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The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease

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ABSTRACT

Background: This study investigated the effects on 24-h lung function and lung volume of a once-daily fixed-dose combination (FDC) of the long-acting muscarinic antagonist tiotropium and the long-acting β_2-agonist olodaterol in patients with chronic obstructive pulmonary disease.
Methods: This was a randomised, double-blind, placebo-controlled, Phase III trial with an incomplete crossover design. Patients received four of the following six treatment options for 6 weeks each: placebo, olodaterol 5 μg, tiotropium 2.5 μg, tiotropium 5 μg, tiotropium + olodaterol FDC 2.5/5 μg and tiotropium + olodaterol FDC 5/5 μg, all delivered via the Respimat® inhaler. The primary end point was forced expiratory volume in 1 s (FEV_1) area under the curve from 0 to 24 h (AUC_{0-24}) response after 6 weeks of treatment; key secondary end points were FEV_1 AUC from 0 to 12 h and AUC from 12 to 24 h, and further end points included lung-volume parameters measured using body plethysmography (subset of patients), measures of peak and trough FEV_1, and incidence of adverse events.
Results: A significant improvement in FEV_1 AUC_{0-24} response was observed with tiotropium + olodaterol 5/5 μg and 2.5/5 μg *versus* placebo and monotherapies after 6 weeks of treatment; mean response with tiotropium + olodaterol 5/5 μg *versus* placebo was 0.280 L ($p < 0.0001$). Differences to monotherapies with tiotropium + olodaterol 5/5 μg were 0.115 L *versus* olodaterol 5 μg, 0.127 L *versus* tiotropium 2.5 μg and 0.110 L *versus* tiotropium 5 μg ($p < 0.0001$ for all comparisons). Secondary end points supported these data. No safety concerns were identified.
Conclusions: Overall, this study demonstrated improvements in lung function over 24 h with an FDC of tiotropium + olodaterol over tiotropium or olodaterol alone, with no observed difference in tolerability. ClinicalTrials.gov number: NCT01559116.

1. Introduction

Tiotropium is an established once-daily long-acting muscarinic antagonist (LAMA) that is effective at improving lung function and patient-reported outcomes in chronic obstructive pulmonary disease (COPD) [1–6]. Olodaterol is a novel once-daily long-acting β_2-agonist (LABA) that is highly selective with nearly full intrinsic activity at β_2 receptors [7,8]. Phase III trials have demonstrated that olodaterol is effective at improving lung function over 24 h in patients with COPD [9–12] and, importantly, also provides improvements in patient-reported symptoms [11].

Abbreviations: AUC_{0-12}, area under the curve from 0 to 12 h; AUC_{0-24}, area under the curve from 0 to 24 h; AUC_{12-24}, area under the curve from 12 to 24 h; COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; $Peak_{0-3}$, maximum value obtained in the first 3 h after dosing; RV, residual volume.

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Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines recognise that combining bronchodilators with different mechanisms may increase the degree of bronchodilation for equivalent or lesser side effects than a single bronchodilator [13]. The complementary pharmacological profiles of tiotropium and olodaterol make them a suitable combination and data from preclinical studies support their combination [14]. Two 4-week Phase II studies demonstrated greater improvements in forced expiratory volume in 1 s (FEV_1) with a once-daily fixed-dose combination (FDC) of tiotropium and olodaterol than either monocomponent [15,16]. These studies also explored the optimal dose for the combination and tiotropium + olodaterol FDC 2.5/5 μg and 5/5 μg were selected for further investigation in Phase III studies.

While other pivotal Phase III trials have investigated the effects of tiotropium + olodaterol FDC on FEV_1 at trough and up to 3 h post-dose, this placebo-controlled trial was designed to provide rigorous spirometric testing over the 24-h interval (for both FEV_1 and forced vital capacity [FVC]), and body plethysmography measurements at peak and trough to place both the lung function and volume effect sizes into context.

Although FEV_1 is a standard measure of lung function in COPD trials, lung volumes may be more closely associated with patient-reported outcomes in COPD [17]. Only a few studies have reported the effect of a LAMA + LABA combination on lung volumes (including functional residual capacity [FRC] and residual volume [RV]) and this study investigated these volumes at peak (2 h 30 min post-dose) and trough (22 h 30 min post-dose) using body plethysmography [18].

The objective of this study was to demonstrate the 24-h lung-function profile and effects on lung volume of tiotropium + olodaterol FDC 2.5/5 μg and 5/5 μg compared to placebo and monocomponents after 6 weeks in patients with moderate to very severe COPD (GOLD 2–4).

