ERJ Express. Published on January 17, 2019 as doi: 10.1183/13993003.02049-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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Please cite this article as: Maltais F, Aumann J-L, Kirsten A-M, *et al*. Dual bronchodilation with tiotropium/olodaterol further reduces activity-related breathlessness *versus* tiotropium alone in COPD. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.02049-2018).

Dual bronchodilation with tiotropium/olodaterol further reduces activity-related breathlessness versus tiotropium alone in COPD

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Take-home message: Tiotropium/olodaterol reduces activity-related breathlessness *versus* tiotropium in COPD

Abstract

The 3-minute constant speed shuttle test (3-min CSST) was used to examine the effect of tiotropium/olodaterol compared with tiotropium at reducing activity-related breathlessness in patients with chronic obstructive pulmonary disease (COPD). This was a randomised, double-blind, two-period crossover study including COPD patients with moderate to severe pulmonary impairment, lung hyperinflation at rest and a Mahler Baseline Dyspnoea Index <8. Patients received 6 weeks of tiotropium/olodaterol 5/5 µg and tiotropium 5 µg in a randomised order with a 3-week washout period. The speed for the 3-min CSST was determined for each patient such that an intensity of breathing discomfort ≥4 ("somewhat severe") on the Modified Borg Scale was reached at the end of a completed 3-min CSST.

After 6 weeks, there was a decrease in the intensity of breathlessness at the end of the 3-min CSST from baseline with both tiotropium (mean –0.968; 95% confidence interval [CI] −1.238 to −0.698; n=100) and tiotropium/olodaterol (mean –1.325; 95% CI −1.594 to −1.056; n=101). The decrease in breathlessness was statistically significantly greater with tiotropium/olodaterol *versus* tiotropium (treatment difference –0.357; 95% CI –0.661 to –0.053) (p=0.0217).

Tiotropium/olodaterol reduced activity-related breathlessness more than tiotropium in dyspnoeic patients with moderate to severe COPD exhibiting lung hyperinflation.

Introduction

Breathlessness during physical exertion is a prominent and distressing symptom of chronic obstructive pulmonary disease (COPD) that causes patients to avoid daily activities, leading to physical deconditioning and reduced quality of life [1–3]. Whilst several clinical trials have confirmed that long-acting muscarinic antagonists (LAMAs) improve activity-related breathlessness [4–6], it is unclear to what extent the addition of a second long-acting bronchodilator further reduces activity-related breathlessness compared with a LAMA alone [7]. This is a relevant question considering that LAMA/long-acting β_2-agonist (LABA) therapy is viewed as the preferred initial treatment option in patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) B and GOLD D COPD, and reducing breathlessness is a major goal of COPD therapy [8].

Activity-related breathlessness can be measured during patients' daily lives using questionnaires such as the Mahler Baseline Index (BDI) or Transition Dyspnoea Index and Chronic Respiratory Questionnaire. Alternatively, activity-related breathlessness may be measured in a laboratory environment using standardised exercise tests, which have the advantage of allowing precise control of the activity that produces breathlessness, an important prerequisite for assessing changes in breathlessness with therapy. We recently developed and validated the 3-minute constant speed shuttle test (3-min CSST), which was specifically designed to assess whether interventions alleviate activity-related breathlessness in patients with COPD [9, 10]. During this test, participants walk at a predetermined and externally imposed cadence for 3 minutes, with dyspnoea score measured at the end of the test. Importantly, the walking cadence is individualised so that a level of dyspnoea sufficiently intense to be amenable to therapy is generated in each participant. The short and fixed duration of the test means that the end-exercise (3 minutes) data point is available for most patients in a clinical trial. The 3-min CSST only requires a small amount of space and minimal equipment, making it relatively easy to perform. Based on these considerations, we propose that this test is particularly well suited to investigate whether LAMA/LABA bronchodilation provides further breathlessness relief compared with LAMA monotherapy.

The aim of this study was to examine the effect of tiotropium/olodaterol compared with tiotropium at reducing breathlessness during the 3-min CSST in patients with COPD exhibiting lung hyperinflation at rest and significant breathlessness during everyday activities. Considering that dual bronchodilation provides further improvements in expiratory flow and resting hyperinflation compared with monotherapy [7, 11], we proposed that tiotropium/olodaterol would provide further breathlessness relief compared with tiotropium during the 3-min CSST.

Methods

Patients

Patients aged 40–75 years with moderate to severe COPD (post-bronchodilator forced expiratory volume in 1 second [FEV_1] ≥30% and <80% predicted), lung hyperinflation at rest (functional residual capacity [FRC] >120% predicted) and a significant degree of breathlessness during everyday activities (Mahler BDI <8) were included. Patients were current or ex-smokers with a smoking history >10 pack-years. Patients were excluded if they had a significant disease other than COPD, a current diagnosis of asthma, an exacerbation in the 6 weeks prior to screening or myocardial infarction within 6 months of screening. Patients with a contraindication for exercise (as per recommendations of the European Respiratory Society Task Force on Standardization of Clinical Exercise Testing [12]) were also excluded.

Study design

This was a multicentre, randomised, double-blind, two-period crossover study (NCT02853123) in which patients received tiotropium/olodaterol 5/5 µg once daily (QD) and tiotropium 5 µg QD for 6 weeks each, in a randomised order with a 3-week washout period in between. Both drugs were delivered once daily via the Respimat® inhaler. Patients on LABAs and/or LAMAs were required to undergo washout from these medications for at least 3 weeks prior to randomisation (Figure 1). Patients prescribed inhaled corticosteroids (ICS) prior to the study continued therapy at a stable

dose throughout the study. Patients receiving a combined ICS/LABA were switched to an equivalent ICS monotherapy. Patients were evaluated for adverse events (AEs) during the study period.

Patients were randomised to a treatment sequence using an interactive voice/web response system. Randomisation was capped such that the proportion of GOLD stage 2 and 3 patients was approximately 50% each.

Outcomes

The primary endpoint was change from baseline to Week 6 in intensity of breathlessness, measured using the Modified Borg Scale at the end of the 3-min CSST.

Secondary endpoints were change from baseline to Week 6 in resting inspiratory capacity (IC), end of exercise IC, 1-hour post-dose FEV_1 and forced vital capacity (FVC), and intensity of breathlessness (Modified Borg Scale) at 1 min, 2 min and 2.5 min during the 3-min CSST.

Incremental shuttle walking test

At the first screening visit, an incremental shuttle walking test (ISWT) was performed for all patients [13]. The ISWT was not required as part of the 3-min CSST protocol, but was included in the study to provide a measure of patients' peak walking capacity at baseline. In this test, patients walk back and forth on a 10-metre course, at a speed dictated by an audio signal.

