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ORIGINAL RESEARCH

Randomized, Double-Blind, Dose-Finding Study for Tiotropium when Added to Olodaterol, Administered via the Respimat® Inhaler in Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Introduction: Combining long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs) is beneficial in chronic obstructive pulmonary disease (COPD), as the two classes of bronchodilator have complementary modes of action. The optimal dose for the fixed-dose combination of the LAMA tiotropium and the LABA olodaterol needed to be determined. In this phase II trial, the dose response of tiotropium on top of olodaterol was investigated in a free-dose combination, while other phase II studies have explored different doses of olodaterol on top of tiotropium, with both drugs delivered using the Respimat® inhaler.

Methods: This was a double-blind incomplete crossover trial in which 233 patients with moderate or severe COPD were randomized to receive four out of eight free-dose combinations of olodaterol (5 or 10 μg) and tiotropium (1.25, 2.5, or 5 μg) or placebo for 4 weeks each. Primary end point was trough forced expiratory volume in 1 s (FEV_1) change from baseline (response) after 4 weeks.

Results: Addition of tiotropium 1.25, 2.5, and 5 μg to olodaterol 5 μg increased mean trough

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FEV_1 response by 0.054, 0.065, and 0.084 L, respectively; addition of tiotropium 1.25, 2.5, and 5 μg to olodaterol 10 μg increased mean trough FEV_1 response by 0.051, 0.083, and 0.080 L, respectively. All treatments were well tolerated and incidence of adverse events was similar with all treatments.

Conclusions: Overall, a dose response for tiotropium on top of both doses of olodaterol was observed, with increasing improvements in trough FEV_1 compared to olodaterol alone as the tiotropium dose was increased.

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Keywords: Bronchodilator; Chronic obstructive pulmonary disease; Dose finding; Long-acting β_2-agonists; Long-acting muscarinic antagonists; Olodaterol; Tiotropium

INTRODUCTION

The two main classes of bronchodilator used in chronic obstructive pulmonary disease (COPD) are long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), and use of LAMA + LABA combination in COPD is supported by international guidelines [1]. Combining bronchodilators with complementary modes of action in COPD offers greater lung function benefits than individual agents, with similar tolerability and safety [2, 3]. A number of LAMA/LABA fixed-dose combinations (FDCs) are now available or in development for the treatment of COPD, and these combinations have shown improvements in lung function, exercise tolerance, and patient-reported outcomes compared to individual agents [3].

Tiotropium is a well-established, once-daily LAMA for the maintenance treatment of COPD [4]. Olodaterol is a once-daily LABA with high β_2 selectivity and a fast onset of action [5, 6] that has demonstrated efficacy and tolerability in phase III trials [7–10] and has been approved for use in COPD in the US, Europe, and several other countries. A clinical program investigating the efficacy and safety of the FDC of tiotropium + olodaterol has been completed, and the FDC has been approved in the US and Canada for the treatment of COPD.

Often when combining drugs in an FDC, it is assumed that the optimal doses should reflect those of the registered components, although this may not always be the case [11]. Prior to the phase III program for the tiotropium + olodaterol FDC, a novel approach was taken to test this assumption and a series of phase II dose–response trials was developed to determine the dose response of each component within the FDC.

Two phase II studies (1237.4 [NCT00696020] and 1237.9 [NCT00720499]) investigated different doses of olodaterol 2–10 μg (1237.9: 2 or 5 μg; 1237.4: 2, 5, or 10 μg) when added to tiotropium 5 μg, compared to tiotropium monotherapy [12]. In the study presented here, the dose response of tiotropium when added to olodaterol as a free-dose combination was investigated to determine the doses to be studied in the phase III tiotropium + olodaterol trials. Tiotropium 1.25, 2.5, and 5 μg were added to olodaterol 5 and 10 μg in free combination. The doses of tiotropium were chosen to provide a robust evaluation of the most relevant part of its dose–response curve and the highest dose included—5 μg—is its licensed dose in the Respimat® inhaler as monotherapy. In this study, a free combination of tiotropium and olodaterol (i.e., using a separate Respimat device for each treatment rather than the combination of treatments being delivered via one device) was used rather than the FDC because an FDC for the lower dose of tiotropium was not available.

The objective of the study reported here was to identify the optimal once-daily doses of tiotropium and olodaterol administered in free combination via the Respimat inhaler in COPD in terms of lung function and tolerability after 4 weeks.

METHODS

Study Design

This was a randomized, double-blind, phase IIb, incomplete crossover trial (ClinicalTrials.gov #NCT01040403; 1237.18) conducted between February 2010 and February 2011. Patients were randomized to receive four out of eight combinations: olodaterol (5 or 10 μg) in combination with tiotropium (1.25, 2.5, or 5 μg) or placebo (in place of tiotropium) for 4 weeks each in a randomized order (Fig. 1). There was a washout period before screening and, following the screening visit, there was a 2-week run-in period prior to randomization to ensure clinical stability. In between each treatment period, there were 3-week washout periods and patients were evaluated for 3 weeks following the final dose of the last treatment.

