)

Treatment comparison	ICS usage			
	Yes		No	
	Adjusted mean±SE (95% CI)	p-value	Adjusted mean±SE (95% CI)	p-value
FEV_1 AUC_{0-3} L				
Common study baseline	1.073±0.009		1.226±0.010	
Tiotropium+olodaterol 5/5 µg				
versus olodaterol 5 µg	0.131±0.012 (0.107–0.154)	<0.0001	0.125±0.012 (0.101–0.148	<0.0001
versus tiotropium 5 µg	0.113±0.012 (0.089–0.137)	<0.0001	0.108±0.012 (0.085–0.132)	<0.0001
Tiotropium+olodaterol 2.5/5 µg				
versus olodaterol 5 µg	0.117±0.012 (0.093–0.141)	<0.0001	0.113±0.012 (0.090–0.137)	<0.0001
versus tiotropium 2.5 µg	0.104±0.012 (0.080–0.128)	<0.0001	0.120±0.012 (0.096–0.143)	<0.0001
versus tiotropium 5 µg	0.099±0.012 (0.075–0.123)	<0.0001	0.097±0.012 (0.074–0.120)	<0.0001
Tiotropium+olodaterol 5/5 µg				
versus tiotropium+olodaterol 2.5/5 µg	0.014±0.012 (–0.010–0.037)	0.2533	0.012±0.012 (–0.012–0.035)	0.3342
Trough FEV_1 L				
Common study baseline	1.075±0.009		1.227±0.010	
Tiotropium+olodaterol 5/5 µg				
versus olodaterol 5 µg	0.087±0.012 (0.063–0.111)	<0.0001	0.082±0.013 (0.057–0.107)	<0.0001
versus tiotropium 5 µg	0.045±0.012 (0.021–0.070)	0.0003	0.076±0.012 (0.052–0.100)	<0.0001
Tiotropium+olodaterol 2.5/5 µg				
versus olodaterol 5 µg	0.068±0.012 (0.044–0.092)	<0.0001	0.056±0.013 (0.031–0.080)	<0.0001
versus tiotropium 2.5 µg	0.030±0.012 (0.006–0.055)	0.0155	0.060±0.012 (0.036–0.084)	<0.0001
versus tiotropium 5 µg	0.026±0.013 (0.001–0.050)	0.0385	0.050±0.012 (0.025–0.074)	<0.0001
Tiotropium+olodaterol 5/5 µg				
versus tiotropium+olodaterol 2.5/5 µg	0.019±0.012 (–0.005–0.043)	0.1134	0.026±0.013 (0.002–0.051)	0.0369

FEV_1: forced expiratory volume in 1 s; AUC_{0-3}: area under the curve from 0 to 3 h; ICS: inhaled corticosteroid.

treatment groups, with the majority being mild to moderate in severity. The proportion of patients who reported at least one adverse event while on treatment was 74.4%. Overall, 6.4% of patients experienced adverse events that were deemed treatment related; rates of serious adverse events were broadly similar across treatment arms. Rates of serious adverse events were 16.4%, with fatality rates of 1.5%. The majority of treatment-emergent adverse events (incidence of >3%) were respiratory events, in particular COPD exacerbations and infections according to Medical Dictionary for Regulatory Activities (MedDRA) classifications. A higher proportion of patients in the tiotropium+olodaterol FDC 2.5/5 µg arm experienced upper respiratory infections while on treatment compared with the other arms. Respiratory events (including COPD exacerbations) were more frequent among patients treated with monotherapies. No significant abnormalities in vital signs or laboratory parameters were observed in either study.

