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Effects of arformoterol twice daily, tiotropium once daily, and their combination in patients with COPD[☆]

D.P. Tashkin^{a,*}, J.F. Donohue^b, D.A. Mahler^c, H. Huang^d, E. Goodwin^d,
K. Schaefer^d, J.P. Hanrahan^{d,e}, W.T. Andrews^{d,f}

^a David Geffen School of Medicine UCLA, 10833 Le Conte Avenue, Los Angeles, CA 90095-1690, USA

^b University of North Carolina School of Medicine, Cb #7020, 4125 Bioinformatics, Pulmonary & Critical Care Medicine, Chapel Hill, NC 27599, USA

^c Dartmouth Medical School, Pulmonary & Critical Care Medicine, 5C, 1 Medical Center Drive, Lebanon, NH 03756-0001, USA

^d Sepracor Inc., 84 Waterford Drive, Marlborough, MA 01752, USA

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Summary

Purpose: Current guidelines support using in combination more than one class of long-acting bronchodilator for COPD patients whose symptoms are not controlled by mono-therapy. This 2-week, multi-center (34 sites), randomized, modified-blind, parallel group study evaluated the efficacy and safety of concomitant treatment with nebulized arformoterol (the formoterol(R,R)-isomer) BID and tiotropium DPI QD.

Methods: COPD patients (mean FEV₁ 1.37 L, 45.4% predicted) were randomized to receive mono-therapy (either arformoterol 15 µg BID [*n* = 76] or tiotropium 18 µg QD [*n* = 80]), or combined therapy (sequential dosing of arformoterol 15 µg BID and tiotropium 18 µg QD [*n* = 78]). Changes in pulmonary function, dyspnea, and rescue levalbuterol use were evaluated, as were safety outcomes.

Results: Mean FEV₁AUC_{0–24} (the primary endpoint) improved similarly from baseline for arformoterol (0.10 L) and tiotropium (0.08 L) treatment groups and greater for the combined therapy group (0.22 L; all *p*-values <0.005). Peak FEV₁, peak FVC, 24-h trough FEV₁, and inspiratory capacity also improved similarly for the mono-therapies and greatest for the combined therapy. Dyspnea (mean transition dyspnea index) improved similarly for arformoterol (+2.3) and tiotropium (+1.8) and greatest with combined therapy (+3.1; *p*-values <0.05).

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* Corresponding author. Tel.: +1 310 825 3163.

E-mail address: dtashkin@mednet.ucla.edu (D.P. Tashkin).

^e Current address: Pulmatrix Inc., Lexington, MA, USA.

^f Current address: Santhera Pharmaceuticals, Cambridge, MA, USA.

Levalbuterol use decreased for all treatment groups (range -1.8 to -2.5 actuations/day). All treatments had similar frequency of adverse events.

Conclusion: In this study, the combination of nebulized arformoterol 15 μg BID plus tiotropium 18 μg DPI QD was the most effective in improving pulmonary function and disease symptoms. Mono-therapy improvement with arformoterol or tiotropium was similar. All three treatments were well tolerated.

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airway flow obstruction that is poorly reversible and is clinically characterized as either chronic bronchitis or emphysema.^{1–3} Worldwide, COPD is one of the most prevalent non-infectious diseases in the world and is the fourth leading cause of death in the United States. It will become the third leading cause of death worldwide by 2020.^{1–3} The health and cost burden of COPD is even more substantial as it contributes to other serious comorbidities including osteoporosis, fractures, respiratory infections, lung cancer, and cardiovascular disease.^{4,5}

Evidence-based guidelines recommend the use of long-acting bronchodilators for maintenance treatment of COPD in patients with moderate to very severe disease.^{1–3} In general, two classes of long-acting bronchodilators are available for treating COPD: the long-acting β_2 -agonists (LABAs) such as salmeterol, formoterol, and arformoterol (the *R,R*-formoterol isomer) which act for 12 h,^{6–10} and the anticholinergic tiotropium which acts for 24 h.^{11–14} Racemic formoterol, arformoterol and tiotropium all improve lung function with an onset of bronchodilation within 2 h, improve quality of life, are well tolerated,^{6,7,12–20} and are associated with little clinically meaningful tolerance.^{8,12,14,16,19}

In the United States, currently available LABAs are administered via dry powdered inhalers (DPI) or by nebulization. Some patients with COPD, particularly the elderly and those with limited manual coordination or compromised lung function, may have difficulty using single breath hand-held inhalers resulting in ineffective respiratory delivery of aerosolized medication.^{21–25} Nebulized formulations of racemic formoterol and arformoterol, which obviate technical difficulties in the use of hand-held inhalers, are approved for the long-term maintenance treatment of bronchoconstriction in COPD.^{6,8}