2. Methods

2.1. Study design

This was a double-blind, placebo-controlled, multicentre, Phase III, incomplete crossover study (NCT01559116; 1237.20, VIVACITO) in which patients were randomised to receive four of the following six treatment options for 6 weeks each, with a 3-week washout period between treatments: placebo, olodaterol 5 μg, tiotropium 2.5 μg, tiotropium 5 μg, tiotropium + olodaterol FDC 2.5/5 μg, tiotropium + olodaterol FDC 5/5 μg, all delivered via the Respimat® inhaler (Fig. 1). Detailed written instructions and training on using the Respimat® inhaler were provided at screening, and instructions were repeated at the start of each treatment period.

Following an initial screening visit, patients entered a 2–6-week baseline period to ensure clinical stability prior to randomisation. A follow-up visit took place 3 weeks after the last dose of study medication in the last treatment period. Patients who discontinued during a treatment period were permitted to continue into their next treatment period.

2.2. Patients

Patients with COPD aged ≥40 years with a smoking history of ≥10 pack-years and relatively stable airway obstruction with a post-bronchodilator FEV_1 <80% of predicted normal (in German sites only, FEV_1 ≥30%) and FEV_1/FVC <70% of predicted normal were included. Exclusion criteria included a history of asthma or significant disease other than COPD, unstable or life-threatening cardiac arrhythmia, hospitalisation for heart failure within the past year, a history of myocardial infarction within 1 year of screening or a history of life-threatening pulmonary obstruction. Full inclusion and exclusion criteria are provided in Supplementary Table S1.

Patients were permitted to continue on inhaled corticosteroids during treatment periods (if taken as maintenance treatment at study entry) but not anticholinergics or LABAs. During the screening and washout periods, short-acting anticholinergics were permitted but had to be stopped 8 h before pulmonary function test at the first visit of the next treatment period. LAMAs and LABAs were not permitted during washout or screening periods. Open-label salbutamol was provided to patients as rescue medication to be used at baseline and during screening, treatment, washout and follow-up periods.

2.3. Study outcomes

The primary end point was FEV_1 area under the curve from 0 to 24 h ($AUC_{0–24}$) response (change from patient baseline [defined as average of period baseline values]) and the key secondary end points were FEV_1 area under the curve from 0 to 12 h ($AUC_{0–12}$) response and FEV_1 area under the curve from 12 to 24 h ($AUC_{12–24}$) response. Secondary end points included the maximum FEV_1 value obtained in the first 3 h after dosing ($peak_{0–3}$ FEV_1) and trough FEV_1 response, and FVC $AUC_{0–24}$, FVC $AUC_{0–12}$ and FVC $AUC_{12–24}$ responses. Additionally, improvements in FRC and RV were determined using body plethysmography in a subset of patients ($n = 143$) who were measured at baseline and Week 6.

2.4. Assessments

Pulmonary function tests were performed at screening, on Day 1 of each treatment phase (30 min pre-dose and at 30 min, 1, 2 and 3 h post-dose) and at Week 6 of each treatment phase (30 min pre-dose and at 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 22, 23 and 23 h 50 min post-dose). Spirometric tests were performed in triplicate, and the highest FEV_1 and FVC were recorded as per American Thoracic Society/European Respiratory Society guidelines.

Body plethysmography tests were performed on a subset of patients at screening and Day 1 (1 h pre-dose treatment baseline) and Week 6 of each treatment period (2 h 30 min and 22 h 30 min post-dose). The body plethysmography procedures were performed as 'linked' manoeuvres, without the patient coming off the mouthpiece in between, as recommended by American Thoracic Society/European Respiratory Society guidelines [19]. Once a quiet tidal volume breathing pattern was confirmed (to ensure a stable end-expiratory lung volume), the shutter was closed at end expiratory lung volume and the patient panted with hands over cheeks. After opening of the shutter, the patient returned to quiet tidal breathing and then completed an expiratory reserve volume manoeuvre to RV, followed by a slow inspiratory vital capacity manoeuvre to total lung capacity. At least three technically acceptable FRC values had to be obtained, differing by ≤5%. If the deviation between values was higher, then the manoeuvre was repeated until this repeatability was achieved to a maximum of six times. After six times, the mean FRC was considered acceptable even if it did not meet the repeatability criteria.

RV was calculated as mean FRC minus mean expiratory reserve volume. Total lung capacity was calculated as RV plus the largest technically acceptable inspiratory vital capacity measure. Inspiratory capacity was calculated for each individual effort as the difference between each inspiratory vital capacity and each end respiratory volume. At least three efforts were performed and if the individual inspiratory capacity values were not within ±6% of the mean, additional measures were performed to a maximum of six.