3-min CSST

The 3-min CSST is performed on a flat, straight walking track. Patients walk back and forth on a 10-metre course, keeping pace with the prerecorded audio signal, and completing a turn at each audio signal. They are allowed to run if necessary.

At the second screening visit, patients completed a minimum of two and up to three 3-min CSSTs at different sets of speeds (2.5, 3.25, 4, 5 or 6 km/hour), always starting at 4 km/hour. This was to determine the highest speed at which patients could complete the entire 3 minutes of the test and reach a Borg breathing discomfort rating of ≥4 out of 10. If the patient did not complete the full 3 minutes at 4 km/hour, a lower walking speed was chosen for the next 3-min CSST (after a minimum

30-minute rest period). If the patient completed the full 3 minutes at 4 km/hour, a higher walking speed was chosen for the next 3-min CSST and the increase in speed was continued (up to 6 km/hour), even if a Borg rating of ≥4 was reached at the end of the 3 minutes, until the patient was unable to complete the full 3 minutes of the test (see Supplementary Figure S1). At a third screening visit, a practice 3-min CSST was performed at the speed selected at the previous visit; this speed was used for all subsequent tests.

Before, during (at 1 min, 2 min and 2.5 min) and at the end of exercise, patients chose the phrase that best described their intensity of breathing discomfort and leg discomfort, from "0 or nothing at all (no discomfort)" to "10 or maximal (most severe discomfort you've ever experienced or could imagine experiencing)". Patients reported their intensity of breathlessness verbally to the investigator walking alongside them during the 3-min CSST, with particular attention taken not to hinder the patient and to avoid any negative impact on the walking test. See the Supplementary Methods for more detail.

The 3-min CSST was performed after spirometry and 2 hours after dosing at on-treatment clinic visits.

As this was the first time the 3-min CSST was used in a multicentre trial, only sites experienced in exercise testing were involved in the study. Detailed instructions were provided, and a proficiency test was implemented and monitored by a trainer to standardise the test across all sites.

Transition Dyspnoea Index

The baseline dyspnoea index was administered at screening and baseline and the Transition Dyspnoea Index (TDI) was administered at the end of each treatment period prior to dosing and study procedures.

Lung function testing

Forced spirometry was conducted at baseline and 1 hour after the administration of study medication according to American Thoracic Society (ATS)/European Respiratory Society criteria [14].

The highest FEV_1 and FVC results obtained on any of three manoeuvres meeting the ATS criteria were selected.

In a slow spirometry manoeuvre, IC was measured at rest using mobile cardiopulmonary exercise equipment (Spiropalm, Cosmed). At least three reproducible measurements were obtained (a maximum of five measurements performed). The mean of the two highest acceptable efforts was used for analysis.

Physiological measures

Ventilation, tidal volume and breathing frequency were continuously recorded during the 3-min CSSTs using the same mobile cardiopulmonary exercise equipment as for the IC measurements. Heart rate and SpO_2% were also recorded during the tests. FRC was measured at the screening visit using constant-volume variable pressure body plethysmography in accordance with the American Thoracic Society/European Respiratory Society guidelines [15].

Analysis

A sample size of 102 was required to detect a difference between tiotropium/olodaterol and tiotropium of 0.5 Borg units with 80% power and a type I error rate of 0.05 (two-sided), assuming a standard deviation of 1.776, based on a previous pilot study [10].

The primary and secondary endpoints were analysed using a restricted maximum likelihood-based mixed effect repeated measures model, with treatment and period as fixed effects, patient as a random effect, and period baseline and patient baseline as covariates. Period baseline is the pre-dose measurement from the first day of each period, whereas patient baseline is the mean of non-missing period baselines for each patient. Patient baseline data are used to calculate change from baseline.

The efficacy analysis was performed in all randomised patients who were documented to have taken any dose of trial medication, and who had both baseline and any evaluable post-baseline

measurement for the primary endpoint. Missing data at a given visit were imputed by the available data from the patient at that visit, and missing visits were handled through the statistical model.

All calculated p-values should be considered descriptive for the analysis of the secondary and further endpoints as no adjustment for multiple testing was done for these comparisons.

A responder analysis was conducted, using a ≥1-point improvement in the modified Borg dyspnoea score as the threshold for response [16].

Results

Patients

The study was conducted in 12 centres in Belgium, Canada, Germany and the Netherlands. Overall, 106 patients were randomised; 52 patients were randomised to receive tiotropium and then tiotropium/olodaterol, with one discontinuing during washout before starting tiotropium/olodaterol. Fifty-four patients were randomised to receive tiotropium/olodaterol first and then tiotropium; three discontinued during the tiotropium/olodaterol period and three during the washout period (Figure 2).

Patient demographics and baseline characteristics are shown in Table 1. Mean post-bronchodilator FEV_1 at baseline was 1.561 L (54.4% predicted) and most patients (95.3%) were receiving COPD therapy prior to study enrolment.

At baseline, mean (SD) distance walked during the ISWT was 434.6 m (128.0); this was achieved during a mean (SD) time of 429.4 seconds (82.9). Mean (SD) Borg scale breathing discomfort at the end of the ISWT was 5.160 (1.318).

The selected speed for the 3-min CSST was 4 km/hour in 27.4% of patients, 5 km/hour in 48.1% of patients and 6 km/hour in 17.9% of patients. It was 2.5 km/hour and 3.25 km/hour in 1.9% and 4.7% of patients, respectively.

The patient baseline mean (SE) intensity of breathing discomfort at the end of the 3-min CSST was 5.158 (0.159) Borg units (a Borg score of 5 is “severe”), while the intensity of leg discomfort was 3.158 (0.223) (a Borg score of 3 is “moderate”). Breathing discomfort scores and IC were similar at the start of the first treatment period and the start of the second treatment period (see Supplementary Results).

Primary endpoint

After 6 weeks of treatment, there was a decrease in the intensity of breathlessness at the end of the 3-min CSST with both tiotropium (mean –0.968; 95% confidence interval [CI] −1.238 to −0.698) and tiotropium/olodaterol (mean –1.325; 95% CI −1.594 to −1.056) compared with baseline. This greater reduction in the intensity of breathlessness with tiotropium/olodaterol *versus* tiotropium was statistically significant (treatment difference –0.357; 95% CI –0.661 to –0.053) (p=0.0217) (Figure 3a).

Secondary endpoints

Intensity of breathlessness during the 3-min CSST

The intensity of breathlessness after 6 weeks with tiotropium/olodaterol and tiotropium at all timepoints during the 3-min CSST is shown in Figure 3b; both drugs showed an improvement from baseline, with significant improvements observed with tiotropium/olodaterol *versus* tiotropium from the 2-minute timepoint until the end of the test.