The trial was carried out in compliance with the Declaration of Helsinki (1964, as revised in 2008), in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and local regulations. Written, informed consent was obtained from all patients.

Patients

Patients aged ≥40 years with COPD and a smoking history of >10 pack-years could be recruited if they had a post-bronchodilator forced expiratory volume in 1 s (FEV_1) of ≥30% and <80% of the predicted normal and a post-bronchodilator FEV_1/forced vital capacity (FVC) of <70% at screening (Global

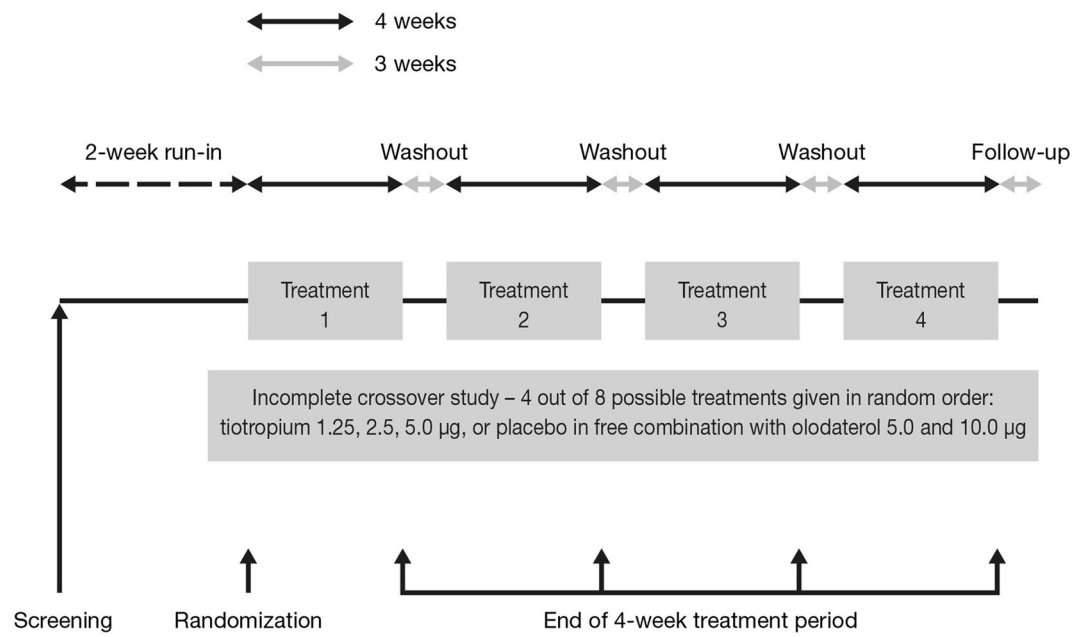

Fig. 1 Trial design

initiative for chronic Obstructive Lung Disease [GOLD] 2–3). Exclusion criteria included a significant disease other than COPD, history of asthma, history of myocardial infarction within the previous year, clinically relevant cardiac arrhythmia, paroxysmal tachycardia, and history of life-threatening pulmonary obstruction.

Patients continued to take inhaled corticosteroids throughout the trial, if used prior to study entry as maintenance therapy. During run-in, washout, and post-treatment follow-up periods, LABAs and short-acting muscarinic antagonists were permitted, with a 48-h washout for LABAs and an 8-h washout for short-acting muscarinic antagonists before pulmonary function testing. LAMAs other than study drug were only permitted during the follow-up period and the short-acting β_2-agonist salbutamol was provided as rescue medication for use throughout the trial.

Treatments

Tiotropium (or placebo) and olodaterol were provided in two separate Respimat inhalers. Patients were to inhale two puffs of each of the assigned Respimat inhalers every morning between 7.00 A.M. and 10.00 A.M. On study visit days, patients were to inhale the study drug at the clinic instead of at home. Patients recorded whether they took the medication in a diary.

Assessments

Pulmonary function tests were performed at screening, on Day 1 of each treatment period (at 1 h pre-dose and 10 min pre-dose, 5 and 30 min post-dose, and 1, 2, and 3 h post-dose), after 4 weeks of each treatment (at same time points as Day 1 plus at 4, 5, and 6 h post-dose), and at follow-up. At each time point, spirometric measurements were performed in triplicate, and the highest FEV_1 and FVC values were recorded. Spirometers and their use, including daily calibration, were to meet American Thoracic Society and European Respiratory Society criteria.