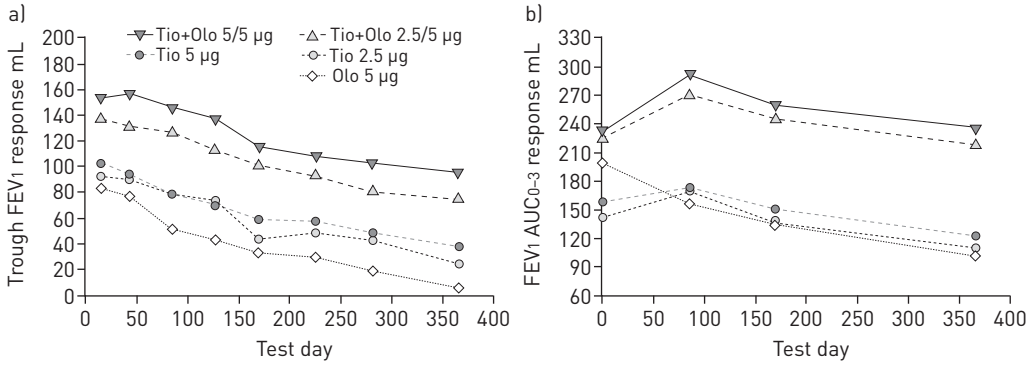

FIGURE 3 Lung function end points (combined data set) over 52 weeks: full analysis set. a) adjusted mean trough forced expiratory volume in 1 s (FEV_1); all comparisons of Tio+Olo 5/5 µg and 2.5/5 µg *versus* the monotherapies were statistically significant ($p<0.001$). b) FEV_1 area under the curve from 0 to 3 h (AUC_{0-3}); all comparisons of Tio+Olo 5/5 µg and 2.5/5 µg *versus* the monotherapies were statistically significant ($p<0.01$). Tio: tiotropium; Olo: olodaterol.

TABLE 4 St George's Respiratory Questionnaire (SGRQ) score at 24 weeks (full analysis set)

	SGRQ total score[#]	SGRQ responders[¶]
Studies 1237.5+1237.6 common study baseline	43.512±0.259	
Olodaterol 5 μg	38.366±0.396	427/954 (44.8)
Tiotropium 2.5 μg	37.792±0.390	476/960 (49.6)
Tiotropium 5 μg	37.907±0.393	465/955 (48.7)
Tiotropium+olodaterol 2.5/5 μg	37.335±0.385	527/990 (53.2)
Tiotropium+olodaterol 5/5 μg	36.674±0.386	563/979 (57.5)

Data are presented as adjusted mean±SE or n/N (%). Data were 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. [#]:number of patients contributing to the mixed model for repeated measurements for adjusted mean SGRQ across both studies: tiotropium+olodaterol 5/5 μg n=979; tiotropium+olodaterol 2.5/5 μg n=990; tiotropium 5 μg n=954; tiotropium 2.5 μg n=960; olodaterol 5 μg n=954; [¶]: a reduction in SGRQ total score at week 24 of ⩾4.0 units from baseline.

Overall incidence of adverse events in the subset of patients with cardiac history was broadly comparable (78.1%, 75.8%, 79.0%, 80.6% and 79.7% in the tiotropium+olodaterol FDC 5/5 μg, tiotropium+olodaterol FDC 2.5/5 μg, tiotropium 2.5 μg, 5 μg and olodaterol 5 μg groups, respectively). Rate ratios for major adverse cardiac events (MACE) and "cardiac disorders" System Organ Class (SOC) are presented in table S8 of the online supplementary material, which demonstrates that the incidences of these events were similar with the FDCs and individual components.

Discussion

This pair of replicate, 52-week studies of the effects of once-daily combination of tiotropium+olodaterol administered *via* the Respimat Soft Mist Inhaler in patients with moderate to very severe COPD confirm statistically significant increases for the primary lung-function end points of trough FEV_1 and FEV_1 $AUC_{0–3}$ response after 24 weeks *versus* either tiotropium or olodaterol alone. These results are supported by a range of secondary lung-function end points over 52 weeks. FEV_1 $AUC_{0–3}$ and trough FEV_1 reflect bronchodilator benefit at the beginning and end of a 24-h cycle and are important measures in the selection of optimum doses and dosing frequency.

Long-acting bronchodilators remain the cornerstone of COPD maintenance therapy [2]. However, the combination of bronchodilators with different modes of action has not been commonly prescribed in clinical practice [1] due, in part, to the lack, until recently, of available FDCs of LAMA+LABA. Olodaterol

TABLE 5 St George's Respiratory Questionnaire (SGRQ) score at 24 weeks (full analysis set): treatment comparisons

Treatment comparison	SGRQ total score[#]	p-value	Responder analysis[¶] odds ratio[§,f]	p-value
Tiotropium+olodaterol 5/5 μg				
versus olodaterol 5 μg	−1.693±0.553 (−2.778–−0.608)	0.0022	1.670±0.153 (1.395–1.999)	<0.0001
versus tiotropium 5 μg	−1.233±0.551 (−2.313–−0.153)	0.0252	1.426±0.131 (1.192–1.706)	0.0001
Tiotropium+olodaterol 2.5/5 μg				
versus olodaterol 5 μg	−1.031±0.552 (−2.113–0.052)	0.0620	1.405±0.128 (1.175–1.679)	0.0002
versus tiotropium 2.5 μg	−0.456±0.548 (−1.531–0.618)	0.4051	1.157±0.105 (0.969–1.383)	0.1071
versus tiotropium 5 μg	−0.571±0.550 (−1.649–0.507)	0.2988	1.199±0.109 (1.004–1.433)	0.0453
Tiotropium+olodaterol 5/5 μg				
versus tiotropium+olodaterol 2.5/5 μg	−0.662±0.545 (−1.731–0.407)	0.2249	1.189±0.108 (0.995–1.421)	0.0565