Lung function

Mean (SE) pre-treatment baseline resting IC was 2.312 L (0.072); after 6 weeks of treatment there was an increase in resting IC of 0.271 L (0.049) for tiotropium and a larger increase of 0.489 L (0.049) for tiotropium/olodaterol (treatment difference of 0.218 L; 95% CI 0.121–0.314) (p<0.0001) (Table 2). Results after 3 weeks are shown in Supplementary Table 2.

FEV_1 and FVC, measured 1 hour post-dose, were also significantly improved with tiotropium/olodaterol *versus* tiotropium (treatment differences of 0.155 L and 0.201 L, respectively) (both p<0.0001) (Table 2).

Intensity of breathlessness responder analysis

For this analysis, being a responder was defined as showing a ≥1-point improvement in the modified Borg dyspnoea score, a threshold based on the assumption that this would represent a clinically meaningful difference [17]. Figure 4 shows the proportion of patients with specific treatment differences in Borg dyspnoea score. Fifty percent (50%) of patients achieved at least a 1-point improvement in the Borg dyspnoea score with tiotropium/olodaterol compared with tiotropium, while 34% of patients achieved at least a 1-point improvement in the Borg dyspnoea score with tiotropium compared with tiotropium/olodaterol. This resulted in a number needed to treat of 7 to achieve a clinically relevant improvement in activity-related breathlessness for tiotropium/olodaterol compared with tiotropium.

TDI focal score

The TDI score was improved from baseline with tiotropium by 0.581 units (95% CI 0.031–1.132) and with tiotropium/olodaterol by 1.225 units (95% CI 0.680–1.770). The difference between treatments was 0.643 units (p=0.0659).

Physiological parameters

Ventilation and tidal volume were significantly increased with tiotropium/olodaterol compared with tiotropium at all timepoints during the 3-min CSST after 6 weeks of treatment (p<0.05 except for the 1-minute timepoint for tidal volume) (Figure 5). At the end of the 3-min CSST, there was an increase in ventilation of 1.732 L/min (95% CI 0.591–0.559) with tiotropium/olodaterol compared with tiotropium, and an increase in tidal volume of 0.073 L (95% CI 0.023–0.124). There were no differences between treatments in breathing frequency during the 3-min CSST (Figure 5).

AEs

Sixty patients (57.1%) in the tiotropium/olodaterol group and 50 patients (50.0%) in the tiotropium group reported AEs. The number of patients reporting serious AEs was small in both groups (five during the tiotropium/olodaterol period and one during the tiotropium period) (Supplementary Table 3).

Discussion

The present study is the first to examine the effects of LAMA/LABA treatment – in this case tiotropium/olodaterol – *versus* a LAMA (tiotropium) on breathlessness during the 3-min CSST, and the first to implement the 3-min CSST in a multicentre, international trial. Our results support the hypothesis that the benefits of tiotropium/olodaterol over tiotropium in terms of improving lung function and reducing hyperinflation lead to a reduction in activity-related breathlessness.

While both bronchodilator treatments were effective at improving breathlessness during the 3-min CSST, the study showed further benefits of tiotropium/olodaterol *versus* tiotropium in patients with lung hyperinflation at rest. The mean treatment difference in Borg score was modest (0.357 Borg score unit difference) and below the 1-unit threshold that is likely to be perceived by patients (i.e. clinically significant) [16, 17], which may be because the comparator in this study was not placebo but tiotropium, a potent treatment to alleviate breathlessness [4]. However, the results also showed that more patients reached the 1-point threshold of breathlessness reduction with tiotropium/olodaterol than with tiotropium, resulting in a number needed to treat of 7 for one additional patient to benefit from tiotropium/olodaterol compared with tiotropium. The number needed to treat is slightly better than that reported for another LAMA/LABA combination versus tiotropium for a 1-point improvement in TDI score (number needed to treat of 11) [18]. Given the favourable safety profile of dual bronchodilators, we suggest that a number needed to treat of 7 for a clinical outcome such as dyspnoea is clinically relevant [19]. In Figure 4, we present the individual

data for changes in intensity of breathlessness with both treatments. There are a minority of patients who appear to do better with bronchodilator monotherapy than with dual bronchodilation. This observation is consistent with previous studies [20, 21]. For example, the BLAZE investigators [21] reported in patients with moderate COPD that the mean difference in TDI score between dual bronchodilation and bronchodilator monotherapy was 0.36, with 95% CI ranging from -0.15 to 0.87, implying that some patients did better on tiotropium alone. Likewise, a recent network meta-analysis of the effects of dual bronchodilation on exercise tolerance in COPD reported data from several individual studies where the improvement in exercise tolerance could be greater with bronchodilator monotherapy than with dual bronchodilator therapy [20]. These observations do not mean that patients are worse with dual bronchodilation, but rather that the translation from improved lung function to clinical outcomes (such as exercise duration or dyspnoea) is not always straightforward. Issues with variation in magnitude of bronchodilation and deflation responses, the interpretation of the questionnaires by patients as well as other factors could modulate the impact of bronchodilation on perceived dyspnoea and other outcomes.

Overall, our study extends the previous finding that dual bronchodilation improves patient-reported breathlessness in COPD compared with bronchodilator monotherapy [21–23] by providing the first demonstration of added benefits of tiotropium/olodaterol over bronchodilator monotherapy to alleviate activity-related breathlessness. Unique to this trial was the use of the 3-min CSST in which the exercise stimulus was standardised across measurements.

The results are also consistent with previous studies in which breathlessness was measured using the TDI [21, 23]. In these studies, LAMA/LABA offered greater benefits than LAMA alone but the benefits of dual bronchodilation over monotherapy were not as great as the difference between the LAMA and placebo. In previous tiotropium/olodaterol trials there was an additive effect of tiotropium and olodaterol on the TDI and St. George's Respiratory Questionnaire responder rates [24], but the mean change was less than the minimal clinically important difference [23]. The TDI

data in the present trial are also similar to what has previously been published, and although the treatment difference did not reach statistical significance, a clinically important mean improvement of >1 [16] from baseline was observed with tiotropium/olodaterol only.

Our data support the role of bronchodilators in improving breathlessness during activity in patients with COPD by improving lung function and reducing hyperinflation [1, 7]. This allows patients to exercise for longer before being limited by symptoms [2, 4]. In previous studies [11], and particularly in another tiotropium/olodaterol exercise trial (MORACTO) [7], it has been difficult to differentiate between LAMA/LABA combinations and monotherapies in terms of activity-related breathlessness. The different findings between the present study and MORACTO can be explained by the study designs. Different exercise tests were used (walking *versus* cycling; time-limited *versus* symptom-limited), and the 3-min CSST used in our trial is specifically designed to measure changes in breathlessness. The patient population also differed: in the present study, a breathlessness signal was required (≥4 units on Borg scale) during the 3-min CSST at study entry.