Current guidelines recommend using the combination of more than one class of long-acting bronchodilator for patients whose symptoms are not controlled by bronchodilator mono-therapy.^{2,3,26} Previous studies have reported that combined therapy with racemic formoterol and tiotropium is effective and safe in treating COPD patients and results in greater improvement in airway function compared with either mono-therapy alone.^{20,27–32} Although arformoterol and racemic formoterol have the same bronchodilator moiety (the *R,R*-isomer), the two drugs differ from one another in formulation, the presence of the *S,S*-isomer, salts, excipients, and dosing amounts raising the possibility that these drugs might have different efficacy and safety profiles. This randomized double-blind

study compared pulmonary function and symptom improvement among patients treated with arformoterol mono-therapy, tiotropium mono-therapy, and both therapies combined, and tested the hypothesis that the combined therapy would afford significantly greater efficacy than either single-therapy.

Methods

This was a 2-week, prospective, multi-center (34 sites), randomized, modified-blind, double dummy, parallel group study designed to evaluate the efficacy and safety of the combination of arformoterol 15 μg BID and tiotropium 18 μg QD (dosed sequentially) versus the individual mono-therapies in the treatment of COPD patients. The study was conducted according to the principles established by the Declaration of Helsinki.³³ Appropriate Institutional Review boards approved the protocol and written informed consent was obtained from the patients.

Study patients

Of 429 patients screened, 235 were randomized to treatment and 234 received at least one dose of study medication (intent-to-treat population [ITT]) (Fig. 1). All patients had non-asthmatic COPD (including emphysema and/or chronic bronchitis). Eligible patients were at least 45 years of age had a ≥ 15 pack-year history of smoking, and had a breathlessness severity based on Medical Research Council Dyspnea Score ≥ 2 .³⁴ They also were required to have a pre-bronchodilator baseline pulmonary function of $\text{FEV}_1 > 0.7$ L, FEV_1/FVC ratio of $\leq 70\%$, and $\text{FEV}_1 \leq 65\%$ predicted. Patients were excluded if they had life-threatening or unstable respiratory status within 30 days of the screening visit. Patients who changed their prescribed dose or type of COPD medication within 14 days prior to screening or who had ever used tiotropium bromide inhalation powder were excluded.

During the study period, the use of LABAs or long- or short-acting anticholinergic bronchodilators (except for the study medication) was prohibited. Use of oral and inhaled corticosteroids was allowed as long as patients were on a stable dosing regimen for at least 14 days prior to study entry that was maintained throughout the study. Patients were required to withhold oral corticosteroids for at least 24 h prior to pulmonary function testing. Leukotriene modifiers and methylxanthines were not allowed for at least 7 days prior to study entry. Levalbuterol MDI (Xopenex[®] Sepracor Inc., Marlborough, MA) was supplied and used as needed for rescue medications for acute

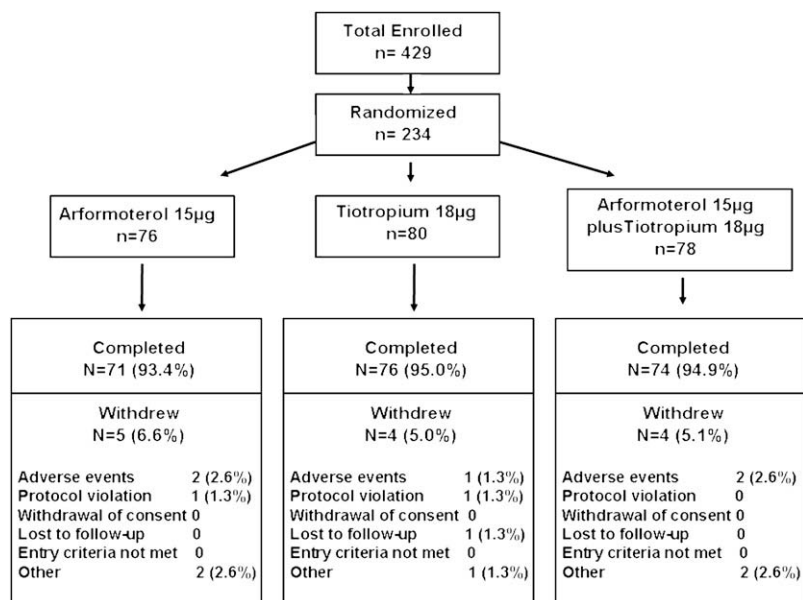


Figure 1 Patient disposition.

bronchospasm and acute treatment of COPD symptoms throughout the trial. Patients were instructed to withhold the use of rescue medication for ≥ 6 h prior to each clinic visit.

