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Therapeutic conversion of the combination of ipratropium and albuterol to tiotropium in patients with chronic obstructive pulmonary disease

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ABSTRACT

Background: Ipratropium and albuterol, combined in a single formulation, is widely used as three to four times daily maintenance therapy in COPD. This trial compared tiotropium, once daily, as a potential alternative to patients already taking the ipratropium/albuterol combination.
Methods: 676 patients with moderate to very severe stable COPD (mean $FEV_1 = 39\%$ of predicted) maintained on ipratropium/albuterol were randomized to receive over an 84 day period either tiotropium (18 mcg) each morning, or continue with ipratropium (26 mcg)/albuterol (206 mcg), 2 actuations 4 times daily, using a parallel group, double-blind, double-dummy design. Six-hour spirometry was assessed on study days 1, 22, and 84, along with safety assessments and other efficacy measures.
Results: In terms of primary outcomes, mean trough FEV_1 at 84 days was larger in the tiotropium arm, as compared with the ipratropium/albuterol arm (difference = 86 ml; 95% CI, 49 to 123 ml, $p < 0.0001$). The mean FEV_1 AUC_{0-6} at 84 days was also larger in the tiotropium arm (difference = 17 ml; 95% CI, −21 to 56 ml), this difference being statistically non-inferior to the ipratropium/albuterol arm ($p < 0.001$), but not statistically superior ($p = 0.37$). Other efficacy measures were similar in the two groups. Lower respiratory adverse events were reported in 40 tiotropium patients vs. 52 ipratropium/albuterol patients. Safety reporting was otherwise similar.
Conclusion: Patients previously maintained on the ipratropium/albuterol combination taken four times daily can be switched to tiotropium once daily with the reasonable expectation of at least equivalent bronchodilation during daytime hours and superior bronchodilation during early morning hours.
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1. Introduction

For many years short-acting inhaled beta-adrenergic agonists and anticholinergics were the mainstay of bronchodilator therapy for symptomatic COPD. Combining a short-acting beta-agonist, albuterol, with a short-acting anticholinergic, ipratropium, provided superior bronchodilation compared to monotherapy with either drug [1,2]. As a consequence, combined therapy with these two short-acting bronchodilators was widely implemented in clinical practice.

Long-acting inhaled beta-adrenergic agonists and anticholinergic bronchodilators have recently been introduced into clinical practice, and they are now recommended as first line maintenance therapy in

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; FEV_1/FVC, ratio of forced expiratory volume in one second to forced vital capacity; PEFR, peak expiratory flow rate; AUC_{0-6}, area under curve between 0 and 6 h; MDI, metered dose inhaler.

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COPD [3]. Tiotropium is a quaternary ammonium compound that is chemically and mechanistically similar to ipratropium but with a substantially longer duration of action [4]. Compared with placebo, once-daily tiotropium provides sustained bronchodilation, along with improved dyspnea and exercise capacity, better respiratory health status, and fewer exacerbations [5–10].

Tiotropium has also been shown to provide superior bronchodilation to active comparators, including ipratropium, given four times daily, and to the twice-daily inhaled beta-adrenergic agonists, salmeterol and formoterol [7–13]. However, there have been no direct comparisons of tiotropium with the ipratropium/albuterol combination. Additionally, given the efficacy and safety profile of tiotropium, a reasonable therapeutic option would be to switch patients maintained on regular, four times daily regimen of two short-acting medications, ipratropium and albuterol. Hence, the purpose of this study was to directly compare the efficacy and safety of once-daily tiotropium with the ipratropium/albuterol combination, administered four times daily, over a 12-week period in COPD patients previously receiving the ipratropium/albuterol combination. Our primary hypothesis was that after 84 days of therapy, tiotropium, compared to ipratropium/albuterol, would significantly increase the trough FEV_1 measured 24 h after the previous dose of tiotropium.

2. Methods

2.1. Design and conduct of the study

This report represents a pooled analysis of data from two separate double-blind, double-dummy, parallel group, controlled trials that used the same protocol and that was conducted at 71 study sites (ClinicalTrials.gov Identifiers: NCT00388882 and NCT00359788). The trial was performed in compliance with the principles in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice. The institutional review board of each participating medical center approved this study. All subjects gave written informed consent.