Patients recruited also had hyperinflation at baseline (FRC >120%), and perhaps because of this, there was a much greater treatment difference in IC than was found in MORACTO (0.218 L compared with 0.101 L), or in a meta-analysis of eight clinical trials comparing LAMA/LABA with LAMA [20]. The 120% predicted FRC threshold was chosen to be consistent with the definition previously used in several COPD exercise studies [4, 5, 25]. Perhaps the greatest effects on activity-related breathlessness may be found in patients with hyperinflation at baseline. Similarly, the selected FRC threshold identifies a subgroup of patients that is more likely to improve exercise endurance following bronchodilation [26].

The large increases in IC, an indirect measure of hyperinflation, represent approximately a half-litre reduction in functional residual capacity (assuming only small changes in total lung capacity following bronchodilator treatment [27]). As expected, and consistent with previous studies [28], there were also improvements in FEV_1 and FVC, and increases in ventilation driven by increases in tidal volume during the 3-min CSST with tiotropium/olodaterol *versus* tiotropium. Notably, the

intensity of breathlessness was diminished despite the increase in ventilation with tiotropium/olodaterol *versus* tiotropium. This suggests that additional lung deflation with dual bronchodilation ultimately resulted in a more favourable positioning of tidal volume on the sigmoidal pressure-volume relation of the relaxed respiratory system. Thus, the attendant reduced mechanical (elastic) loading and functional weakness of the inspiratory muscle and expanded inspiratory reserve volume would be expected to reduce inspiratory neural drive to the inspiratory muscles, an important source of respiratory discomfort in COPD [25].

The changes in breathing pattern were likely related to improvements in airflows, an important determinant of ventilatory capacity and IC [10, 29, 30]. From a physiological perspective, these increases in ventilation and tidal volume were likely beneficial to increase alveolar ventilation. On the other hand, the reduction in breathlessness with dual bronchodilation could have been even larger than currently reported had the Borg score been corrected for the increased ventilation.

This study shows that the 3-min CSST can be successfully implemented in a multicentre clinical trial, and is a sensitive enough tool to detect a difference in breathlessness between LAMA/LABA and LAMA. Great care was taken in selecting a shuttle speed that allowed all patients to complete the full 3 minutes at each study visit while still eliciting at least a “somewhat severe” breathlessness (score ≥4) that would be amenable to therapy. The baseline results show that a meaningful degree of dyspnoea was achieved with the 3-min CSST, with little heterogeneity between patients. There were, however, a few limitations of our study. Despite the care taken, some patients who met the inclusion criteria in the screening 3-min CSST were either unable to complete the 3-minute test during baseline tests or rated breathing discomfort less than “somewhat severe” at the end of the test in visits following the determination of the final speed used during the trial. These patients continued in the trial per the protocol. This is likely unavoidable given the day-to-day variability in COPD patients’ clinical status. The selection of shuttle speed is labour-intensive; future work to determine an appropriate shuttle speed based on patient characteristics may be of value.

Additionally, the results at 3 weeks were not consistent with the results at 6 weeks (Supplementary Figure S2). This was a surprising finding, and it is not clear what caused this difference.

Beside these clinical results, our study provides potentially useful information about the 3-min CSST, a novel tool to assess exertional dyspnoea, an area where there is a need for methodological development [31]. The demonstration of the feasibility of using the 3-min CSST in the context of a multicentre clinical trial and of its responsiveness to interventions may be worthwhile for the design of future clinical trials evaluating the impact of various therapies on dyspnoea, a key outcome parameter in COPD.

The safety data show a slightly higher proportion of patients with AEs in the tiotropium/olodaterol period compared with the tiotropium period, but this was a small population and a relatively short trial. A large safety database of longer-term and larger trials has shown that there is no difference between tiotropium/olodaterol and tiotropium in the proportion of patients with AEs [32, 33].

Overall, we report that tiotropium in combination with olodaterol was more effective than tiotropium monotherapy at alleviating activity-related breathlessness in patients with COPD and hyperinflation. The study provides supporting evidence for the use of dual bronchodilation in COPD because it offers the best chances of optimising dyspnoea status in this disease.

Acknowledgments

Medical writing assistance, in the form of the preparation and revision of the manuscript, was supported financially by Boehringer Ingelheim and provided by Claire Scofield at MediTech Media, under the authors' conceptual direction and based on feedback from the authors.

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Table 1. Patient demographics and baseline characteristics (treated set).

Demographics	**Total (n=106)**
Male, n (%)	66 (62.3)
Mean age, years (SD)	63.6 (7.2)
Mean smoking history, pack-years (SD)	45.6 (20.7)
Baseline dyspnoea index (SD)	5.8 (1.3)
Post-bronchodilator lung function at screening	
Mean FEV_1, L (SD)	1.561 (0.525)
Mean FEV_1 % predicted (SD)	54.4 (13.0)
GOLD stage 2, n (%)	60 (56.6)
GOLD stage 3, n (%)	46 (43.4)
Mean FEV_1 change from pre-bronchodilator, L (SD)	0.232 (0.188)
Mean FEV_1 % change from pre-bronchodilator, (SD)	19.5 (15.5)
Mean FVC, L (SD)	3.433 (1.025)
Mean FEV_1/FVC, % (SD)	45.8 (8.9)
Mean FRC % predicted (SD)	155.4 (28.2)
Mean total lung capacity, L (SD)	7.3 (1.5)
Pulmonary medications prior to study enrolment, n (%)	
Any	101 (95.3)
LABA monotherapy	0 (0)
LAMA monotherapy	18 (17.0)
LABA/ICS[a]	7 (6.6)
LAMA/ICS[a]	1 (0.9)
LAMA/LABA[a]	18 (17.0)
LAMA/LABA/ICS[a]	41 (38.7)

[a]Free or fixed-dose combination. LABA, LAMA discontinued prior to randomisation for duration of study; ICS continued if used prior to study enrolment.

FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonists; LAMA, long-acting muscarinic antagonists; SD, standard deviation.

Table 2. Lung function parameters after 6 weeks of treatment (full analysis set).

Measure	Treatment	Mean, L (SE)	Mean change from baseline, L (SE)	Mean difference *vs* tio, L (95% CI)	p-value[a]
Resting IC	Baseline	2.312 (0.072)			
	Tio (n=100)	2.590 (0.049)	0.271 (0.049)		
	T/O (n=101)	2.808 (0.049)	0.489 (0.049)	0.218 (0.121–0.314)	<0.0001
FEV_1	Baseline	1.325 (0.049)			
	Tio (n=99)	1.485 (0.021)	0.163 (0.021)		
	T/O (n=103)	1.641 (0.021)	0.318 (0.021)	0.155 (0.117–0.194)	<0.0001
FVC	Baseline	3.054 (0.100)			
	Tio (n=99)	3.307 (0.040)	0.258 (0.040)		
	T/O (n=103)	3.507 (0.039)	0.459 (0.039)	0.201 (0.134–0.267)	<0.0001

[a]Between-group differences.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; SE, standard error; T/O, tiotropium/olodaterol; Tio, tiotropium.