Study protocol

At the screening visit, baseline values were obtained for COPD symptoms, Modified Medical Research Council (MMRC) Dyspnea Scale, heart rate, vital signs, and pulmonary function tests. Medical event calendars and medication logs that were to be completed daily, and rescue medication were also dispensed. The medication logs were used to assess compliance by monitoring the number of UDV/DPI doses taken.

Eligible patients were randomized to receive one of three treatments for 14 days: nebulized arformoterol 15 µg (Brovana™, Sepracor Inc., Marlborough, MA) BID and placebo DPI QD, nebulized placebo BID and tiotropium 18 µg (Spiriva® HandiHaler® Boehringer Ingelheim, Ridgefield, CT) DPI QD, or nebulized arformoterol 15 µg BID and tiotropium 18 µg DPI QD. The nebulized drug was administered first using the PARI LC Plus® nebulizer driven by the Duraneb 3000® compressor (Pari: Pari Respiratory Equipment Inc., Midlothian, VA) at a flow rate of 3.3 L/min followed (within 5 min) by the DPI administration (HandiHaler®). The tiotropium and placebo DPI capsules were identical in size and shape but differed in color. For this reason, patients who had previously used tiotropium were excluded (see above) and the DPI capsules were dispensed and collected by an independent Study Drug Coordinator who was not otherwise involved in the study visits.

At week 0 and week 2, medical event calendars and blood samples were collected and vital signs and heart measurements analyzed. At week 0, spirometry was performed pre-morning dose, immediately (within 5 min) and

at 30 min, 1, 2, 4, 6, 8, 10, and 12 h post-first dose. After the 12-h pulmonary function test patients self-administered the evening dose of study medication. At week 2, serial spirometry was also performed as at week 0, as well as immediately (within 5 min) following the evening dose (administered 12 h after the morning dose) and 12.5, 13, 14, 16, 23, and 24 h post-morning dose. Inspiratory capacity was evaluated pre-dose and at 2 h post-morning dose at week 0, and pre-dose and 2, 11, 14, and 24 h post-morning dose at week 2. All inspiratory capacity measurements were the mean of acceptable inspiratory capacity maneuvers, two of which were reproducible. Prior to an inspiratory capacity maneuver a patient had to have a stable expiratory level for about 10 breaths. Once the stable level was achieved, at the end of exhalation of a normal breath the patient was asked to make a steady and full inhalation at normal inspiratory flow rates until the lungs were completely full, and then to exhale at a normal rate. Trough FEV₁ and trough inspiratory capacity measurements were evaluated 24 h after the first (morning) dose of a clinic visit.

All pulmonary function values used were the highest among the three acceptable maneuvers. The Investigator ensured that all spirometry was performed in accordance with the American Thoracic Society/European Respiratory Society Standardisation of Spirometry guidelines.³⁵ Centralized over-reading of spirometry and inspiratory capacity pulmonary function measures were used for quality control.

At screening, the baseline dyspnea index (BDI)³⁶ was assessed prior to the first clinic dose, and at week 2 the transition dyspnea index (TDI)³⁶ was evaluated before first morning dose. The baseline focal score (range 0–12) and the transition focal score (range –9 to 9) were the sums of the functional impairment, magnitude of task, and magnitude of effort scores.³⁶ Higher scores indicate less dyspnea at baseline (BDI) or greater improvement in dyspnea from baseline (TDI).

Statistical methods

Based on previous findings,^{6,7} the study was designed to detect a mean treatment difference of time normalized FEV₁AUC over 24 h (FEV₁AUC_{0–24}) (the primary endpoint) of 0.075 L with a standard deviation of 0.160 L when comparing combined therapy with mono-therapy, using a two-sided 5% significance level, following 2 weeks of dosing for the primary comparison with 80% power. All efficacy analyses were performed on the ITT population. All statistical testing was 2-tailed and conducted at the 5% significance level, unless otherwise indicated. The primary comparison was between the arformoterol plus tiotropium group versus tiotropium alone. The key secondary analysis comparison was between the arformoterol plus tiotropium group versus arformoterol alone. To control for multiple comparisons, statistical tests of mean treatment group differences were considered significant if the overall treatment effect in the model was statistically significant at the 5% level. Pulmonary function severity subgroup analysis was performed *post hoc* by stratifying patients according to the GOLD COPD guidelines² (<30%, ≥30% to <50%, and ≥50%, respectively). Pair-wise comparisons between treatment groups were performed using least square means (LS means) from the linear model with the study baseline (or pre-dose where applicable) as a covariate and the treatment group as a fixed effect.