The study group consisted of patients of either sex who were 40 years of age or older and who had a diagnosis of clinically stable COPD. Principal eligibility criteria included (1) current or former cigarette smoker with lifetime consumption of $\geq$10 pack-years, (2) use of Combivent® (18 mcg ipratropium bromide monohydrate/103 mcg albuterol sulfate per actuation at the mouthpiece) MDI for one or more months prior to first study visit, and (3) post-bronchodilator $FEV_1 \leq 70\%$ of predicted at enrollment visit and pre-bronchodilator $FEV_1 \leq 65\%$ of predicted with $FEV_1/FVC \leq 70\%$ at randomization visit. Principal exclusion criteria included (1) primary clinical diagnosis of asthma, (2) daily home oxygen use for more than one hour, (3) prednisone (or its equivalent) in daily dose of more than 10 mg or an unstable pattern, (4) COPD exacerbation within previous 6 weeks, (5) myocardial infarction within prior six months, (6) life threatening cardiac arrhythmia or hospitalization for heart failure in the prior year, (7) current radiation therapy or chemotherapy for malignancy, (8) participation in another investigational drug trial within prior 30 days, (9) use of tiotropium in prior three months, and (10) use of any anticholinergic bronchodilator other than Combivent® within the prior 30 days.

2.2. Treatments

Following a 2-week run-in period, patients were randomized in equal numbers to one of two treatment arms for 84 days. The two comparative treatments were one capsule of tiotropium (18 mcg) inhaled via a HandiHaler® dry powder device each morning or two actuations of Combivent® MDI four times a day. Patients randomized to tiotropium received a placebo MDI to be used four times daily while patients randomized to ipratropium/albuterol received placebo capsules to be taken once daily in the HandiHaler®. Concomitant medications allowed throughout the trial included inhaled corticosteroids, theophylline, and stable doses of prednisone (not to exceed 10 mg daily or its equivalent). Patients were not allowed to take any long-acting beta-adrenergic bronchodilator for the duration of the trial. All patients were provided with albuterol MDI to use as needed. Albuterol was withheld for 8 h, short-acting theophylline for 24 h, and long-acting theophylline for 48 h, prior to study visits. Patients were also asked not to take study medications or inhaled corticosteroids on the morning of each visit. We permitted antibiotic courses and prednisone bursts for up to 2 weeks as treatment for exacerbations. Scheduled pulmonary function tests could be postponed for up to 2 weeks after completing treatment for an exacerbation without withdrawing the patient from the trial.

2.3. Observations

Patients who met all eligibility criteria at the second site visit were randomized and given their first doses of study drugs (study day 1). In addition to 6-hour spirometry testing, we obtained a medical history, measured vital signs, and performed a physical examination. We assessed COPD severity by a physician global evaluation and a patient global evaluation on study days 1, 42, and 84. The global evaluation is a non-validated 8-point scale with a text anchor from poor to excellent. The patients were provided with an electronic device to record PEFR and FEV_1 twice-daily and to record information daily about use of study medications, use of rescue albuterol, and information about shortness of breath. At return visits on study days 42 and 84, changes in the patient's medical condition, adverse events, COPD disease severity, and vital signs were assessed. Information from the electronic peak flow meters was downloaded and 6-hour spirometry testing was performed.

2.4. Spirometry

Spirometry was performed on study days 1, 42, and 84. On all test days, spirometry was initiated for each patient between 7:00 AM and 10:00 AM for each visit. Pre-dose (trough) measurements were obtained 10 ± 3 min prior to administering the doses of study medications. The measurements were repeated at 15 and 30 min and at 1, 2, 3, 4, and 6 h after study medications had been taken. Study sites performed spirometry using the same predictive nomogram and with equipment and methods that conformed to expert recommendations [14,15]. Spirometry data were submitted electronically to a central location for quality control.