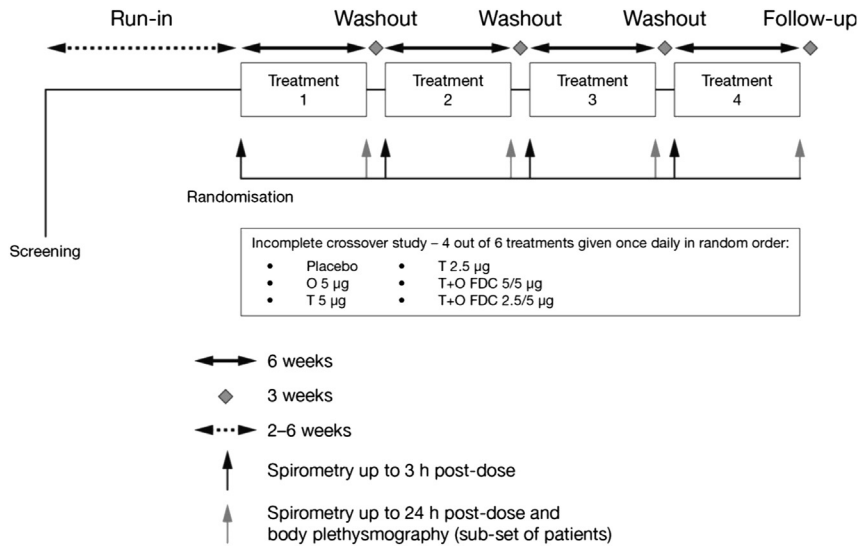

Fig. 1. Trial design. O, olodaterol; T, tiotropium; FDC, fixed-dose combination.

The mean of the inspiratory capacities calculated for each time point for each patient was used for analysis.

All adverse events were recorded, and 12-lead electrocardiogram was performed at screening and at 40 min pre-dose and 50 min post-dose on Day 1 and Week 6 of all treatment periods. Vital signs (pulse rate and blood pressure) were measured prior to pulmonary function tests on Day 1 and Week 6 of each treatment period, 30 min before and 50 min, 2 and 3 h after study drug administration. After 3 weeks of each treatment, patients were contacted by telephone to report adverse events and changes in concomitant medicines.

2.5. Statistical analysis

To detect a difference between treatments of 60 mL in FEV_1 AUC_{0-24} with 90% power, including an adjustment for the incomplete crossover design and assuming a standard deviation of 190 mL (based on previous studies), 180 patients were required to complete the trial. An additional 36 were added to allow for drop-outs, resulting in a required sample size of 216 patients.

The full analysis set was defined as any patient who had taken at least one dose of study medication and had any period baseline and any evaluable post-dose data for the primary end point at the 6-week time point. This was used for all analyses presented here.

The primary end point, key secondary end points and all other continuous secondary end points were analysed using a restricted maximum likelihood-based mixed effects model with repeated measures that included treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates. Patient baseline was calculated as the mean of all of the patient's period baseline values. Hypotheses were tested in a hierarchical order based on adjusted means, with each hypothesis considered confirmatory only if all of the previous hypotheses were successful (Supplementary Fig. S1).

3. Results

3.1. Patient disposition and baseline characteristics

Overall, 259 patients were enrolled in the study from 29 centres in seven countries (Belgium, Canada, Denmark, Germany, Hungary, The Netherlands and the USA), and 219 were randomised into the trial and treated (Fig. 2). The discontinuation rate in each treatment period ranged from 0.7% (with tiotropium + olodaterol FDC 2.5/5 µg and FDC 5/5 µg) to 5.8% (with placebo) (Fig. 2).

Patient demographics and baseline characteristics are shown in Table 1; the majority of patients had GOLD 2 (63.5%) or 3 (34.2%) COPD, with only five patients (2.3%) having GOLD 4. Most patients (83.1%) were taking pulmonary medications at baseline and also had concomitant diagnoses (95.4%); the most common were vascular disorders (Table 1). Baseline body plethysmography data are shown in Supplementary Table S2.