Figure legends

Figure 1. Trial design.

*Speed determination.
**At visits 4 and 7, a period baseline 3-min CSST was completed prior to dosing. At visits 5, 6, 8 and 9 a constant speed test was conducted 2 hours (+ 15 minutes) after inhalation of the study medication.
3-min CSST, 3-minute constant speed shuttle test; ISWT, incremental shuttle walking test; T/O, tiotropium/olodaterol; Tio, tiotropium.

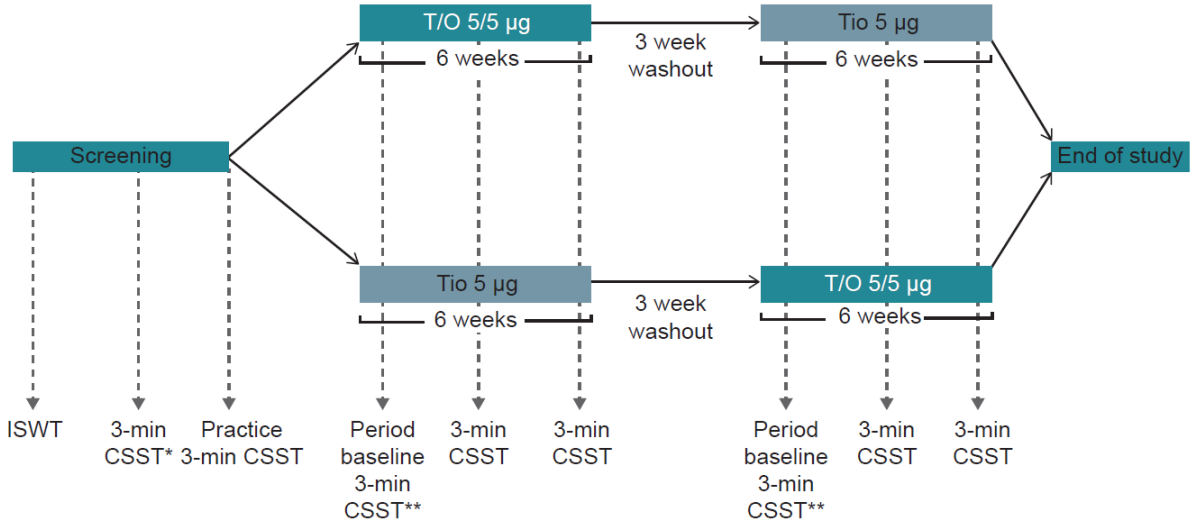


Figure 2. Patient disposition (crossover trial).

[a]Reasons for exclusion (screen failures) are shown in Supplementary Table 1. [b]Due to other AE. [c]All due to exacerbations.

AE, adverse event; COPD, chronic obstructive pulmonary disease; T/O, tiotropium/olodaterol; Tio, tiotropium.

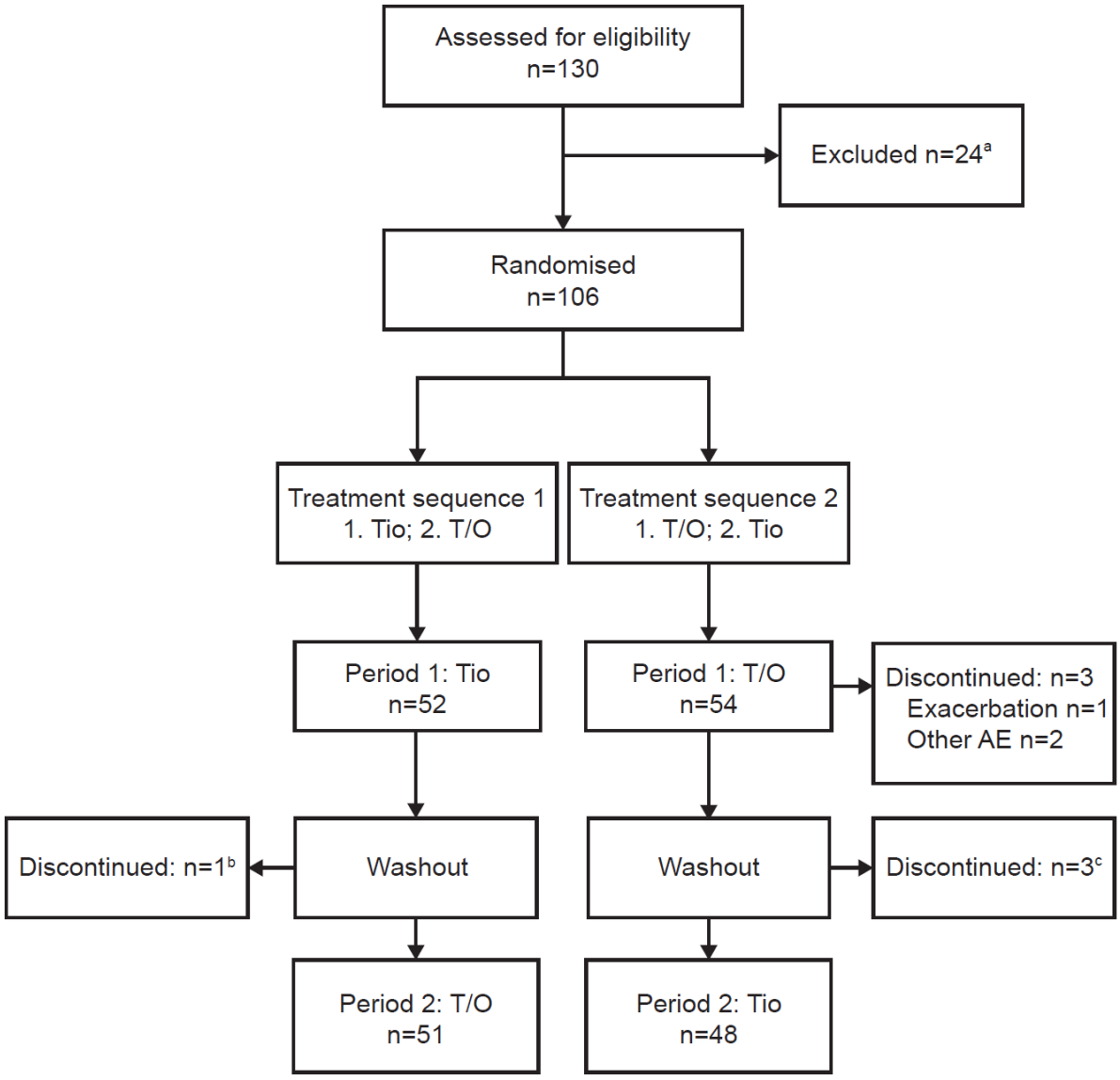
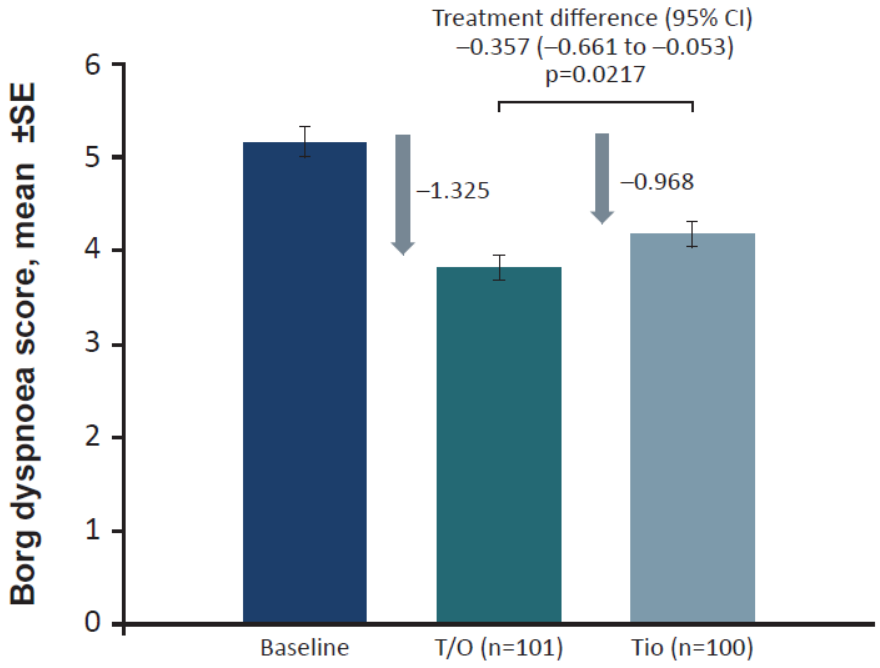