2.5. Statistical analysis

The primary efficacy endpoints were the trough FEV_1 and FEV_1 AUC_{0-6} after 84 days of treatment. Trough FEV_1 is the FEV_1 value measured prior to study medication administration on the test day, approximately 24 h since the previous administration of tiotropium or its placebo. The mean trough FEV_1 and mean FEV_1 AUC_{0-6} between tiotropium and ipratropium/albuterol groups at week 12 was compared using the analysis of covariance model with terms for treatment and center as fixed effects and baseline as a covariate. Baseline was defined as the FEV_1 measured at the randomization visit immediately prior to administration of the first dose of study drug. The following step-wise procedure was used to compare the treatments: the treatments were compared with respect to mean trough FEV_1; if tiotropium was demonstrated to be superior to ipratropium/albuterol in trough FEV_1 then treatment with

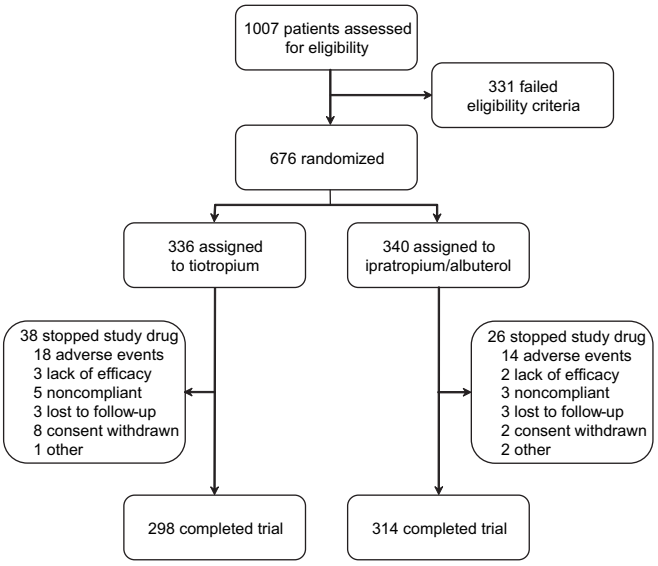

Fig. 1. Trial flow chart.

tiotropium was to be tested for non-inferiority to ipratropium/albuterol for mean FEV_1 AUC_{0-6}; if tiotropium was demonstrated to be non-inferior to ipratropium/albuterol in FEV_1 AUC_{0-6} then treatment with tiotropium was to be tested for superiority to ipratropium/albuterol for mean FEV_1 AUC_{0-6}. If any of the steps were not successful, the subsequent analysis was considered as exploratory. The non-inferiority margin was considered to be 50 ml. The power to detect a difference in trough FEV_1 was more than 99%, and the power to establish non-inferiority in FEV_1 AUC_{0-6} was 92%. The analysis of covariance model was performed for all secondary efficacy endpoints. The diary symptoms and other FEV_1 measurements were summarized using descriptive statistics. Results are expressed as means ± standard error unless otherwise specified. Statistical significance is considered at $p < 0.05$.

3. Results

Of the 1,007 patients evaluated for the trial, 676 met all eligibility criteria, of whom 336 were randomized to tiotropium and 340 to ipratropium/albuterol (Fig. 1). The first patient was randomized on July 31, 2006 and the last patient completed the trial on October 8, 2007. Thirty eight (11%) patients prematurely stopped study drug in the tiotropium arm while 26 (8%) patients did so in the ipratropium/albuterol arm. Adverse events accounted for about one half of withdrawals in both study arms (Fig. 1). As assessed with the electronic diary, overall study drug compliance was 90% with the HandiHaler® and 79% with the MDI.

The two treatment groups were well matched with regard to age, gender, ethnicity, smoking history, duration and severity of COPD, and use of respiratory medications (Table 1).

3.1. Pulmonary function testing

Results of FEV_1 and FVC measurements are reported in Tables 2 and 3 and shown graphically in Fig. 2A and B. In terms of the primary study outcomes, mean trough FEV_1 change from baseline on study day 84 was significantly larger in the tiotropium group, as compared with the ipratropium/albuterol group (difference, 86 ml; 95% CI, 49 to 133 ml; $p < 0.0001$). Mean FEV_1 AUC_{0-6} on study day 84 in the tiotropium arm was statistically non-inferior to the ipratropium/albuterol arm (difference, 17 ml; 95% CI, −21 to 56 ml, $p = 0.0003$), but not statistically superior ($p = 0.37$).