3.2. Efficacy

The 24-h FEV_1 time profiles showed a consistent improvement in FEV_1 with all active treatments compared to placebo after 6 weeks of treatment (Fig. 3). The tiotropium + olodaterol FDCs demonstrated a greater improvement in FEV_1 over 24 h than the monotherapies (Fig. 3). This is quantified by the significantly greater responses in FEV_1 AUC_{0-24} with tiotropium + olodaterol FDCs *versus* placebo and monotherapies; improvements in lung function from baseline were 0.241 and 0.244 L with tiotropium + olodaterol 2.5/5 µg and 5/5 µg, respectively, and ranged between 0.117 and 0.133 L for monotherapies (Table 2). Similarly, FEV_1 AUC_{0-12} and FEV_1 AUC_{12-24} responses were consistently greater with the tiotropium + olodaterol FDCs *versus* placebo and monotherapies (Table 2); FEV_1 AUC_{0-12} responses were 0.310 and 0.305 L with tiotropium + olodaterol 2.5/5 µg and 5/5 µg, respectively, and 0.171–0.186 L with monotherapies. FEV_1 AUC_{12-24} responses were 0.172 and 0.182 L with tiotropium + olodaterol 2.5/5 µg and tiotropium + olodaterol 5/5 µg, respectively, and between 0.062 and 0.081 L with monotherapies. Differences between treatments are shown in Table 3; there were no significant differences between tiotropium + olodaterol 2.5/5 µg and 5/5 µg in any of these end points.

As with the FEV_1 time profiles, FVC 24-h time profiles also demonstrated improvement with tiotropium + olodaterol FDCs *versus* monotherapies and placebo after 6 weeks of treatment (Supplementary Fig. S2). FVC AUC_{0-24} responses are shown in Supplementary Table S3.

Table 4 shows the $peak_{0-3}$ FEV_1 and trough FEV_1 responses at 6 weeks; all treatments showed significant improvements *versus*

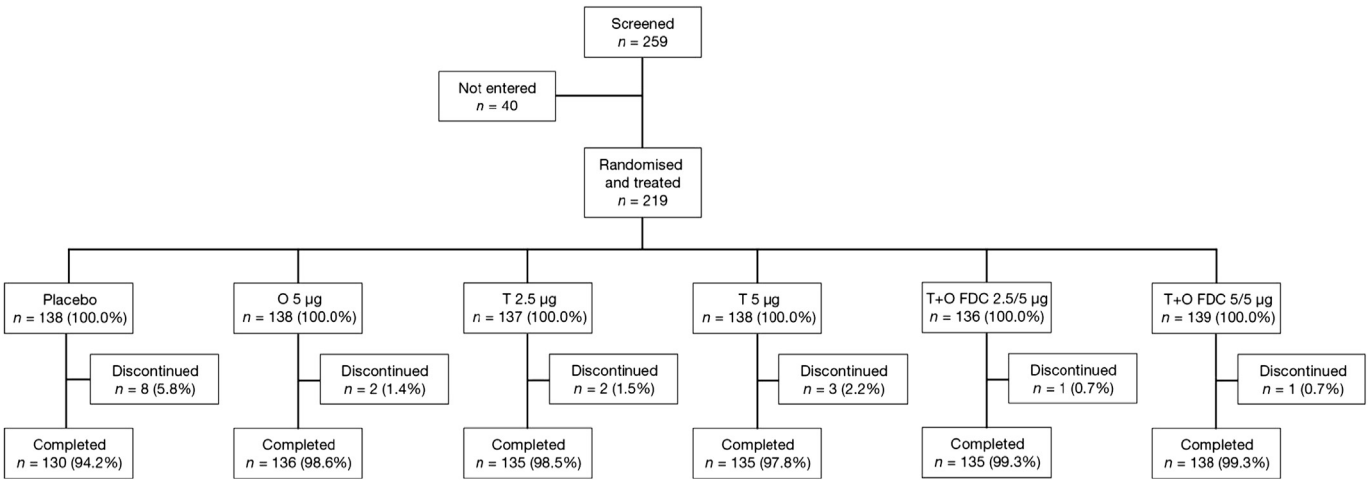

Fig. 2. Patient disposition. O, olodaterol; T, tiotropium; FDC, fixed-dose combination.

placebo and both FDCs showed significant improvements *versus* all monotherapies ($p < 0.0001$ for all comparisons).

FRC was measured using body plethysmography in a subset of 143 patients after 6 weeks of treatment. The tiotropium + olodaterol FDCs both provided significantly greater improvements at 2 h 30 min post-dose than placebo ($p < 0.0001$) or any of the monotherapies (tiotropium + olodaterol 2.5/5 µg *versus* monotherapies, $p < 0.0001 - p = 0.007$; tiotropium + olodaterol 5/5 µg *versus* monotherapies, $p < 0.0001 - p = 0.044$) (Fig. 4). The changes from baseline at 2 h 30 min post-dose were −0.052 L with placebo, −0.435, −0.279 and −0.431 with olodaterol 5 µg, tiotropium 2.5 µg and tiotropium 5 µg, respectively, and −0.587 and

Table 1
Baseline demographics and patient characteristics.