Data are presented as adjusted mean±se, unless otherwise stated. Data were 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. [#]:number of patients contributing to the mixed model for repeated measurements for adjusted mean SGRQ across both studies: tiotropium+olodaterol 5/5 μg n=979; tiotropium+olodaterol 2.5/5 μg n=990; tiotropium 5 μg n=954; tiotropium 2.5 μg n=960; olodaterol 5 μg n=954; [¶]: a reduction in SGRQ total score at week 24 of ⩾4.0 units from baseline. [§]: responder analysis results are from fitting a logistic-regression model with treatment as covariate and a logit link function; [f]: number of patients contributing to SGRQ responder analysis across both studies: tiotropium+olodaterol 5/5 μg n=979; tiotropium+olodaterol 2.5/5 μg n=990; tiotropium 5 μg n=955; tiotropium 2.5 μg n=960; olodaterol 5 μg n=954.

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TABLE 6 Summary of adverse events: combined analysis (treated set)

	Olodaterol 5 µg	Tiotropium 2.5 µg	Tiotropium 5 µg	Tiotropium+olodaterol 2.5/5 µg	Tiotropium+olodaterol 5/5 µg
Patients n	1038	1032	1033	1030	1029
All adverse events	795 (76.6)	758 (73.4)	757 (73.3)	769 (74.7)	761 (74.0)
Treatment-related adverse events	69 (6.6)	62 (6.0)	63 (6.1)	62 (6.0)	73 (7.1)
Adverse events leading to discontinuation	103 (9.9)	90 (8.7)	93 (9.0)	57 (5.5)	76 (7.4)
Serious adverse events	181 (17.4)	156 (15.1)	172 (16.7)	168 (16.3)	169 (16.4)
Fatal	14 (1.3)	12 (1.2)	17 (1.6)	14 (1.4)	18 (1.7)
Life-threatening	3 (0.3)	5 (0.5)	2 (0.2)	5 (0.5)	5 (0.5)
Disabling/incapacitating	1 (0.1)	3 (0.3)	2 (0.2)	0 (0.0)	3 (0.3)
Requiring hospitalisation	162 (15.6)	144 (14.0)	155 (15.0)	149 (14.5)	153 (14.9)
Prolonging hospitalisation	12 (1.2)	10 (1.0)	3 (0.3)	7 (0.7)	6 (0.6)
Other	20 (1.9)	16 (1.6)	18 (1.7)	18 (1.7)	12 (1.2)
Specific adverse events with an incidence >3%					
Respiratory, thoracic and mediastinal disorders	470 (45.3)	453 (43.9)	441 (42.7)	393 (38.2)	405 (39.4)
COPD	370 (35.6)	352 (34.1)	340 (32.9)	301 (29.2)	332 (32.3)
Cough	31 (3.0)	46 (4.5)	45 (4.4)	43 (4.2)	40 (3.9)
Dyspnoea	38 (3.7)	44 (4.3)	51 (4.9)	37 (3.6)	39 (3.8)
Infections and infestations	393 (37.9)	363 (35.2)	348 (33.7)	394 (38.3)	374 (36.3)
Nasopharyngitis	131 (12.6)	123 (11.9)	121 (11.7)	134 (13.0)	128 (12.4)
Upper respiratory tract infection	56 (5.4)	61 (5.9)	57 (5.5)	69 (6.7)	54 (5.2)
Pneumonia	36 (3.5)	24 (2.3)	26 (2.5)	31 (3.0)	34 (3.3)
Bronchitis	33 (3.2)	23 (2.2)	23 (2.2)	28 (2.7)	31 (3.0)
Gastrointestinal disorders	165 (15.9)	152 (14.7)	154 (14.9)	146 (14.2)	143 (13.9)
Diarrhoea	33 (3.2)	23 (2.2)	27 (2.6)	29 (2.8)	24 (2.3)
Musculoskeletal and connective tissue disorders	124 (11.9)	119 (11.5)	117 (11.3)	155 (15.0)	156 (15.2)
Back pain	35 (3.4)	23 (2.2)	19 (1.8)	40 (3.9)	37 (3.6)
Nervous system disorders	87 (8.4)	93 (9.0)	101 (9.8)	100 (9.7)	84 (8.2)
Headache	31 (3.0)	23 (2.2)	41 (4.0)	30 (2.9)	27 (2.6)
Vascular disorders	72 (6.9)	54 (5.2)	50 (4.8)	58 (5.6)	62 (6.0)
Hypertension	48 (4.6)	28 (2.7)	30 (2.9)	35 (3.4)	30 (2.9)