Fig. 2A illustrates a more detailed comparison of bronchodilator responses in the two study groups on the various study days. Mean FEV_1 trough value in the tiotropium arm was larger by 125 ml on day 42 ($p < 0.001$). On study days 42 and 84, average FEV_1 responses became larger in the tiotropium arm about 2–3 h after administration of study drug, and they remained so for the duration of the 6-hour period. Mean peak FEV_1 responses were larger in the ipratropium/albuterol arm compared with the tiotropium arm on each of the three study days, with differences ranging from 120 to 134 ml ($p < 0.001$). Differences in FVC responses closely mirrored those observed with the FEV_1 (Fig. 2B). As compared with the ipratropium/albuterol group, mean FVC trough for the tiotropium group was significantly larger on study days 42 and 84 ($p < 0.01$ for both comparisons), but the AUC_{0-6} was not ($p > 0.5$ for both comparisons).

3.2. Other efficacy outcomes

Compared with the ipratropium/albuterol arm, weekly mean morning peak expiratory flow and FEV_1, measured prior to study medications, were both significantly larger in the tiotropium arm for morning measurements ($p < 0.05$), but not for evening measurements. No statistically significantly treatment-related differences were detected in albuterol rescue therapy, physician global evaluations, or patient reported shortness of breath. Total albuterol use, calculated from the sum of rescue albuterol and scheduled ipratropium/albuterol, was significantly lower in the tiotropium group (5.3 vs 6.8 puffs per day based on weekly means, $p < 0.001$). Mean patient global evaluations were statistically significantly better ($p < 0.05$) for the tiotropium group on study day 42, but not on study day 84.

3.3. Adverse events

Adverse events according to treatment group are summarized in Table 4. One hundred nine (32%) patients in the ipratropium/albuterol arm experienced an adverse event as compared to 94 (28%) in the tiotropium group. The most common adverse event related to disorders of the lower respiratory tract. Forty (12%) patients

Table 1
Baseline characteristics.

Characteristic	Tiotropium $n = 336$	Ipratropium/albuterol $n = 340$
Male gender, n (%)	270 (80)	283 (83)
Race, n (%)		
White	311 (92)	318 (93)
Black	25 (7)	21 (6)
Asian	0 (0)	1 (0)
Age, mean (SD)	64 (8)	65 (8)
Current smokers, n (%)	141 (42)	128 (38)
Duration of COPD, mean (SD)	9 (8)	8 (7)
Spirometry, mean (SD)		
FEV_1, L	1.09 (0.39)	1.10 (0.40)
% predicted FEV_1	39 (12)	39 (12)
FVC, L	2.64 (0.79)	2.73 (0.82)
FEV_1/FVC	42 (11)	41 (11)
Respiratory medications, n (%)		
Long-acting inhaled beta-agonist	79 (24)	74 (22)
Inhaled corticosteroid	129 (38)	143 (42)
Oral corticosteroids	11 (3)	8 (2)
Theophylline	12 (4)	13 (4)

Table 2
FEV_1 differences according to treatment group.

Trough FEV_1, 24 h after study drug							
	Study day	Tiotropium ml (SE) $n = 302$	Ipratropium/albuterol ml (SE) $n = 309$	Mean difference ml (SE)	95% CI's ml	*P*-value	
Mean change	42	104 (12)	−21 (11)	125 (16)	92, 157	< .0001	
	84	94 (13)	8 (13)	86 (19)	48, 123	< .0001	
FEV_1 area under curve, 0–6hours after study drug							
	Study day ml (SE)	Tiotropium ml (SE) $n = 302$	Ipratropium/albuterol ml (SE) $n = 309$	Mean difference ml (SE)	95% CI's ml	Non-inferiority *P*-value	Superiority *P*-value
Mean	1	134 (9)	213 (8)	−79 (12)	−102, −55	0.99	< .0001
	42	209 (13)	164 (13)	45 (18)	9, 80	< .0001	0.0132
	84	194 (14)	177 (14)	17 (19)	−21, 56	0.0003	0.369

Baseline is defined as the FEV_1 measured at the randomization visit immediately prior to administering the first dose of study drug. Overall mean was 1,103 ml and this value was used to compute both the trough FEV_1 and the FEV_1 under the curve for both groups.

experienced such events in the tiotropium arm versus 56 (16%) in the ipratropium/albuterol arm. There were 19 patients with serious adverse events in each treatment arm; 8 were attributed to COPD exacerbation in the ipratropium/albuterol arm and 4 in the tiotropium arm. Under the broader category of lower respiratory tract serious adverse events (which includes exacerbations), there were 13 patients in the ipratropium/albuterol arm and 9 patients in the tiotropium arm. Four patients experienced fatal adverse events in each treatment arm.