	Patients ($n = 219$)
Male, *n* (%)	129 (58.9)
Mean (SD) age, years	61.1 (7.7)
Smoking status, *n* (%)	
Ex-smoker	82 (37.4)
Current smoker	137 (62.6)
Pre-bronchodilator mean (SD) FEV_1, L	1.361 (0.471)
Post-bronchodilator	
Mean (SD) FEV_1, L	1.553 (0.487)
Mean (SD) % predicted normal FEV_1	54.0 (13.0)
Mean (SD) FEV_1/FVC, %	48.0 (10.9)
Mean (SD) change from pre- to post-bronchodilator FEV_1, L	0.193 (0.151)
Mean (SD) % change from pre- to post-bronchodilator FEV_1	15.9 (12.8)
GOLD, *n* (%)	
2	139 (63.5)
3	75 (34.2)
4	5 (2.3)
Most common concomitant diagnoses, *n* (%)	
Vascular disorders	125 (57.1)
Metabolism and nutrition disorders	118 (53.9)
Musculoskeletal and connective tissue disorders	114 (52.1)
Surgical and medical procedures	88 (40.2)
Baseline pulmonary medication (>1% of patients), *n* (%)	
SAMA[a]	17 (7.8)
LAMA[b]	88 (40.2)
LABA[b]	99 (45.2)
SABA[c]	133 (60.7)
Mucolytics	10 (4.6)
ICS	90 (41.1)
Xanthines	8 (3.7)

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; LABA, long-acting β_2-agonist; SABA, short-acting β-agonist; ICS, inhaled corticosteroid.

[a] Not permitted during treatment periods but allowed during screening and washout periods.

[b] Not permitted during treatment, screening or washout periods.

[c] Provided for rescue medication use to all patients throughout the study.

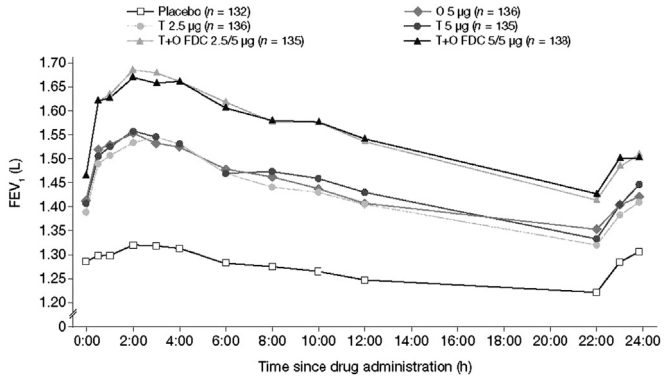

Fig. 3. Adjusted mean 24-h FEV_1 profile after 6 weeks of treatment (full analysis set). FEV_1, forced expiratory volume in 1 s; T, tiotropium; O, olodaterol; FDC, fixed-dose combination.

−0.547 with tiotropium + olodaterol 2.5/5 µg and 5/5 µg, respectively (Fig. 4). At 22 h 30 min post-dose, tiotropium + olodaterol 5/5 µg provided significantly greater improvements than placebo ($p < 0.0001$) and monotherapies (*versus* olodaterol 5 µg, $p = 0.030$; tiotropium 2.5 µg, $p = 0.017$; tiotropium 5 µg, $p = 0.003$), and tiotropium + olodaterol 2.5/5 µg separated from placebo ($p = 0.0004$) and tiotropium 5 µg ($p = 0.039$) (Fig. 4).

There were also significant improvements in RV response with the FDCs *versus* placebo and monotherapies at 2 h 30 min and 22 h 30 min post-dose (*versus* placebo, $p < 0.0001$; *versus* monotherapies, $p < 0.05$) (Fig. 4).

All treatments increased inspiratory capacity compared to placebo at 2 h 30 min and 22 h 30 min post-dose, and tiotropium + olodaterol 5/5 µg increased it compared to all monotherapies at 2 h 30 min post-dose. Inspiratory capacity and total lung capacity results are provided in Supplementary Table S4.

3.3. Safety

Incidence of adverse events was similar between treatment groups, with no difference between tiotropium + olodaterol FDC 2.5/5 µg and FDC 5/5 µg and the monotherapies or placebo (Supplementary Table S5). The most common individual adverse events were nasopharyngitis, with incidences between 6.5% and 10.1%, and COPD worsening, with incidences between 5.1% and 12.3% (Supplementary Table S5).