Patients recorded the number of puffs of rescue medication they took during the day and at night in a diary. Patient's global rating was assessed at the end of each treatment period (before spirometry); patients rated their own respiratory health compared to the day before commencing each treatment period on a 7-point scale from "very much better" (1) to "very much worse" (7). Physician's global evaluation was assessed on the first and last day of each treatment period; the investigator rated the patient's overall clinical condition from "poor" (1–2) to "excellent" (7–8).

All adverse events (AEs) were recorded at each visit. Clinical laboratory testing was conducted at screening and at the end of each treatment period, and a standard 12-lead electrocardiogram was performed at screening and at all treatment visits 30 and 40 min post-dose. Any abnormalities or worsening of baseline conditions were reported as AEs.

Study Outcomes

The primary end point was trough FEV_1 response (change from baseline) after 4 weeks of treatment. Trough FEV_1 was defined as the mean of the two pre-treatment FEV_1 values (at 1 h and 10 min before dosing, respectively) at the end of the dosing interval, and baseline FEV_1 was defined as the mean of the two pre-treatment FEV_1 values (1 h pre-dose and 10 min pre-dose) measured prior to administration of the first dose of study medication.

Secondary end points included trough FVC, FEV_1, and FVC area under the curve from 0 to 6 h ($AUC_{0–6}$), mean weekly rescue medication use, physician's global evaluation, and patient's global rating. Incidence and severity of AEs were reported irrespective of causality, and pulse rate and blood pressure were recorded in conjunction with spirometry at 10 min pre-dose and 30 min post-dose.

Statistical Analysis

To detect a treatment difference of 0.050 L in trough FEV_1 with 90% power, assuming a standard deviation of 0.140 L, 85 patients were required to complete the study (based on a complete crossover design). To determine the number of patients required for the incomplete-block design used in this trial, the equation $n = 7\,m/3$ was used, where m is the number of patients required for a complete crossover study. Allowing for a discontinuation rate of 12%, 224 patients needed to be randomized.

The full analysis set was defined as treated patients who provided baseline data and at least one on-treatment value for the primary end point after 4 weeks of treatment. This set of patients was used for all efficacy analyses presented here.

Comparison between treatment groups for the primary and secondary end points was based on a mixed-effect repeated measures model including treatment and period as fixed effects, patient as a random effect, and (study) baseline as a covariate. Adjusted mean values and treatment comparisons are presented with corresponding 95% confidence intervals. Statistical analysis was carried out using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Disposition and Baseline Characteristics

In total, 283 patients were enrolled into the study and 233 were randomized to treatment. One randomized patient was withdrawn before receiving any medication due to an episode of atrial fibrillation. Overall, 91.8% of patients completed all four assigned treatments (Fig. 2).

Patient demographics and baseline characteristics are shown in Table 1; 37.5% of patients were GOLD 2 and 59.9% were GOLD 3. Most patients were taking pulmonary medications in the 3 months prior to screening (91.4%), most commonly LABAs, short-acting β_2-agonists, inhaled corticosteroids, and LAMAs (Table 1). The most common concomitant diagnoses were hypertension (41.4%) and hypercholesterolemia (18.1%); all other concomitant diagnoses had an incidence <10%.

Efficacy

Lung Function

Trough FEV_1 responses with olodaterol 5 and 10 μg were 0.071 and 0.083 L, respectively, after 4 weeks of treatment. Trough FEV_1 responses increased with tiotropium + olodaterol doses compared to olodaterol monotherapy after 4 weeks of treatment. Compared to olodaterol 5 μg monotherapy, the addition of tiotropium 1.25, 2.5, and 5 μg increased trough FEV_1 response by 0.054, 0.065, and 0.084 L, respectively, and compared to olodaterol 10 μg, the addition of tiotropium 1.25, 2.5, and 5 μg increased trough FEV_1 by 0.051, 0.083, and 0.080 L, respectively (Table 2).