Descriptive statistics were calculated by treatment for baseline characteristics and each efficacy parameter. Adverse events were summarized using counts and percentages. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA).³⁷ A COPD exacerbation was pre-defined as an increase in symptoms that necessitated any change in baseline medication other than bronchodilators (e.g. anti-inflammatory agents, antibiotics, supplemental oxygen therapy, etc.) or caused the patient to require additional medical attention (hospitalization, emergency room visit, etc.).

Results

Of the 429 patients enrolled in this study, 235 were randomized and 234 received at least one dose of study medication (ITT population) (Fig. 1). Demographic and baseline characteristics, including FEV₁, FVC, and inspiratory capacity values, were similar among treatment groups (Table 1). Of the patients in the ITT population, 94.4% completed the 2-week study with similar rates of completion for all three treatment groups (Fig. 1). The most common reason for discontinuation was the occurrence of adverse events ($n = 5$ [2.1%]) (Fig. 1). Approximately 97% of patients among the treatment groups were compliant with the therapies throughout the study.

Pulmonary function outcomes

FEV₁ at each time point and time normalized FEV₁AUC_{0–24}, improved from baseline for all treatment groups (Fig. 2a and b; Table 2). The two mono-therapies had comparable improvement for both FEV₁ and FEV₁AUC_{0–24} and the combined treatment group had the greatest improvement

after 2 weeks of treatment. The greater improvement in FEV₁AUC_{0–24} (the primary endpoint) for the combined therapy versus the mono-therapies was significant ($p < 0.001$). Peak change in FEV₁, changes in trough (at end of dosing interval) FEV₁, and peak change in FVC improved significantly from baseline following all treatments (Table 2). The mono-therapy groups improved to a similar extent and the combined therapy group had the greatest improvement. The greater increase in peak FEV₁ for combined therapy was significant versus either mono-therapies ($p < 0.005$). The 150 mL improvement in trough FEV₁ for the combined therapy was statistically significant versus the tiotropium mono-therapy ($p = 0.002$) but not significant versus arformoterol mono-therapy ($p = 0.07$). The 60 mL mean improvement in peak FVC for the combined therapy was numerically greater than that observed for either mono-therapy (tiotropium 40 mL and arformoterol 48 mL), a difference that reached statistical significance versus tiotropium ($p = 0.05$) but not versus arformoterol ($p = 0.07$).

The LS mean (±SE) peak improvement in FEV₁ from *visit* pre-dose was similar for the three treatment groups (0.19 ± 0.02 L for arformoterol, 0.19 ± 0.02 L for tiotropium and 0.22 ± 0.02 L for the arformoterol plus tiotropium).

Mean (SD) inspiratory capacity improved from baseline 2-h post-dosing for all three treatment groups, and the greatest improvement was observed for the combined therapy group (arformoterol, 0.20 ± 0.32 L, tiotropium, 0.19 ± 0.32 L, and arformoterol plus tiotropium, 0.29 ± 0.39 L) (Fig. 3). At trough (the 24-h time point since first dose of visit) the inspiratory capacity was significantly increased from study baseline for the combined treatment group and approached significance for the arformoterol treatment group (Table 2). Improvement in trough inspiratory capacity for the combination therapy was significantly greater than tiotropium mono-therapy ($p = 0.03$) but not arformoterol mono-therapy ($p = 0.21$).

Symptom responses: rescue medication use and BDI/TDI

Between screening and randomization (pre-dose week 0) about 80% of patients in all treatment groups used levalbuterol MDI as rescue medication (Table 3). Baseline rescue use averaged approximately 3 actuations per day and about 4.5 days per week. The use of levalbuterol MDI decreased over the second week of treatment for all three treatment groups by a mean of 1.8 actuations per day for the mono-therapies and 2.5 actuations per day for the combined therapy groups. Differences for combined therapy versus mono-therapies were not statistically significant.