Incidences of serious adverse events with each treatment were 2.9% with placebo, 5.8% with olodaterol 5 µg, 3.6% with tiotropium 2.5 µg, 2.2% with tiotropium 5 µg, 2.9% with tiotropium + olodaterol FDC 2.5/5 µg and 0.7% with tiotropium + olodaterol FDC 5/5 µg. No safety concerns were detected in vital signs (pulse rate or blood pressure).

Table 3
Adjusted mean FEV_1 results after 6 weeks, differences between treatments (full analysis set).

End point	Treatment	Treatment differences		
		Mean (SE), L	*p* value	95% CI
FEV_1 AUC_{0-24}	T+O 5/5 µg *vs*:			
	Placebo	0.280 (0.014)	<0.0001	0.252, 0.309
	O 5 µg	0.115 (0.014)	<0.0001	0.087, 0.143
	T 2.5 µg	0.127 (0.014)	<0.0001	0.099, 0.155
	T 5 µg	0.110 (0.014)	<0.0001	0.082, 0.139
	T+O 2.5/5 µg	0.003 (0.014)	0.8238	−0.025, 0.031
	T+O 2.5/5 µg *vs*:			
	Placebo	0.277 (0.015)	<0.0001	0.249, 0.306
	O 5 µg	0.111 (0.014)	<0.0001	0.083, 0.140
	T 2.5 µg	0.124 (0.014)	<0.0001	0.096, 0.152
	T 5 µg	0.107 (0.014)	<0.0001	0.079, 0.136
FEV_1 AUC_{0-12}	T+O 5/5 µg *vs*:			
	Placebo	0.319 (0.015)	<0.0001	0.289, 0.349
	O 5 µg	0.126 (0.015)	<0.0001	0.096, 0.156
	T 2.5 µg	0.134 (0.015)	<0.0001	0.104, 0.164
	T 5 µg	0.119 (0.015)	<0.0001	0.089, 0.149
	T+O 2.5/5 µg	−0.005 (0.015)	0.7558	−0.035, 0.025
	T+O 2.5/5 µg *vs*:			
	Placebo	0.323 (0.015)	<0.0001	0.293, 0.354
	O 5 µg	0.131 (0.015)	<0.0001	0.101, 0.161
	T 2.5 µg	0.139 (0.015)	<0.0001	0.109, 0.169
	T 5 µg	0.124 (0.015)	<0.0001	0.093, 0.154
FEV_1 AUC_{12-24}	T+O 5/5 µg *vs*:			
	Placebo	0.243 (0.015)	<0.0001	0.212, 0.273
	O 5 µg	0.103 (0.015)	<0.0001	0.074, 0.133
	T 2.5 µg	0.120 (0.015)	<0.0001	0.090, 0.150
	T 5 µg	0.102 (0.015)	<0.0001	0.072, 0.132
	T+O 2.5/5 µg	0.011 (0.015)	0.4794	−0.019, 0.041
	T+O 2.5/5 µg *vs*:			
	Placebo	0.232 (0.015)	<0.0001	0.201, 0.262
	O 5 µg	0.093 (0.015)	<0.0001	0.063, 0.123
	T 2.5 µg	0.110 (0.015)	<0.0001	0.080, 0.140
	T 5 µg	0.091 (0.015)	<0.0001	0.061, 0.121

$n = 132$ (placebo); $n = 136$ (O 5 µg); $n = 136$ (T 2.5 µg); $n = 135$ (T 5 µg); $n = 135$ (T+O 2.5/5 µg); $n = 138$ (T+O 5/5 µg).
FEV_1, forced expiratory volume in 1 s; SE, standard error; CI, confidence interval; AUC_{0-24}, area under the curve from 0 to 24 h; T, tiotropium; O, olodaterol; AUC_{0-12}, area under the curve from 0 to 12 h; AUC_{12-24}, area under the curve from 12 to 24 h.

4. Discussion

4.1. Key findings

This study demonstrated improvements in the 24-h lung function profile for an FDC of tiotropium + olodaterol on dynamic and static lung volumes. Both tiotropium + olodaterol FDC doses showed a clear and consistent improvement in FEV_1 over the full

Table 2
Adjusted mean FEV_1 AUC responses after 6 weeks of treatment (full analysis set).