4. Discussion

A major finding of this trial is that once-daily tiotropium provides sustained bronchodilation, such that morning mean trough FEV_1, measured 24 h after the previous dose, is significantly superior to that obtained with four times daily ipratropium/albuterol in COPD patients who were using ipratropium/albuterol for at least 4 weeks prior to enrollment in the trial. Additionally, tiotropium-induced bronchodilation was found to be statistically non-inferior to that of ipratropium/albuterol for six hours after administering morning doses of study drugs. Twice-daily self-measurements of FEV_1 and PEFR made at home further support these findings.

Our results are generally consistent with the known bronchodilator profiles of the drugs studied. The ipratropium/albuterol combination elicits a faster and larger peak response, but the tiotropium response is more sustained with larger mean FEV_1 values observed 2–3 hours after administration of study drugs and beyond. The mean differences in trough FEV_1, of 124 ml at 42 days and of 86 ml at 84 days, are comparable to other trials where tiotropium has been compared to either ipratropium or placebo and reflects the 24-hour effects with once daily dosing [6,9–11].

Whether tiotropium improves clinical outcomes in comparison with ipratropium/albuterol remains unclear. There were no clear differences between the two treatment arms in terms of albuterol rescue therapy, daily shortness of breath scores as captured by electronic diaries, patient global evaluation, or physician global evaluation. It bears emphasizing also that the instruments used to capture patient reported outcomes in this trial have not been validated and their sensitivities for detecting clinically meaningful changes are not known. The relatively high rates of concomitant inhaled corticosteroid use might also have muted true treatment differences [15]. There was a trend towards fewer exacerbations, including a reduction in serious lower respiratory events in the tiotropium arm, but the trial was greatly underpowered to draw any firm conclusion. In prior studies of tiotropium, increases of mean trough FEV_1 values in the range of 100–150 ml, similar to those observed in this trial, have been associated with reductions in COPD exacerbations and in some studies with hospitalizations [5,6,9–11].

Short and long-acting inhaled bronchodilators are recommended as first line medication options for the treatment of patients with moderate to very severe COPD (GOLD Stages II to IV) [3]. Furthermore, the international guidelines also recommend long-acting over short-acting inhaled bronchodilators as being more effective and convenient. However, the references supporting the recommendation are based on single short-acting agents compared to a single long-acting agent [6,16–18]. The combination of ipratropium and albuterol provides benefits above of either drug alone and it is commonly prescribed [1,2]. Given the consistent clinical benefits of tiotropium on multiple relevant outcomes along with the convenience and potentially compliance implications associated with once daily compared to four times daily administration, tiotropium may represent a reasonable therapeutic alternative to patients already receiving maintenance treatment with a combination of ipratropium/albuterol. In addition, it is generally considered advantageous if patients can be exposed to potential adverse effects associated with one class of drugs rather than two classes of drugs.

Table 3
FVC differences according to treatment group.

Trough FVC, 24 h after study drug						
	Study day	Tiotropium ml (SE) $n = 302$	Ipratropium/albuterol ml (SE) $n = 309$	Mean difference ml (SE)	95% CI's ml	*P*-value
Mean change	42	235 (24)	8 (24)	228 (34)	160, 295	< .0001
	84	222 (28)	99 (27)	122 (39)	46, 199	0.0018
FEV_1 area under curve, 0–6hours after study drug						
	Study day ml (SE)	Tiotropium ml (SE) $n = 302$	Ipratropium/albuterol ml (SE) $n = 309$	Mean difference ml (SE)	95% CI's ml	*P*-value
Mean	1	310 (20)	470 (20)	−160 (28)	−216, −105	< .0001
	42	435 (25)	413 (24)	22 (35)	−47, 90	0.5346
	84	412 (26)	428 (26)	−15 (37)	−88, 57	0.6771

Baseline is defined as the FVC measured at the randomization visit immediately prior to administering the first dose of study drug. Overall mean was 2,714 ml and this value was used to compute both the trough FVC and the FVC under the curve for both groups.