Dyspnea, as measured by TDI, improved from baseline for all three treatment groups and to a significantly greater extent for the combined treatment group (Table 4). The majority of patients in the three treatment groups had an improvement in TDI of ≥1 unit, the minimal clinically important difference. The combined therapy group had a greater proportion of patients with ≥1 unit improvement in TDI compared with the other two therapy groups, and this difference was statistically significant between the combined and tiotropium therapies (95% CI 0.06, 0.35).

Table 1 Demographics and baseline characteristics (ITT).

	Arformoterol 15 µg BID (n = 76)	Tiotropium 18 µg QD (n = 80)	Arformoterol 15 µg BID plus tiotropium 18 µg QD (n = 78)
Mean age, years (SD)	61.6 (8.4)	61.2 (9.5)	62.2 (7.6)
Male, n (%)	39 (51.3)	43 (53.8)	42 (53.8)
Race, n (%)			
Caucasian	71 (93.4)	74 (92.5)	70 (89.7)
Black	5 (6.6)	6 (7.5)	7 (9.0)
Other	0	0	1 (1.3)
Current smoker, n (%)	49 (64.5)	54 (67.5)	39 (50)
Pack-years smoked			
≥15 to <30 years, n (%)	4 (5.3)	5 (6.2)	10 (12.8)
≥30 years, n (%)	72 (94.7)	75 (93.8)	68 (87.2)
Corticosteroid users, n (%) ^a	16 (21.1)	21 (26.3)	16 (20.5)
MMRC dyspnea scale, mean (SD)	2.7 (0.6)	2.9 (0.7)	2.9 (0.6)
Mean FEV ₁ , L (SD)	1.37 (0.46)	1.38 (0.46)	1.35 (0.41)
Mean percent predicted FEV ₁ , L (SD)	45.4 (11.9)	45.7 (11.5)	44.9 (12.0)
Mean FEV ₁ % reversibility (SD)	15.4 (10.0)	15.2 (10.8)	15.7 (13.3)
Mean FVC, L (SD)	2.69 (0.78)	2.70 (0.77)	2.60 (0.67)
Mean inspiratory capacity, L (SD)	2.01 (0.62)	1.98 (0.56)	1.92 (0.52)

^a Indicates the percentage of patients started taking inhaled or systemic corticosteroids during the screening period.

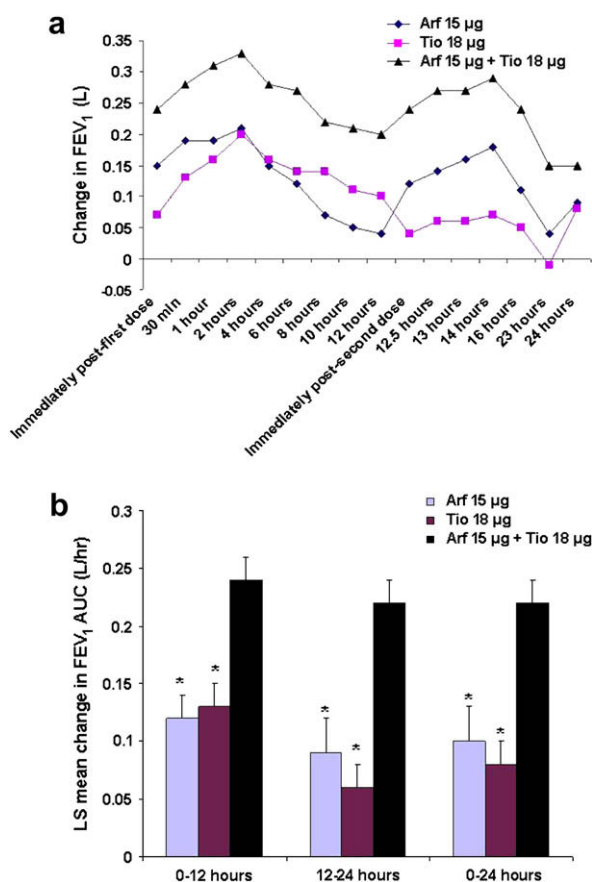


Figure 2 (a) Mean change in FEV₁ from study baseline at week 2. (b) Mean change in time normalized FEV₁AUC₀₋₂₄ from study baseline at week 2.