Treatment	Patients, *n*	FEV_1 AUC_{0-24} mean (SE) response, L	FEV_1 AUC_{0-12} mean (SE) response, L	FEV_1 AUC_{12-24} mean (SE) response, L
Placebo	132	−0.037 (0.014)	−0.013 (0.015)	−0.060 (0.014)
O 5 µg	136	0.129 (0.013)	0.179 (0.015)	0.079 (0.013)
T 2.5 µg	136	0.117 (0.013)	0.171 (0.015)	0.062 (0.013)
T 5 µg	135	0.133 (0.014)	0.186 (0.015)	0.081 (0.014)
T+O 2.5/5 µg	135	0.241 (0.014)	0.310 (0.015)	0.172 (0.014)
T+O 5/5 µg	138	0.244 (0.013)	0.305 (0.015)	0.182 (0.013)

FEV_1, forced expiratory volume in 1 s; AUC_{0-24}, area under the curve from 0 to 24 h; SE, standard error; AUC_{0-12}, area under the curve from 0 to 12 h; AUC_{12-24}, area under the curve from 12 to 24 h; O, olodaterol; T, tiotropium.

Table 4
Adjusted mean peak$_{0-3}$ FEV_1 and trough FEV_1 responses at 6 weeks (full analysis set).

	n	Peak$_{0-3}$ FEV_1, L (SE)	*n*	Trough FEV_1, L (SE)
Placebo	135	0.072 (0.017)	132	−0.006 (0.015)
O 5 μg	138	0.291 (0.016)[a]	136	0.109 (0.015)[a]
T 2.5 μg	136	0.290 (0.016)[a]	136	0.095 (0.015)[a]
T 5 μg	137	0.300 (0.016)[a]	135	0.122 (0.015)[a]
T+O 2.5/5 μg	135	0.422 (0.016)[a,b]	135	0.196 (0.015)[a,b]
T+O 5/5 μg	138	0.411 (0.016)[a,b]	138	0.201 (0.015)[a,b]

Common patient baseline mean (SE), 1.301 L (0.030).
Peak$_{0-3}$, maximum value obtained in the first 3 h after dosing; FEV_1, forced expiratory volume in 1 s; SE, standard error; O, olodaterol; T, tiotropium.
[a] $p < 0.0001$ *vs* placebo.
[b] $p < 0.0001$ *vs* monotherapies.

24-h period compared to placebo and monotherapies, as expected from combining a LAMA and a LABA [20]. The improvement in trough FEV_1 with tiotropium + olodaterol FDCs *versus* placebo (0.207 L with tiotropium + olodaterol 5/5 μg) was greater than is considered clinically important [21]. Both tiotropium + olodaterol FDC doses also demonstrated a greater increase in FEV_1 AUC_{0-24} than tiotropium 5 μg alone, a well-established and widely used once-daily LAMA. These improvements were accompanied by a tolerability profile similar to tiotropium 5 μg, olodaterol and placebo. In this study, no differences in spirometric variables were observed in effect size between the two FDC doses, although in longer-term studies differences have been observed with some end points [22]. This difference may be due to the shorter-term nature of this study.

The improvements in FEV_1 with the FDCs *versus* monotherapies and placebo were also seen with FVC over the 24-h period. The body plethysmography substudy provided evidence for an incremental benefit of the tiotropium + olodaterol combination in terms of hyperinflation, as greater reductions in FRC were seen with combined tiotropium + olodaterol compared to the monotherapies at 2 h 30 min post-dose. Trapped air volume, as measured by RV, was also reduced to a greater extent with the combined treatments compared to the monotherapies at peak and trough.

4.2. Possible mechanisms

When taken together, the data suggest that tiotropium + olodaterol FDC reduces airflow limitation over 24 h, which improves lung emptying at the end of tidal breathing and reduces hyperinflation (FRC), as well as reducing the trapped air volume (RV). Our results suggest that the positive effects on lung volume, which are known to correlate better with patient-reported improvements than FEV_1, are maintained over the full 24-h dosing interval.

By targeting both routes to airway smooth muscle relaxation, β_2-agonism and muscarinic antagonism, the combination of a LAMA with a LABA achieves greater bronchodilation than either drug alone, exceeding clinically important differences for FEV_1 *versus* placebo and monocomponents. Complementary interactions between these two pathways may also play a role in the greater improvements demonstrated in this study with dual therapy *versus* monotherapy [23].

4.3. Comparison with relevant findings from other published studies

The effects of tiotropium + olodaterol FDC on 24-h lung function, as demonstrated here by rigorous pulmonary function testing over the full dosing interval, are consistent with the effects on trough FEV_1 from Phase II tiotropium + olodaterol data [15,16] and on both trough and FEV_1 area under the curve from 0 to 3 h from Phase III long-term study results [22]. They are also consistent with the results of adding twice-daily β_2-agonists such as formoterol and salmeterol to tiotropium [23].