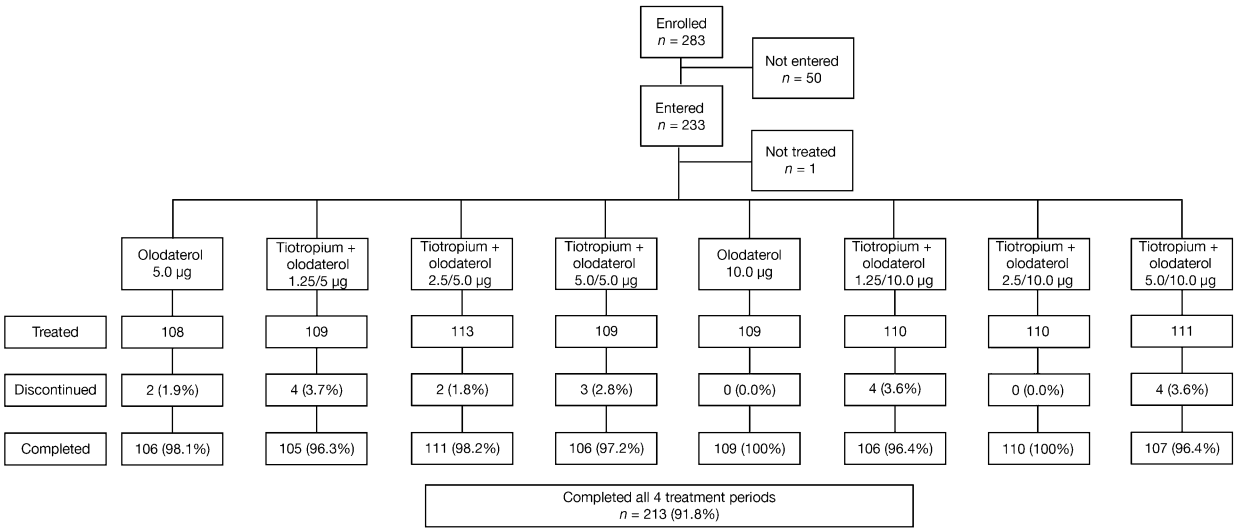

Fig. 2 Patient disposition

The FEV_1 profiles after 4 weeks of treatment showed clear improvements with tiotropium + olodaterol compared to olodaterol monotherapy and improvements in FEV_1 with increasing tiotropium doses on top of olodaterol 5 and 10 µg (Fig. 3). FEV_1 $AUC_{0–6}$ responses showed incremental increases with increasing dose of tiotropium with both olodaterol doses (Table 2). The additional benefits from adding each dose of tiotropium to olodaterol were larger for FEV_1 $AUC_{0–6}$ than for trough FEV_1 although, in both cases, FEV_1 response was greater overall with the combination therapy compared to olodaterol (Table 2).

The FVC profiles showed improvements with the addition of tiotropium to both olodaterol doses (Fig. 4) and FVC $AUC_{0–6}$ and trough FVC results showed greater improvements with tiotropium + olodaterol compared to olodaterol alone. Tiotropium added to olodaterol 5 µg showed increases in trough FVC between 0.099 and 0.120 L compared to olodaterol 5 µg, while tiotropium added to olodaterol 10 µg increased trough FVC by 0.127–0.131 L. FVC $AUC_{0–6}$ also increased with the addition of tiotropium 1.25, 2.5, and 5 µg compared to olodaterol 5 µg alone by 0.131–0.150 L, and added to olodaterol 10 µg by 0.179–0.213 L (Table 3).

Other Secondary End Points

Weekly mean rescue medication use decreased from baseline levels with all treatments after 4 weeks, with no notable differences between treatment arms. Mean number of puffs per day were 1.4, 1.5, 1.3, and 1.4 with olodaterol 5 µg, tiotropium + olodaterol 1.25/5, 2.5/5, and 5/5 µg, respectively, and 1.6, 1.3, 1.2, and 1.3 puffs per day with olodaterol 10 µg, tiotropium + olodaterol 1.25/10, 2.5/10, and 5/10 µg, respectively. Daytime and nighttime rescue medication use was also decreased with all treatments (Table S1 in the supplementary material).

There were improvements compared to baseline in physician's global evaluation after 4 weeks in all treatment arms, with the smallest increases with olodaterol monotherapies (Table S2 in the supplementary material). Patients generally rated their health as "a little better" on the patient's global rating after

Table 1 Baseline demographics and patient characteristics (treated set)

	Patients ($n = 232$)
Male, *n* (%)	133 (57.3)
Mean (SD) age, years	63.3 (8.2)
Smoking status, *n* (%)	
Ex-smoker	125 (53.9)
Current smoker	107 (46.1)
Mean (SD) smoking history, pack-years	41.6 (19.4)
Mean (SD) pre-bronchodilator FEV_1, L	1.379 (0.482)
Mean (SD) post-bronchodilator	
FEV_1, L	1.551 (0.499)
% predicted normal FEV_1	55.03 (13.12)
FEV_1/FVC, %	50.99 (10.34)
Mean (SD) change from pre- to post-bronchodilator FEV_1, L	0.172 (0.143)
Mean (SD) % change from pre- to post-bronchodilator FEV_1	14.11 (12.64)
GOLD, *n* (%)	
1	1 (0.4)
2	139 (59.9)
3	87 (37.5)
Concomitant diagnoses with incidence >10%, *n* (%)	
Hypertension	96 (41.4)
Hypercholesterolemia	42 (18.1)
Baseline pulmonary medication (any), *n* (%)	212 (91.4)
SAMA	39 (16.8)
LAMA	130 (56.0)
LABA	145 (62.5)
SABA[a]	133 (57.3)
ICS[b]	131 (56.5)
Oral steroids[b]	6 (2.6)
Xanthines	14 (6.0)

FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *GOLD* Global initiative for chronic Obstructive Lung Disease, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *SAMA* short-acting muscarinic antagonist, *SABA* short-acting β-agonist, *SD* standard deviation

[a] Only salbutamol permitted during treatment periods as rescue medication

[b] Patients permitted to continue during treatment periods

4 weeks across treatment arms (Table S2 in the supplementary material).