Pulmonary function and disease symptom outcomes stratified by patient's baseline lung function severity

Pulmonary results stratified by baseline disease severity (pre-dose FEV₁ <50% predicted or ≥50% predicted), demonstrated that patients with lower baseline lung function had greater improvement in all pulmonary lung function measures than patients with higher baseline lung function (see Supplemental Tables 1, 2, and 3). The greater improvement in pulmonary function measures for those patients with more compromised baseline lung function (<50% FEV₁ predicted) was evident for both absolute (L) and relative (percentage) improvements. Patients with <50% FEV₁ predicted demonstrated significant improvement for all five forced expiratory measures evaluated for both the mono-therapies and combined therapy groups. In contrast, patients with ≥50% FEV₁ predicted had no significant improvement in trough FEV₁ for any therapy group, and FEV₁AUC₀₋₂₄ only demonstrated improvement for the combined therapy group.

The use of rescue medications decreased for both disease severity groups (Supplemental Table 4). Both subsets of patients had improved dyspnea following any of the three therapies (Supplemental Table 4). Patients with <50% predicted FEV₁ at baseline treated with the combined therapy had significantly greater improvement in TDI (3.5 units) than those treated with either arformoterol (2.3 units) or tiotropium (1.6 units) (Supplemental Table 5).

Safety

Adverse events were infrequent with similar occurrence among the three treatment groups (Table 5). Both COPD exacerbations and cardiovascular adverse events were observed in only a small proportion of patients (between

Table 2 Change in spirometry measurements from baseline at week 2.

	Arformoterol 15 µg BID (n = 76)	Tiotropium 18 µg QD (n = 80)	Arformoterol 15 µg BID plus tiotropium 18 µg QD (n = 78)
Change in FEV ₁ AUC _{0–24} , (L), mean (SD) (95% CI)	0.10 (0.21) (0.05, 0.16)	0.08 (0.20) (0.04, 0.12)	0.22 (0.20) (0.18, 0.27)
Difference between combined therapy and mono-therapies, (L), LS mean (95% CI; <i>p</i> -value)	0.12 (0.05, 0.18; <i>p</i> <0.001)	0.14 (0.08, 0.20; <i>p</i> <0.001)	
Peak change in FEV ₁ over 12 h, (L), mean (SD) (95% CI)	0.27 (0.21) (0.22, 0.32)	0.27 (0.23) (0.21, 0.32)	0.38 (0.22) (0.33, 0.43)
Difference between combined therapy and mono-therapies, (L), LS mean (95% CI; <i>p</i> -value)	0.11 (0.03, 0.18; <i>p</i> =0.004)	0.11 (0.04, 0.19; <i>p</i> =0.002)	
Change in trough FEV ₁ (L), mean (SD) (95% CI) ^a	0.09 (0.23) (0.03, 0.14)	0.08 (0.21) (0.03, 0.13)	0.15 (0.22) (0.10, 0.21)
Difference between combined therapy and mono-therapies, (L), LS mean (95% CI; <i>p</i> -value)	0.07 (–0.01, 0.14; <i>p</i> =0.07)	0.07 (0.0, 0.14; <i>p</i> =0.05)	
Peak change in FVC over 12 h (L), mean (SD) (95% CI)	0.48 (0.37) (0.39, 0.57)	0.40 (0.34) (0.32, 0.48)	0.60 (0.43) (0.50, 0.70)
Difference between combined therapy and mono-therapies, (L), LS mean (95% CI; <i>p</i> -value)	0.12 (–0.01, 0.25; <i>p</i> =0.07)	0.20 (0.08, 0.33; <i>p</i> =0.002)	
Change in trough inspiratory capacity (L), mean (SD) (95% CI) ^a	0.07 (0.30) (0.00, 0.15)	0.02 (0.29) (–0.05, 0.09)	0.15 (0.36) (0.07, 0.24)
Difference in trough FEV ₁ between combined therapy and mono- therapies (L), LS mean (95% CI; <i>p</i> -value)	0.07 (–0.04, 0.18; <i>p</i> =0.21)	0.12 (0.02, 0.23; <i>p</i> =0.03)	

^a Trough is defined as the given pulmonary function variable measured at the 24-h time point after morning dose.

0 and 3.9%). Only one patient (arformoterol 15 µg) reported a serious adverse event (small intestinal obstruction).

Discussion

The combined use of bronchodilators with different pharmacological mechanisms of action for COPD patients is supported by current evidence based guidelines.^{2,3,26} This study investigated the efficacy and safety of the combination of two long-acting bronchodilators: arformoterol administered via nebulizer and tiotropium administered as a DPI. In particular, it compared efficacy between the two mono-therapies and evaluated whether the combined use

of these drugs resulted in greater pulmonary improvement than either single-agent alone. This is the first reported study to compare pulmonary function and symptoms improvement in COPD patients treated with a nebulized LABA (arformoterol) mono-therapy, tiotropium mono-therapy, and both therapies combined. It is also unique in that it presents data on how COPD patients with differing disease severity respond to arformoterol and tiotropium monotherapies, as well as the LABA/LAMA (arformoterol/tiotropium) combined therapy.