Figure 3. Mean Borg dyspnoea score a) at the end of the 3-min CSST (primary endpoint) and b) during the 3-min CSST, after 6 weeks of treatment.

*p<0.05 T/O *vs* Tio.
3-min CSST, 3-minute constant speed shuttle test; CI, confidence interval; SE, standard error; T/O, tiotropium/olodaterol 5/5 µg; Tio, tiotropium 5 µg.

a)



b)

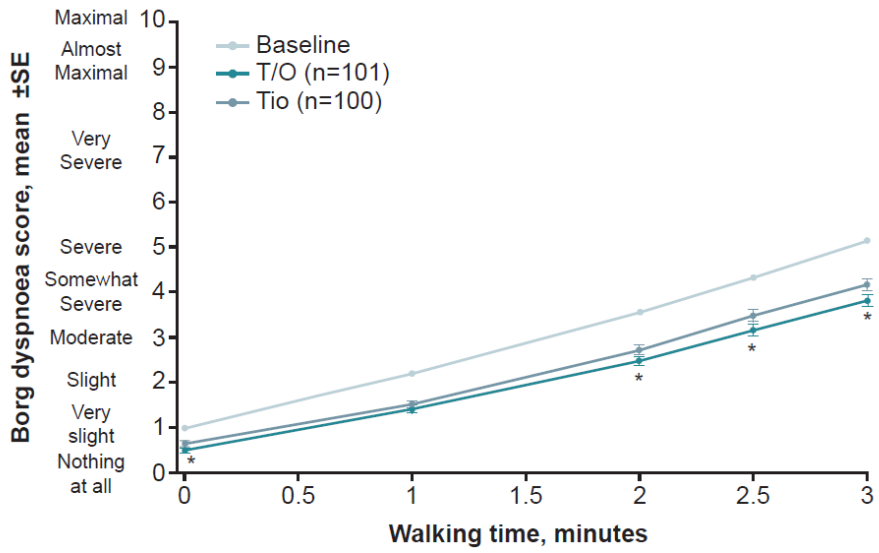


Figure 4. Treatment difference in Borg dyspnoea score at 6 weeks.

Each individual patient is represented by a single point. Negative scores indicate a larger reduction in Borg dyspnoea score with tiotropium/olodaterol and positive scores indicate larger reduction in Borg dyspnoea score with tiotropium. The dotted lines represent changes in Borg dyspnoea score ≥1 unit in both direction. Period baseline was used for this analysis.