Safety

AEs are summarized in Table 4; the most common were nasopharyngitis and COPD exacerbation. AEs leading to discontinuation occurred in <2% of patients with any treatment. The incidence of serious AEs is presented in Table 4; two patients died during the washout period following olodaterol 10 μg treatment. Both deaths were caused by myocardial infarction and were not considered by investigators to be related to study drug. Across treatment arms, incidence of AEs was similar, with no increase in AEs for tiotropium + olodaterol versus olodaterol or with increasing doses of tiotropium. There were no notable changes in vital signs with any treatment.

DISCUSSION

This trial demonstrated that the combination of tiotropium + olodaterol delivered via the Respimat inhaler resulted in greater

Table 2 FEV_1 trough and AUC_{0-6} responses after 4 weeks of treatment (full analysis set)

Treatment	Trough FEV_1 mean (SE) response, L	Difference from O monotherapy, L (95% CI)	*P* value	FEV_1 AUC_{0-6} mean (SE) response, L	Difference from O monotherapy, L (95% CI)	*P* value
O 5 μg	0.071 (0.018)			0.188 (0.020)		
+T 1.25 μg	0.125 (0.018)	0.054 (0.016, 0.092)	0.0057	0.267 (0.020)	0.078 (0.040, 0.117)	<0.0001
+T 2.5 μg	0.136 (0.018)	0.065 (0.027, 0.103)	0.0009	0.287 (0.020)	0.099 (0.060, 0.137)	<0.0001
+T 5 μg	0.155 (0.018)	0.084 (0.046, 0.122)	<0.0001	0.307 (0.020)	0.118 (0.080, 0.157)	<0.0001
O 10 μg	0.083 (0.018)			0.198 (0.020)		
+T 1.25 μg	0.134 (0.018)	0.051 (0.013, 0.089)	0.0092	0.296 (0.020)	0.098 (0.060, 0.136)	<0.0001
+T 2.5 μg	0.166 (0.018)	0.083 (0.045, 0.122)	<0.0001	0.320 (0.020)	0.121 (0.083, 0.159)	<0.0001
+T 5 μg	0.163 (0.018)	0.080 (0.042, 0.119)	<0.0001	0.342 (0.020)	0.144 (0.105, 0.182)	<0.0001

AUC_{0-6} area under the curve from 0 to 6 h, *CI* confidence interval, *FEV_1* forced expiratory volume in 1 s, *O* olodaterol, *SE* standard error, *T* tiotropium