All three therapies demonstrated clinically meaningful improvement in pulmonary function from baseline after 2 weeks of treatment. However, the combined use of arformoterol and tiotropium was associated with significantly larger increases in time normalized FEV₁ over a 24-h period and peak change in FEV₁ than either arformoterol or tiotropium mono-therapies. Trough FEV₁ (24 h post-dose at week 2), another efficacy measure for a maintenance bronchodilator, improved for all three treatment groups indicating that bronchodilation was maintained throughout the dosing interval. The combination therapy resulted in a 70 mL greater improvement in trough FEV₁ than either mono-therapy. These findings are consistent with previous reports that investigated the combination of tiotropium with racemic formoterol^{20,27,28,30,31,38} which found that the combination of tiotropium and racemic formoterol resulted in greater improvement in pulmonary function than either single-agent alone. On the other hand, another study that examined the effect of adding either salmeterol alone or

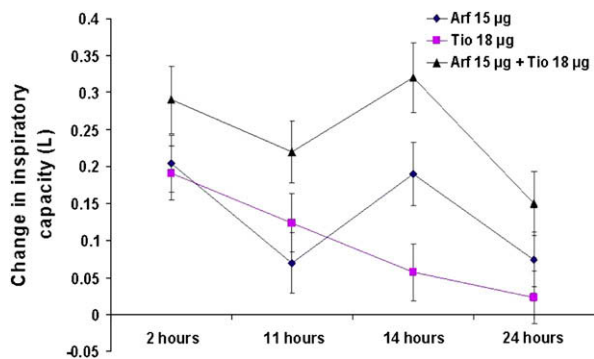


Figure 3 Change in inspiratory capacity from study baseline at week 2.

Table 3 Daily rescue medication (levalbuterol) use.

	Arformoterol 15 µg BID (n = 76)	Tiotropium 18 µg QD (n = 80)	Arformoterol 15 µg BID plus tiotropium 18 µg QD (n = 78)
Baseline (prior to first dose week 0)			
Used levalbuterol, n (%)	61 (80.3)	64 (80.0)	65 (83.3)
Number of actuations per day, mean (SD)	3.2 (3.2)	2.8 (2.8)	3.1 (2.7)
Number of days per week, mean (SD)	4.4 (2.8)	4.3 (2.9)	4.6 (2.8)
Week 2 (change from baseline)			
Used levalbuterol, n (%)	40 (52.6)	38 (47.5)	26 (33.3)
Number of actuations per day, mean (SD)	-1.8 (2.2)	-1.8 (2.8)	-2.5 (2.3)
Number of days per week, mean (SD)	-2.1 (2.6)	-2.2 (2.7)	-3.3 (3.0)

the salmeterol/fluticasone combination to tiotropium over a 1-year treatment period failed to find an additive effect of salmeterol when added to tiotropium on trough FEV₁.³⁸

In this study, the improvement in FEV₁ after arformoterol mono-therapy dosing differed between the morning and evening dose. The mean FEV₁ improvement 2 h after the morning dose and evening dose were approximately 213 mL and 182 mL, respectively. This temporal difference in response has been reported for racemic formoterol administered BID,³¹ and was suggested to reflect circadian changes in the activity of the adrenergic system and vagal system.^{27,31} The adrenergic system is most prominent during the day and the parasympathetic system activity increases during the night.³⁹ The relative reduction in the effect of tiotropium mono-therapy between 12 and 23 h may also result from this circadian nocturnal drop in airway function and the waning effect of tiotropium that dosed once daily in the morning.⁴⁰

Inspiratory capacity and dyspnea, both reflections of hyperinflation, improved in this study after dosing for all three treatments and to a greater extent in the combined treatment group. Similar to the findings for trough FEV₁, the fact that trough inspiratory capacity (at the 24-h time point at week 2) was greater than baseline indicates that the effect of the three therapies (arformoterol 15 µg BID, tiotropium 18 µg QD, and arformoterol 15 µg BID plus tiotropium 18 µg QD) on this outcome persisted for 24 h. In contrast to prior reports that examined the combination of tiotropium and racemic formoterol,^{27,20} this study found that the combined effect of tiotropium and arformoterol on trough inspiratory capacity was significantly greater than that of tiotropium alone. Dyspnea improved by more than 1 unit (the MCID)⁴¹ for all three therapies and greatest (mean TDI; +3.1 units) for the combined therapy. Rescue short-

acting β₂-agonist use decreased with all three therapies and again to a slightly greater extent with combination therapy than either mono-therapy. These findings are consistent with earlier reports that found that treatment with racemic formoterol, tiotropium,^{17,20,32,42,43,44} or the combination of racemic formoterol plus tiotropium²⁰ improved dyspnea²⁰ and reduced rescue racemic albuterol use.^{17,20,32,42-44}