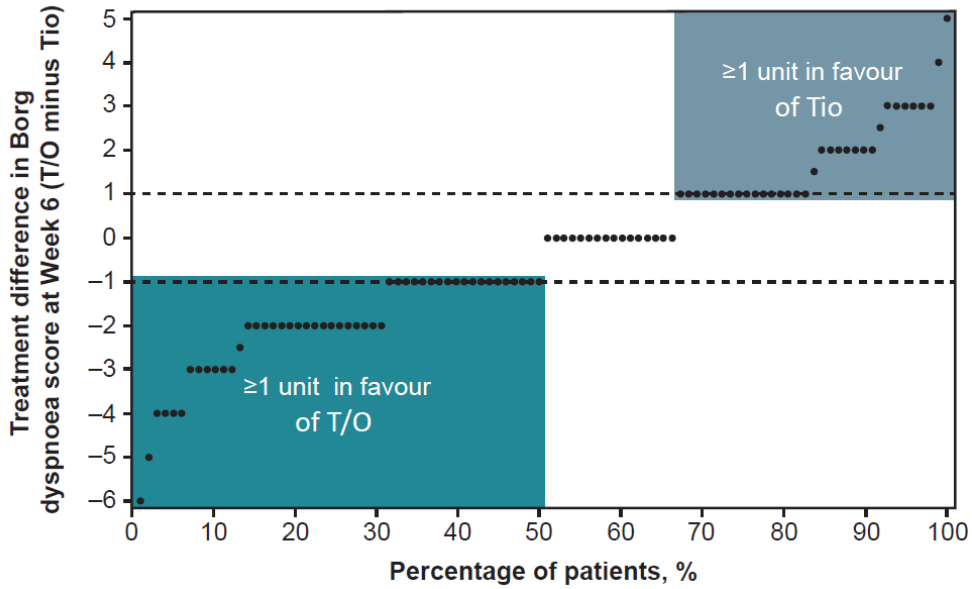
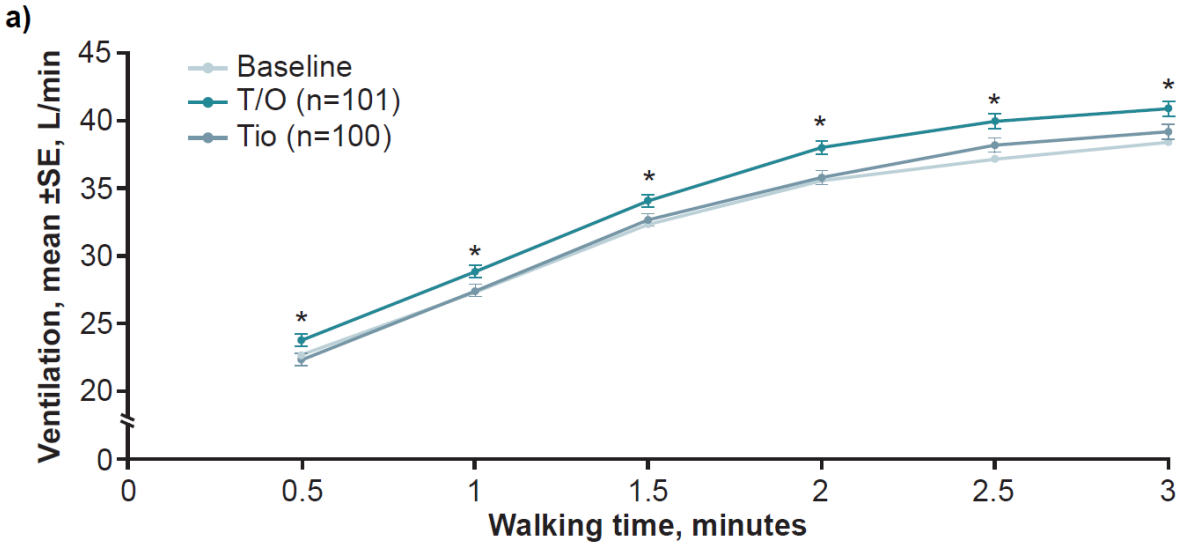
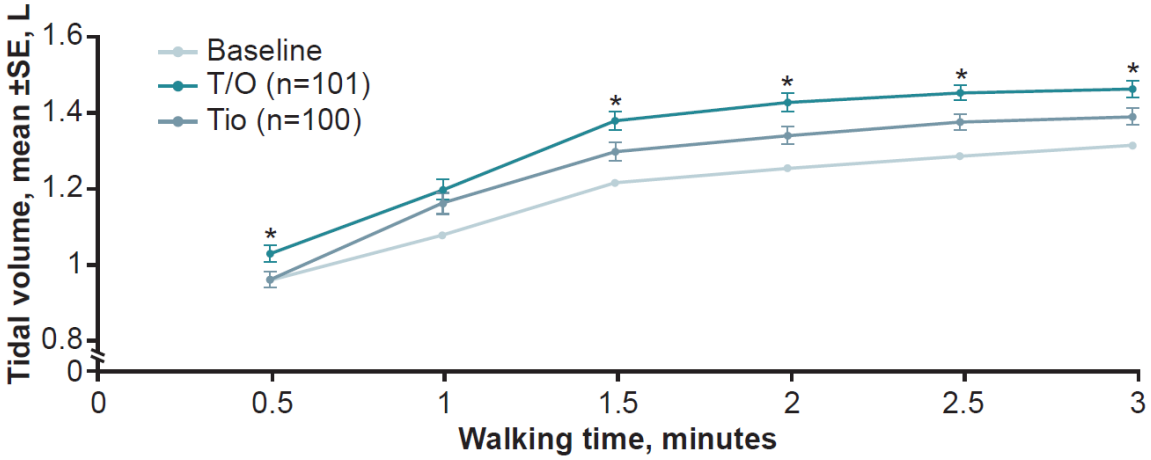


Figure 5. Physiological parameters measured during the 3-min CSST at 6 weeks: a) ventilation, b) tidal volume and c) breathing frequency.

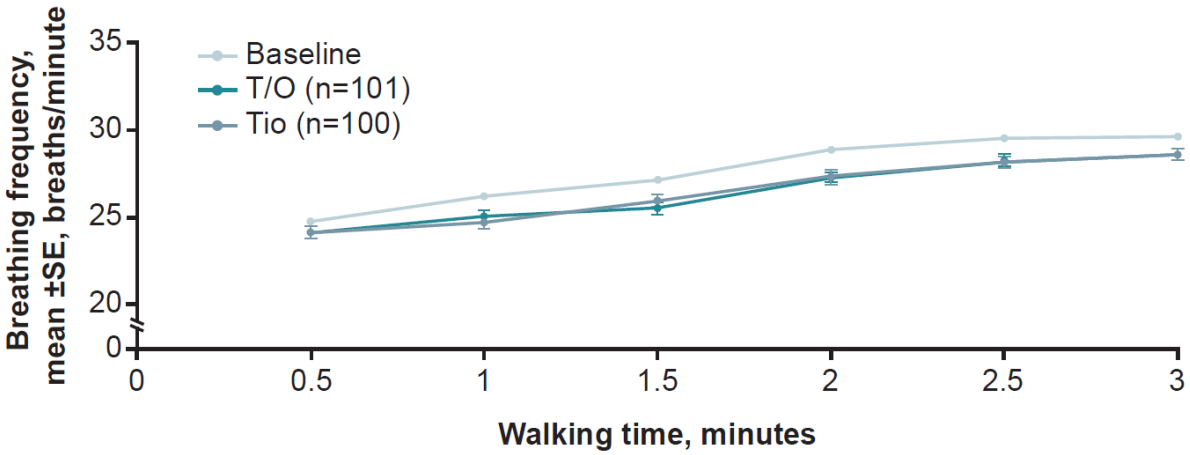
3-min CSST, 3-minute constant speed shuttle test; SE, standard error; T/O, tiotropium/olodaterol; Tio, tiotropium.



b)


Tidal volume, mean ±SE, L
1.6
1.4
1.2
1
0.8
0
Baseline
T/O (n=101)
Tio (n=100)
*
*
*
*
0
0.5
1
1.5
2
2.5
3
Walking time, minutes

c)


Breathing frequency, mean ±SE, breaths/minute
35
30
25
20
0
Baseline
T/O (n=101)
Tio (n=100)
0
0.5
1
1.5
2
2.5
3
Walking time, minutes

Supplementary Material

Supplementary methods

Modified Borg Scale

Patients were given the following instructions:

"We will be using the BORG Scale to help us understand the intensity or severity of your breathing discomfort and the intensity or severity of your leg discomfort. We will ask you to use this scale to rate the intensity of your breathing discomfort and your leg discomfort before, during, and after your exercise test.

Please review the scale to see the various levels from which you can choose.

For breathing discomfort:

The top of the scale, '0 or nothing at all,' means no breathing discomfort at all.

The bottom of the scale, '10 or maximal,' means the most severe breathing discomfort that you have ever experienced or could imagine experiencing.