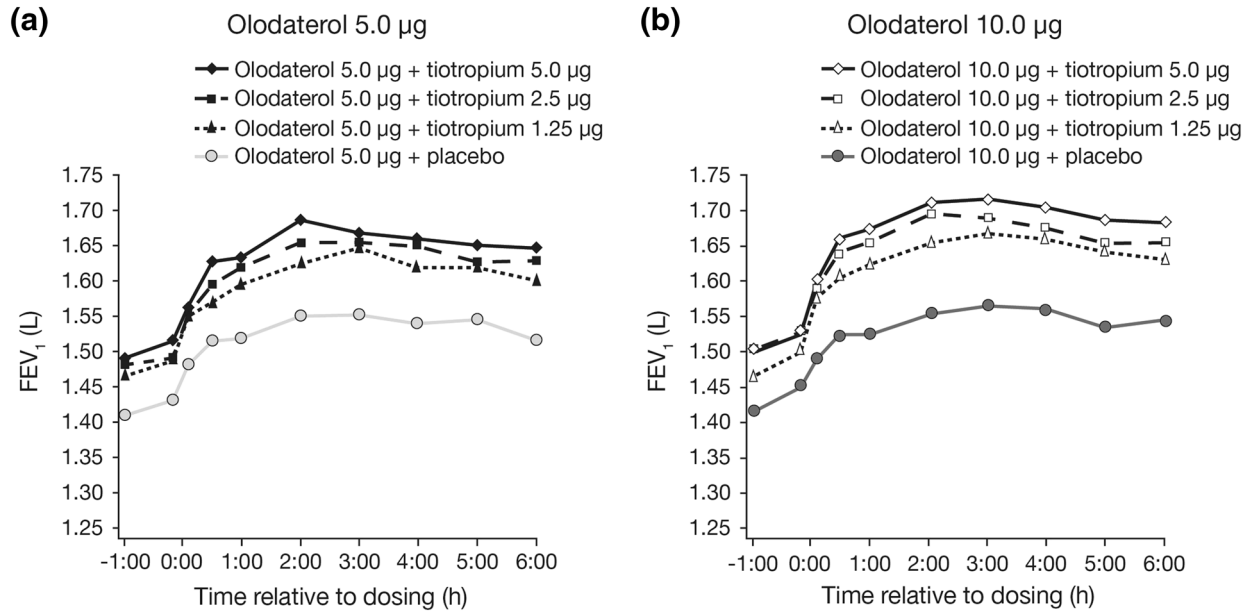

Fig. 3 FEV_1 profiles after 4 weeks of treatment with tiotropium 1.25, 2.5, 5 μg, and placebo on top of olodaterol 5 μg (**a**) and 10 μg (**b**). −1:00 value is mean of 1 h pre-treatment and 10 min pre-treatment values. $P < 0.05$ for all tiotropium + olodaterol versus olodaterol 5 μg in (**a**) and versus olodaterol 10 μg in (**b**). *FEV_1* forced expiratory volume in 1 s

improvements in lung function than olodaterol monotherapy, as shown by trough FEV_1 (primary end point) after 4 weeks of treatment. Dose-related increases in trough FEV_1 were observed with increasing doses of tiotropium on top of both doses of olodaterol, and

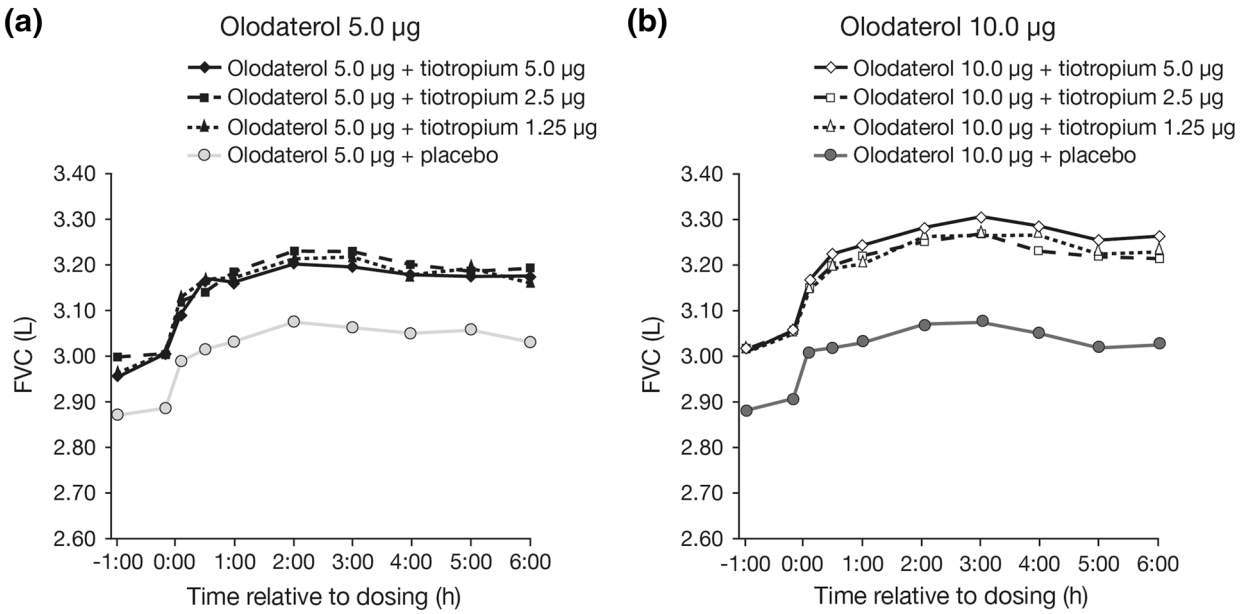

Fig. 4 FVC profiles after 4 weeks of treatment with tiotropium 1.25, 2.5, 5 µg, and placebo on top of olodaterol 5 µg (**a**) and 10 µg (**b**). −1:00 value is mean of 1 h pre-treatment and 10 min pre-treatment values. $P < 0.05$ for all tiotropium + olodaterol versus olodaterol 5 µg in (**a**) and versus olodaterol 10 µg in (**b**). *FVC* forced vital capacity

Table 3 FVC trough and AUC_{0-6} responses after 4 weeks of treatment (full analysis set)