Only a few prior publications have addressed the question how patients with differing severity of baseline COPD respond to therapy.^{7,45} In this study, stratified analysis of the response of patients based on baseline GOLD guideline classification of disease severity (e.g. very severe and severe: <50% predicted FEV₁; and moderate: ≥50% predicted FEV₁)³ demonstrated that patients with more severe COPD had greater airway improvement than those with moderate COPD. Pre-dose (trough) and post-dose FEV₁ values increased more for patients with more severe COPD compared with those with moderate disease. Moreover, trough inspiratory capacity increased only for patients with more severe disease. Improvements in dyspnea (TDI), in contrast, were similar between disease severity groups. These findings suggest that disease severity influences the degree of bronchodilator improvements in forced expiratory maneuvers and inspiratory capacity. These findings are in contrast to a prior study that found that patients with very severe COPD (GOLD stage III and IV) had less responsiveness to large doses of the short-acting β₂-agonist racemic albuterol plus ipratropium bromide than patients with moderate COPD.⁴⁶ The difference between these studies may reflect differences in experimental design and/or medication studied.

This study supports the recommendations of the GOLD guidelines³ that advise the combination of two different classes of long-acting bronchodilators for treatment of patients with moderate to severe COPD. The administration

Table 4 Baseline dyspnea (BDI)/transitional dyspnea index (TDI) at week 2 for the ITT population.

	Arformoterol 15 µg BID (n = 76)	Tiotropium 18 µg QD (n = 80)	Arformoterol 15 µg BID plus tiotropium 18 µg QD (n = 78)
BDI, mean (SD)	5.8 (2.0)	5.8 (1.9)	5.5 (2.1)
TDI, mean (SD)	2.3 (2.4)	1.8 (2.8)	3.1 (2.4)
Difference between combined therapy and mono-therapies (L), LS mean (95% CI)	0.9 (0.03, 1.7)	1.3 (0.5, 2.2)	
Patients with change ≥1 unit, n (%)	50 (66.7)	44 (57.1)	60 (77.9)

Table 5 Adverse events.

	Arformoterol 15 µg BID (n = 76)	Tiotropium 18 µg QD (n = 80)	Arformoterol 15 µg BID plus tiotropium 18 µg QD (n = 78)
Any adverse event, n (%)	19 (25.0)	22 (27.5)	24 (30.8)
COPD exacerbations	3 (3.9)	0	0
Overall cardiovascular adverse events, n (%)	2 (2.6)	1 (1.3)	0
Discontinued due to adverse events, n (%)	2 (2.6)	1 (1.3)	2 (2.6)
Serious adverse events, n (%)	1 (1.3)	0	0

of tiotropium QD plus arformoterol BID resulted in significantly superior bronchodilation to either agent alone as well as significantly greater improvement in symptom relief. Tiotropium and arformoterol mono-therapy were equally efficacious and improved dyspnea and reduced rescue medication use to a similar extent, consistent with prior studies that compared tiotropium and racemic formoterol.^{28,31,47} This is in contrast to prior literature that evaluated the LABA salmeterol and tiotropium mono-therapies which suggested that tiotropium exhibited advantages over salmeterol in treating COPD patients.^{14,18,44,48} COPD subjects with more severe degree of airway function compromise had greater improvement in lung function and symptoms than those with moderate impairment. Long-term studies are needed to understand the potential impact of arformoterol and tiotropium combined therapy on long-term health outcomes, such as COPD exacerbations and hospitalizations. In addition, investigations of existing and emerging therapies are needed to determine optimal individual treatment for patients affected by different subtypes and severity of disease.

Conflict of interest statement

Dr D.P. Tashkin was an investigator in this study and he and Drs J.F. Donohue and D.A. Mahler helped analyze the data and prepare the manuscript. Dr W.T. Andrews, H. Huang, Dr E. Goodwin and K. Schaefer are Sepracor employees. Dr J.P. Hanrahan is a former Sepracor employee.

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Supplemental material

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