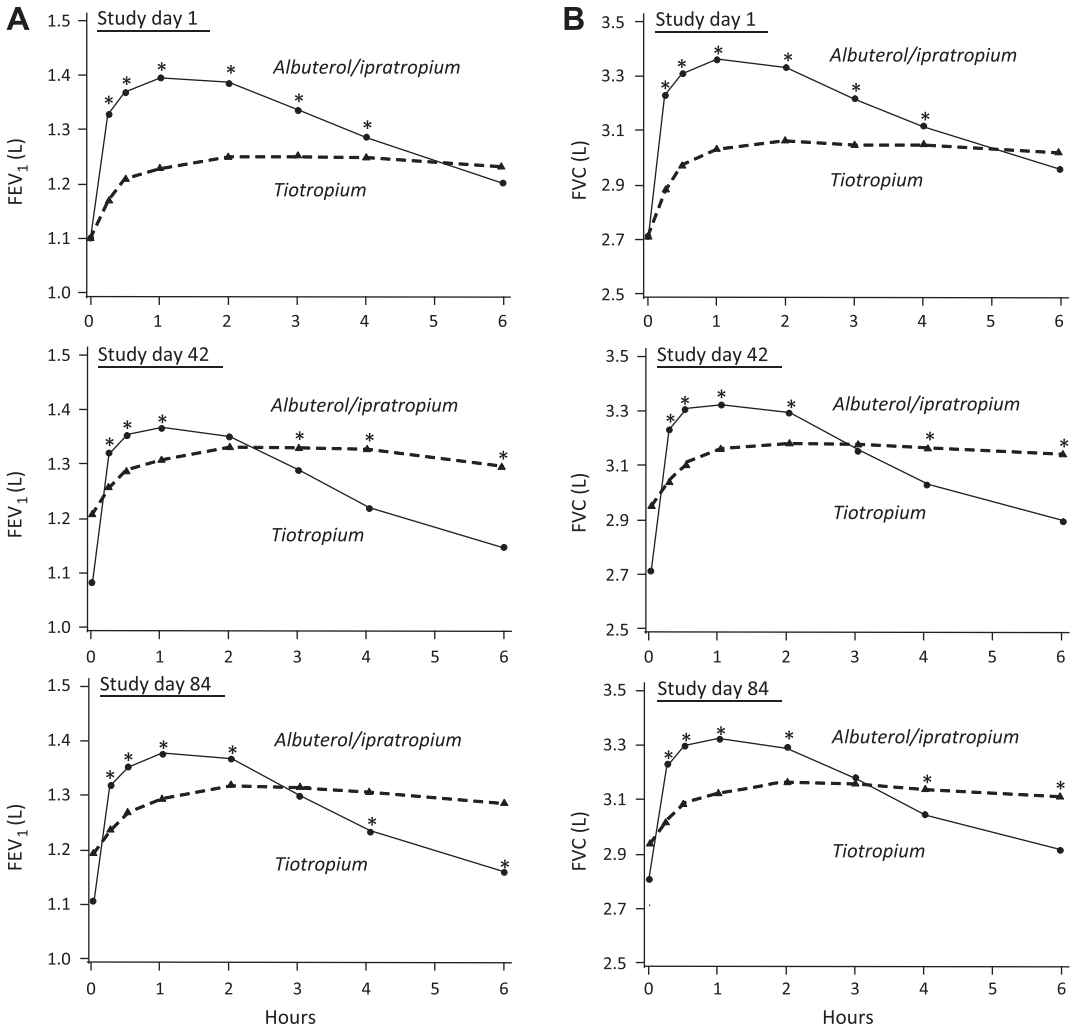

Fig. 2. (A). FEV_1 responses over six hours on various study days, according to treatment assignment. Solid line, ipratropium/albuterol; dashed line, tiotropium. $^*p < 0.05$ for superiority. (B). FVC responses over six hours on various study days, according to treatment assignment. Solid line, ipratropium/albuterol; dashed line, tiotropium. $^*p < 0.05$ for superiority.