Similar lung function and symptomatic benefits *versus* their respective monocomponents have also been reported with other LAMA + LABA combinations: umeclidinium + vilanterol, indacaterol + glycopyrronium and glycopyrrolate + formoterol, reviewed by Tashkin and Ferguson [23] and Bateman et al. [20]. An indacaterol + glycopyrronium study used body plethysmography to investigate lung-volume measures after 3 weeks of treatment at up to 1 h post-dose and found improvements *versus* placebo [18], so the data presented here at 6 weeks, and at a longer period post-dose, extend these effects. In this study, we also demonstrate an improvement *versus* monotherapies as well as *versus* placebo in FRC and RV. The improvements *versus* placebo in FRC are similar to those previously reported with another LAMA + LABA combination [18], although the difference from placebo in post-dose RV is greater in the present study, and in VIVACITO a significant improvement *versus* monotherapies is also reported.

4.4. Limitations of the present study

Although no safety concerns were raised in the trial, the short duration of the study and the crossover design limit the safety information that can be established from this trial alone. The two 52-

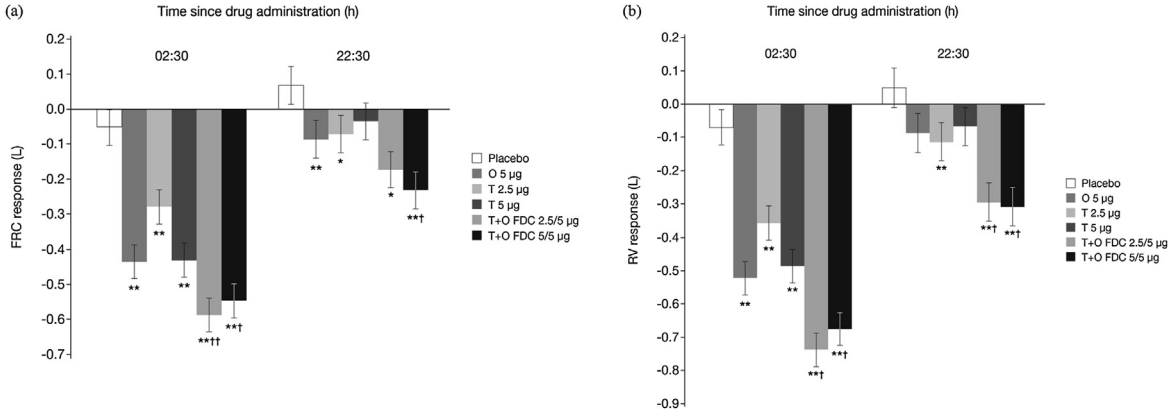

Fig. 4. Adjusted mean FRC (a) and RV (b) responses at 6 weeks ± SE, measured by body plethysmography at 2 h 30 min and 22 h 30 min post-dose. $^{*}p < 0.05$ *versus* placebo; $^{**}p < 0.0001$ *versus* placebo; $^{\dagger}p < 0.05$ *versus* all monotherapies; $^{\dagger\dagger}p < 0.01$ *versus* all monotherapies. FRC, functional residual capacity; RV, residual volume; SE, standard error; O, olodaterol; T, tiotropium; FDC, fixed-dose combination.

week parallel-group trials that investigated the two FDCs *versus* monocomponents also demonstrated a tolerability profile with tiotropium + olodaterol similar to monotherapies [22].

Another limitation is that the 24-h profile was calculated using data from 0 to 12 and 22 to 24 h to allow patients to get a relatively full night's sleep, so the profile from 12 to 22 h is interpolated. However, given the linear profile from the peak to 22 h, this is a reasonable compromise, and the consistency between treatment groups in diurnal variation suggests that treatment differences are likely to be consistent in the 12 to 22 h period, as found in a previous tiotropium study where FEV_1 was measured throughout the night [24]. It is possible, however, that the lowest point in the 24-h period is not at 22 h but at some point between 12 and 22 h.

4.5. Clinical implications

Overall, this study provides strong evidence for an incremental benefit in lung function with tiotropium + olodaterol FDC compared to placebo or tiotropium or olodaterol alone.

5. Conclusions

Tiotropium + olodaterol FDC 2.5/5 μg and tiotropium + olodaterol FDC 5/5 μg demonstrated greater improvements in lung-function profile over 24 h than either tiotropium or olodaterol alone, with no observed differences in safety.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pupt.2015.04.002.

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