When we ask you to rate the intensity of your breathing discomfort, please state the number that best describes the intensity that you are experiencing at that moment. Please let us know if you have any questions before we begin."

Incremental shuttle walk test

In this test, patients walk back and forth on a 10-metre course, at a speed dictated by an audio signal. The speed increases every minute, and the test continues until the patient is limited by their symptoms, is unable to maintain the pace, is unable to continue safely in the opinion of the supervising technician/physician or completes the full 12 minute ISWT duration. Patients who completed the full 12 minutes of the ISWT were excluded from the trial.

Results

Baseline visits

Baseline breathlessness at the visit before the first treatment period and the visit before the second treatment period were similar. Mean Borg scale of breathing discomfort at the end of exercise was 5.07 (standard deviation [SD] 1.76) before the first treatment period and 5.22 (SD 1.81) before the second treatment period. IC at rest was also similar between the two baseline visits (2.309 L [SD 0.772] at the first and 2.340 L [SD 0.747] at the second).

Supplementary Table 1. Most frequent reasons for screen failure.

Number of patients[a]	**Reason for exclusion**
4	Adverse event
9	Absence of hyperinflation at rest, defined as functional residual capacity >120% predicted
4	Did not reach a Borg dyspnoea score ≥4 at the end of the 3-min CSST
3	Oxygen saturation SpO_2 < 85% (on room air) at rest or during exercise
3	COPD exacerbation in the 6 weeks prior to screening
2	Treated with oral corticosteroids at unstable doses (i.e. less than 4 weeks on a stable dose, or doses in excess of 10 mg per day or 20 mg every other day)
2	Receiving antibiotics for any reason
2	Unable to comply with pulmonary medication restrictions prior to randomisation
2	Did not meet spirometric criteria or did not have diagnosis of COPD
1	Contraindications for exercise testing
1	Not within age range (40–75 years)
1	Unable to perform technically acceptable pulmonary function tests or body plethysmography, or unable to complete multiple shuttle tests during the study period

[a]Some patients had more than one reason for exclusion. In total, 24 patients were screened and not included. Data for screen failures was not systematically reviewed/verified by the trial team.

3-min CSST, 3-minute constant speed shuttle test; COPD, chronic obstructive pulmonary disease; SpO_2, oxygen saturation.

IC and breathlessness after 3 weeks of treatment

After 3 weeks of treatment, there was a reduction in the intensity of breathlessness during the 3-min CSST for both treatments compared to baseline, but there was no difference between tiotropium/olodaterol and tiotropium (Supplementary Figure S2). However, there was a significant difference between treatments in resting IC (Supplementary Table 2).

Supplementary Table 2. Resting IC after 3 weeks of treatment.

Measure	**Treatment**	**Mean, L (SE)**	**Mean change from baseline, L (SE)**	**Mean difference *vs* tio, L (SE)**	**p-value**
Resting IC	Baseline	2.317 (0.073)			
	Tio (n=97)	2.519 (0.042)	0.203 (0.042)		
	T/O (n=102)	2.738 (0.041)	0.421 (0.041)	0.219 (0.130–0.308)	<0.0001

IC, inspiratory capacity; SE, standard error; T/O, tiotropium/olodaterol; Tio, tiotropium.

Supplementary Table 3. Summary of adverse events (treated set).

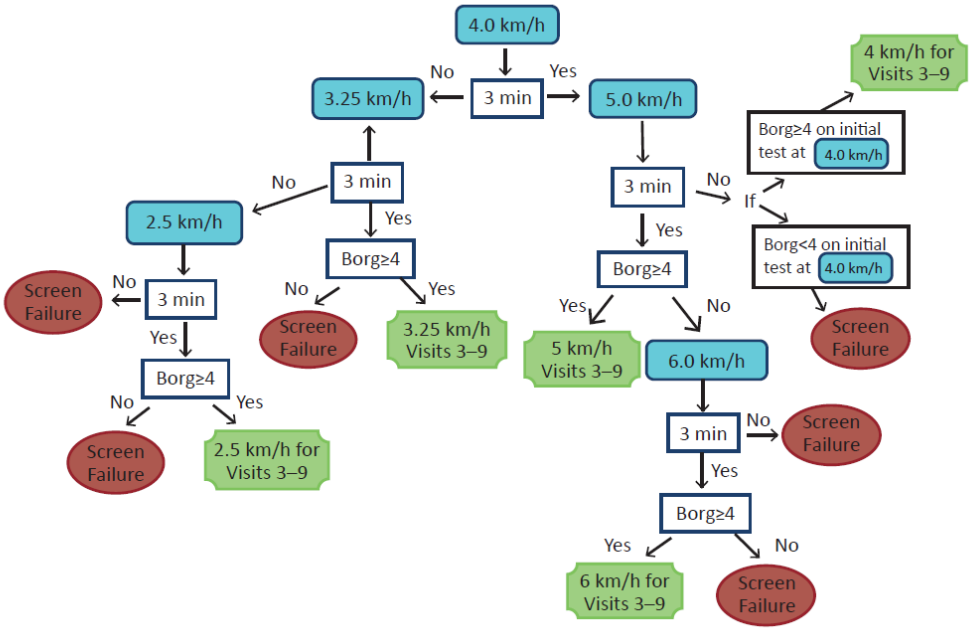
No. of patients, n (%)	T/O (n=105)	Tio (n=100)	Total (n=106)
Any AE	60 (57.1)	50 (50.0)	82 (77.4)
Drug-related AEs	3 (2.9)	2 (2.0)	4 (3.8)
AE leading to discontinuation	6 (5.7)	1 (1.0)	7 (6.6)
Serious AEs	5 (4.8)	1 (1.0)	6 (5.7)
Fatal	0	0	0
Requiring hospitalisation	4 (3.8)	1 (1.0)	5 (4.7)
Disability/ incapacitated	1 (1.0)	0	1 (0.9)
Serious AEs (preferred terms)[a]			
Cerebrovascular accident	0	1 (1.0)	1 (0.9)
Pneumonia[b]	2 (1.9)	0	2 (1.9)
Neoplasms	2 (1.9)	0	2 (1.9)
Coma	1 (1.0)	0	1 (0.9)
Ileus	1 (1.0)	0	1 (0.9)
Nephrolithiasis	1 (1.0)	0	1 (0.9)

[a]Patients may have had an AE that was classed as more than one condition. [b]Including influenzal pneumonia.

AE, adverse event; T/O, tiotropium/olodaterol; Tio, tiotropium.

Figure legends

Supplementary Figure S1. Speed selection at the second screening visit.



Supplementary Figure S2. Intensity of breathlessness during the 3-min CSST after 3 weeks of treatment.

3-min CSST, 3-minute constant speed shuttle test; SE, standard error; T/O, tiotropium/olodaterol; Tio, tiotropium.