Treatment	Trough FVC mean (SE) response, L	Difference from O monotherapy, L (95% CI)	*P* value	FVC AUC_{0-6} mean (SE) response, L	Difference from O monotherapy, L (95% CI)	*P* value
O 5 µg	0.114 (0.029)			0.282 (0.032)		
+T 1.25 µg	0.214 (0.029)	0.099 (0.040, 0.159)	0.0010	0.421 (0.032)	0.139 (0.081, 0.197)	<0.0001
+T 2.5 µg	0.234 (0.029)	0.120 (0.061, 0.179)	<0.0001	0.432 (0.032)	0.150 (0.092, 0.207)	<0.0001
+T 5 µg	0.215 (0.029)	0.100 (0.041, 0.160)	0.0010	0.414 (0.032)	0.131 (0.073, 0.189)	<0.0001
O 10 µg	0.122 (0.029)			0.277 (0.032)		
+T 1.25 µg	0.253 (0.029)	0.131 (0.071, 0.190)	<0.0001	0.466 (0.032)	0.189 (0.131, 0.247)	<0.0001
+T 2.5 µg	0.253 (0.029)	0.131 (0.072, 0.191)	<0.0001	0.456 (0.032)	0.179 (0.121, 0.236)	<0.0001
+T 5 µg	0.249 (0.029)	0.127 (0.067, 0.187)	<0.0001	0.490 (0.032)	0.213 (0.155, 0.271)	<0.0001

AUC_{0-6} area under the curve from 0 to 6 h, *CI* confidence interval, *FVC* forced vital capacity, *O* olodaterol, *SE* standard error, *T* tiotropium

pronounced improvements in trough FEV_1 were observed with the combined tiotropium and olodaterol doses. Primary end point data were supported by the FEV_1 and FVC profiles from 0 to 6 h. Trough FEV_1 was selected as the primary end point for this study to allow an evaluation of the effect of the drug combination at the end of the dosing period and, together with the

Table 4 Summary of AEs (treated set)

	O 5 µg, *n* (%) (*n* = 108)	**T + O 1.25/5 µg, *n* (%) (*n* = 109)**	**T + O 2.5/5 µg, *n* (%) (*n* = 113)**	**T + O 5/5 µg, *n* (%) (*n* = 109)**	**O 10 µg, *n* (%) (*n* = 109)**	**T + O 1.25/ 10 µg, *n* (%) (*n* = 110)**	**T + O 2.5/10 µg, *n* (%) (*n* = 110)**	**T + O 5/10 µg, *n* (%) (*n* = 111)**
Any AE	35 (32.4)	42 (38.5)	38 (33.6)	35 (32.1)	36 (33.0)	32 (29.1)	37 (33.6)	39 (35.1)
Drug-related[a]	2 (1.9)	4 (3.7)	1 (0.9)	4 (3.7)	2 (1.8)	1 (0.9)	2 (1.8)	5 (4.5)
AEs leading to discontinuation	1 (0.9)	2 (1.8)	2 (1.8)	2 (1.8)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)
Serious AEs	4 (3.7)	1 (0.9)	3 (2.7)	1 (0.9)	2 (1.8)	1 (0.9)	5 (4.5)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to hospitalization	4 (3.7)	1 (0.9)	3 (2.7)	1 (0.9)	0 (0.0)	1 (0.9)	5 (4.5)	0 (0.0)
AEs with incidence >3%								
Nasopharyngitis	11 (10.2)	12 (11.0)	8 (7.1)	3 (2.8)	7 (6.4)	8 (7.3)	4 (3.6)	2 (1.8)
COPD	7 (6.5)	4 (3.7)	4 (3.5)	8 (7.3)	6 (5.5)	7 (6.4)	5 (4.5)	4 (3.6)
Cough	1 (0.9)	4 (3.7)	1 (0.9)	4 (3.7)	0 (0.0)	4 (3.6)	2 (1.8)	3 (2.7)
Dyspnea	4 (3.7)	1 (0.9)	1 (0.9)	3 (2.8)	1 (0.9)	0 (0.0)	2 (1.8)	1 (0.9)
Headache	2 (1.9)	4 (3.7)	2 (1.8)	2 (1.8)	1 (0.9)	2 (1.8)	1 (0.9)	1 (0.9)

AE adverse event, *COPD* chronic obstructive pulmonary disease, *O* olodaterol, *T* tiotropium

[a] Investigator-defined

FEV_1 0 to 6-h profiles, allows investigation of the 24-h lung function profile.

The free combination of tiotropium + olodaterol was well tolerated at all doses in this trial, with no specific safety concerns or cardiovascular safety concerns raised. There was no increase in AEs with tiotropium + olodaterol compared to monotherapies and no dose dependency observed for AEs. The safety of the combination has subsequently been assessed in a pooled safety analysis of two replicate phase III tiotropium + olodaterol FDC studies (Study 1237.5: NCT01431274; Study 1237.6: NCT01431287). Tiotropium + olodaterol FDC was well tolerated in these trials, with comparable AE incidence to monotherapy [13].