Data are presented as n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease.

is a novel once-daily LABA that has been designed as a combination partner for tiotropium, with matching pharmacokinetic and pharmacodynamic profiles [11]. Initial results have indicated that olodaterol may augment the beneficial effects of tiotropium in patients with COPD [21, 22].

The results of our trial are broadly similar with those reported for other LAMA+LABA FDCs [24–26]. However, comparisons between trials are inadvisable owing to differences in study design, including duration and patient population. Compared with those performed with indacaterol/glycopyrronium [24, 25], our studies included a higher proportion of patients with severe or very severe COPD; the fact that, in general, patients with lower lung function show smaller responses to treatment in clinical trials may explain why the increases with dual bronchodilator treatment were slightly lower. An earlier study with the FDC of tiotropium+olodaterol that included fewer patients with very severe disease showed larger effect sizes than the current studies [27].

Symptomatic benefit of the FDC was demonstrated by statistically significant improvements in mean SGRQ total score; compared with monotherapy, this was observed with tiotropium+olodaterol FDC 5/5 µg but not with 2.5/5 µg. Improvements in SGRQ that exceeded the minimum clinically important difference of 4 units for this measure were seen in all treatment arms, but the difference between the FDCs and the monotherapies did not meet this threshold [28]. Since there was no placebo arm, further analysis of the relevance of these improvements is limited. Responder analyses have been proposed as an additional approach to assessing efficacy of treatments in COPD, particularly for studies in which second and third treatments are added to current therapy [28]. In our studies, responder rates, defined as a reduction in

SGRQ total score of ⩾4 units from baseline, were significantly greater for tiotropium+olodaterol FDC 5/5 μg compared with its monotherapy components and for 2.5/5 μg compared with olodaterol 5 μg.

The doses of tiotropium and olodaterol used in these studies were based on previously published dose–response studies of this drug combination [21, 22]. In the latter, although a dose response for lung function was observed with increasing doses of tiotropium added to a fixed dose of olodaterol, the increase with tiotropium 2.5 μg when added to olodaterol was smaller than the increase with 5 μg when added to olodaterol [21, 22]. Overall, based on the results of the current studies and TIOSPIR, the optimum dose of tiotropium is considered to be 5 μg, both as monotherapy and in combination with olodaterol.

The assessment of safety in our studies yielded no specific concerns in spite of the inclusion of a relatively large proportion of patients with GOLD stage 4 disease and a substantial proportion with co-morbidities. The number of adverse events in the arms with tiotropium+olodaterol FDCs were not higher than in those receiving the individual components; there was also no difference in incidence of adverse events with the higher and lower doses of tiotropium.

"Dry mouth" (typically associated with LAMAs) was reported as a side effect in <2% of patients, possibly attributable to the fact that the majority of patients included in these trials had previously received tiotropium. Additionally, there appears to be no increase in risk of experiencing either a MedDRA SOC "cardiac" or MACE with tiotropium+olodaterol FDC *versus* the mono-components, and no imbalances between treatment groups were seen in the subgroup of patients with a history of cardiac disease.

Our studies have several limitations. Firstly, there was no placebo group; it was considered inappropriate to deny patients with symptomatic COPD the use of even one long-acting bronchodilator in a study lasting 1 year. Furthermore, these studies were not designed to assess the impact of tiotropium+olodaterol on COPD exacerbations. However, the limited exacerbation data from these studies are encouraging and in line with results for other LAMA+LABA combinations [25]. Further studies powered to examine this end point are planned.

Conclusions

These replicate studies confirm the efficacy and safety of once-daily dosing with tiotropium+olodaterol FDC as maintenance therapy in patients with moderate to very severe COPD (GOLD stage 2–4). The fixed dose of 5 μg of each appears to be optimal in the combination, providing significant improvement in all three primary end points (trough FEV_1, FEV_1 $AUC_{0–3}$ and health status) compared to tiotropium or olodaterol administered alone.

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