The only other evaluations have compared an ipratropium/albuterol combination in maintenance treatment has been to another combination product (fluticasone/salmeterol) in short term trials of 8 weeks duration [19]. That study did not require patients to have previously used the combination of ipratropium/albuterol. The advantages of the present study relate to the clinical decision regarding converting patients from two products to one product, which requires data with patients using ipratropium/albuterol prior to randomization.

In summary, this trial demonstrates that in patients already using ipratropium/albuterol, switching to tiotropium provides better overnight bronchodilation and equivalent results during daytime hours. The trend towards reduced lower respiratory adverse events with tiotropium along with the reduction in overall beta-agonist use may indicate symptomatic and longer-term benefits that would need confirmation in a larger study with a longer duration. Overall, our results indicate that once-daily tiotropium is a safe and effective alternative to ipratropium/albuterol given four times daily.

Table 4
Adverse events.

	Tiotropium N (%) $n = 336$	Ipratropium/albuterol N (%) $n = 340$
Patients with any adverse event	94 (28)	109 (32)
Patients with investigational drug related adverse events	4 (1)	0 (0)
Patients with other significant adverse events	11 (3)	5 (2)
Patients with adverse events leading to discontinuation of study drug	18 (5)	14 (4)
Patients with serious adverse events	19 (6)	19 (6)
Patients with fatal adverse events	4 (1)	4 (1)

Conflicts of interest

Dr. Niewoehner received advisory fees, honoraria, or research grants from Boehringer Ingelheim, Pfizer, Adams Respiratory Therapeutics, AstraZeneca, and GlaxoSmithKline. Dr. Lapidus received consulting fees, speaking honoraria, or research grants from Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Dey, and Novartis. Dr. Cote received speaking honoraria or fees for enrolling patients in clinical trials from Boehringer Ingelheim, Pfizer, Altana Pharma, Replidyne, Bayer, Biomarck, and GlaxoSmithKline. Dr. Sharakhaneh received consulting fees, speaking honoraria, or research grants from GlaxoSmithKline, Dey, and Boehringer Ingelheim. Dr. Plautz received research grants or in-kind benefits from ParinGenex, Bayer, Boehringer Ingelheim, and Novartis. Mr.Johnson and Dr. Kesten are employees of Boehringer Ingelheim.

Role of the funding source

Boehringer Ingelheim Pharmaceuticals and Pfizer were the study sponsors and provided all funding. The sponsors collaborated with Dr. Niewoehner in developing the protocol. The sponsor collected the data and performed the analyses. Dr. Niewoehner drafted the manuscript with the assistance of the sponsors and the coauthors.

Appendix

Site investigators in the United States included: Murray Altose, Cleveland, OH; Steven Scharf, Pamela Amelung, Baltimore MD; Hilary Cain, West Haven, CT; Allen Cooper Jr., Birmingham, AL; Leonard Moses, Thomas Ferro, Richmond, VA; Ashok Fulmbarker, North Chicago, IL; Daniel Gottlieb, MD, West Roxbury, MA; Michael Habib, Tucson, AZ; Peter Krumpe, Reno, NV; Ware Kuschner, Palo Alto, CA; Kees Mahutte, MD, Long Beach, CA; Kathryn Rice, Minneapolis, MN; Sanjay Sethi, Buffalo, NY; John Shigeoka, Salt Lake City; UT; Jeffrey Curtis, Ann Arbor, MI; Michael Cutaia, Brooklyn, NY; Rafael Perez, Decatur, GA; Jing Liu, Wichita, KS; Allen Blaivis, East Orange, NJ; Richard Robbins, Phoenix, AZ; Ralph J. Panos, Cincinnati, OH; Sandra Adams, San Antonio, TX; George Sarosi, Indianapolis, IN; Linda Nici, Providence, RI;

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Site investigators in the United Kingdom included: Jonathan Corne, Nottingham; Moyra Anderson, Carrickfergus; Roderick Reed, Buckinghamshire; Richard Russell, Berkshire; Ann Millar, Bristol; Anthony Gunstone, Cambridgeshire; Emrys Evans, Swansea.

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