This trial was part of a novel approach to dose finding with drug combinations, in which the dose response of each component within the FDC was explored to confirm whether it is the same as the dose response when used as monotherapy. The dose response of olodaterol alone was investigated in olodaterol dose-finding studies, which identified olodaterol 5 and 10 µg as the doses to be taken forward to the phase III trials [14], and the dose response of tiotropium monotherapy in the Respimat inhaler has been investigated [15], with 5 µg performing best and subsequently licensed in COPD. The present study was not powered to detect differences between different combined doses of tiotropium + olodaterol, but it was sufficient to identify dose ordering for

FEV_1 responses for the dose combinations. These data, together with the results of olodaterol and tiotropium dose-finding studies and the two other tiotropium + olodaterol dose-finding studies, led to tiotropium + olodaterol 2.5/5 and 5/5 μg FDCs being investigated in the phase III program. The results of this study of the free combinations of tiotropium + olodaterol 2.5/5 and 5/5 μg are consistent with the results from the phase III trials that were subsequently performed with FDCs of tiotropium + olodaterol 2.5/5 and 5/5 μg, and demonstrated similar effect sizes compared to tiotropium [16].

The results showed that with this drug combination, it may have been acceptable to simply use the doses of each agent that are considered optimal as monotherapies. However, the preclinical studies had suggested that there may be some synergistic effect with the combination of tiotropium + olodaterol at sub-optimal doses [17] and this is one of the reasons why this study was performed. It is not known whether this effect occurs in humans at sub-optimal doses, but it does not appear that the optimal dose of tiotropium + olodaterol is any lower than the approved doses of the monotherapies. This study demonstrated that the most suitable combination of tiotropium + olodaterol was at the licensed doses of the individual therapies; however, this result is specific to this combination of therapies and may not necessarily be the same for other combinations of therapies.

In addition to the main investigation of lung function in this study, a number of additional end points were included in the trial to explore the effects of the drug combination. The data presented here demonstrate that rescue medication use decreased compared to baseline with all treatments, but the differences between treatment groups were small. It is challenging in phase II studies to investigate effects on symptoms given relatively low patient numbers, but the results of subsequent tiotropium + olodaterol FDC phase III studies demonstrated that lung function improvements were translated into symptom improvements. There were greater reductions in rescue medication use with combined therapy than with monotherapies over 52 weeks in two phase III studies (1237.5; 1237.6) [16]. Physician's global evaluation scores improved with all treatments, and patients generally rated their health as "a little better" on the patient's global rating scale, but the results across treatment arms were similar.

Consistent with the results of the olodaterol phase III program [7–10], there was little difference in efficacy between olodaterol 5 and 10 μg in this study. Both tiotropium + olodaterol 2.5/5 and 5/5 μg have subsequently demonstrated efficacy and acceptable tolerability in large phase III trials investigating the FDCs in the Respimat inhaler [16, 18]. The phase III program was designed to determine whether the improvements in lung function seen in the phase II trials translated into long-term benefits in lung function and improvements in patient-reported outcomes, as well as investigating the risk:benefit ratio of the FDCs compared to monotherapies. Two replicate 12-month studies have demonstrated improvements in lung function with tiotropium + olodaterol FDC compared to monotherapies at 24 weeks and improvements in St. George's Respiratory Questionnaire score compared to monotherapies (tiotropium + olodaterol 5/5 μg) [16].

One potential limitation of the study is that, because the lower dose of tiotropium was not available in an FDC, the tiotropium + olodaterol doses were administered as free-dose combinations in separate inhalers.

However, it should be possible to extrapolate the results to the FDCs. As the formulations for the FDC are very similar to those used in the monotherapies, the differences in administration are minor (it takes only a little more time to use two inhalers rather than one) and compliance with two bronchodilators is generally relatively high. Another possible limitation is the lack of a placebo group, which may have further put the effect sizes into context. As this was not central to the primary objectives of the study, and there were already a large number of treatment arms, it was not possible. Phase III trials have subsequently investigated tiotropium + olodaterol with a placebo arm [19]. The study also excluded patients with GOLD 4 COPD; again, these patients have been included in later phase III trials [16, 19].

CONCLUSION

Overall, the addition of all tiotropium doses to olodaterol resulted in improvements in lung function compared to olodaterol alone after 4 weeks, and incremental increases in FEV_1 were observed with increasing doses of tiotropium on top of each olodaterol dose. The free combination of tiotropium and olodaterol was well tolerated at all doses, with a similar AE incidence to olodaterol alone.

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Compliance with ethics guidelines. The trial was carried out in compliance with the Declaration of Helsinki (1964, as revised in 2008), in accordance with the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and local regulations. Written, informed consent was obtained from all patients.

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