Original Article

The Effect of Tiotropium in Symptomatic Asthma Despite Low- to Medium-Dose Inhaled Corticosteroids: A Randomized Controlled Trial

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What is already known about this topic? Tiotropium, a once-daily long-acting anticholinergic bronchodilator, has demonstrated efficacy in patients with asthma who were symptomatic despite treatment with at least medium- to high-dose inhaled corticosteroids (ICS).

What does this article add to our knowledge? Once-daily tiotropium Respimat add-on to low- to medium-dose ICS maintenance therapy was an efficacious bronchodilator in adult patients with mild to moderate asthma, and its safety and tolerability were comparable with those of placebo at 12 weeks.

How does this study impact current management guidelines? The data presented here provide further evidence for tiotropium Respimat as an efficacious alternative bronchodilator therapy when added on to ICS in inadequately controlled asthma.

BACKGROUND: Tiotropium, a once-daily long-acting anticholinergic bronchodilator, has demonstrated efficacy in patients with asthma who were symptomatic despite treatment with medium- to high-dose inhaled corticosteroids (ICS).
OBJECTIVE: The objective of this study was to evaluate the efficacy and safety of once-daily tiotropium Respimat (5 μg or 2.5 μg), compared with placebo Respimat, as add-on therapy to low- to medium-dose ICS for adults with symptomatic asthma.
METHODS: A phase III, double-blind, placebo-controlled trial was conducted (NCT01316380). Adults with symptomatic asthma receiving low- to medium-dose ICS (200-400 μg budesonide or equivalent dose) and a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥60% and ≤90% of predicted normal were randomized to 12 weeks of treatment with once-daily tiotropium Respimat 5 μg or 2.5 μg, or placebo Respimat, as add-on therapy to ICS. The primary endpoint was peak $FEV_{1(0\text{-}3h)}$ response.
RESULTS: In total, 464 patients were randomized (61% female; mean age 43 years; mean baseline FEV_1 78% of predicted normal). After 12 weeks, both tiotropium Respimat doses were superior to placebo (adjusted mean difference from placebo: 5 μg, 128 mL; 2.5 μg, 159 mL; both $P < .001$). Both doses of tiotropium Respimat were also superior to placebo with regard to the secondary endpoints of adjusted mean trough FEV_1 and FEV_1 area under the curve$_{(0\text{-}3h)}$ responses, and the other endpoints of morning and evening peak expiratory flow. Adverse events were comparable across the treatment groups.

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Conflicts of interest: P. Paggiaro is on the AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Novartis boards; has received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Mundipharma, Novartis, and Zambon. D. M. G. Halpin has received consulting fees from AstraZeneca, Almirall, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Pfizer; has received travel support from Boehringer Ingelheim and Novartis. R. Buhl has received personal fees from AstraZeneca, Chiesi, GlaxoSmithKline, and Takeda; and has received grants and personal fees from Boehringer Ingelheim, Novartis, and Roche. M. Engel and P. Moroni-Zentgraf are employed by Boehringer Ingelheim, Ingelheim am Rhein, Germany. V. B. Zubek is employed by Boehringer Ingelheim, Ridgefield, Conn, USA. Z. Blahova is employed by Boehringer Ingelheim, Vienna, Austria. E. Pizzichini has received consultancy fees from Novartis, Boehringer Ingelheim, GlaxoSmithKline, and Merck Sharp & Dohme; and has received lecture fees from Novartis, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp & Dohme, Chiesi, and Ache.

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Abbreviations used
ACQ-7- 7-question Asthma Control Questionnaire
AE- Adverse event
AUC- Area under the curve
CI- Confidence interval
FVC- Forced vital capacity
FEV_1- Forced expiratory volume in 1 second
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroids
LABA- Long-acting β_2-agonist
Peak $FEV_{1(0\text{-}3h)}$- Peak forced expiratory volume in 1 second within 3 hours of dosing
PEF- Peak expiratory flow
PEF_{AM}- Morning peak expiratory flow
PEF_{PM}- Evening peak expiratory flow
SE- Standard error

CONCLUSIONS: Once-daily tiotropium Respimat add-on therapy to low- to medium-dose ICS in adults with symptomatic asthma is an efficacious bronchodilator, and its safety and tolerability are comparable with those of placebo Respimat. **(J Allergy Clin Immunol Pract 2016;4:104-13)**

Key words: *Tiotropium; Respimat; Anticholinergic; Mild; Asthma; Bronchodilators; ICS; Symptomatic; Control; GINA*

According to current Global Initiative for Asthma (GINA) guidelines, the recommended treatment option in patients with mild to moderate asthma that remains uncontrolled with low-dose inhaled corticosteroids (ICS) is to add a long-acting β_2-agonist (LABA) such as formoterol or salmeterol, before increasing the ICS dose.[1] Other controller options are the addition of a leukotriene receptor antagonist or low-dose theophylline.[1] However, some patients do not respond to these agents, whereas a substantial proportion of patients continue to have symptomatic disease despite currently available therapies.[2-4] Therefore, in patients with mild to moderate, uncontrolled asthma, there is an unmet need for alternative therapeutic options. In such a population of patients, there is value in the option to prescribe an agent with an alternative mechanism of action to LABAs, such as a long-acting anticholinergic, for example, because the side effects associated with LABA therapy may be unacceptable in patients with mild disease.

Tiotropium is a once-daily long-acting anticholinergic bronchodilator indicated as maintenance treatment to relieve the symptoms of patients with chronic obstructive pulmonary disease. Phase II and phase III trials evaluated tiotropium delivered via the Respimat Soft Mist inhaler (hereinafter also referred to as tiotropium Respimat; Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany) in patients with symptomatic asthma despite maintenance treatment with medium-dose ICS or high-dose ICS plus a LABA.[5-8] In these studies, tiotropium Respimat improved lung function and reduced exacerbation risk.[5-8]

Another investigation studied tiotropium HandiHaler (Boehringer Ingelheim) in 210 patients with inadequately controlled asthma while receiving low-dose ICS: the addition of tiotropium HandiHaler was superior to doubling the dose of ICS with regard to improvements in lung function and asthma symptoms.[9] Here, we report the first clinical trial of tiotropium Respimat as add-on in patients with not fully controlled, mild to moderate asthma despite low- to medium-dose ICS maintenance therapy. In this phase III, 12-week study, the lung function efficacy and safety of tiotropium (5 μg or 2.5 μg) were evaluated compared with those of placebo.

METHODS

Study design

The efficacy and safety of once-daily tiotropium Respimat 5 μg or 2.5 μg add-on to low- to medium-dose ICS maintenance therapy were compared with those of placebo Respimat in a phase III, international, placebo-controlled, parallel-group study (NCT01316380). Eligible patients completed a 4-week screening period before randomization and entry into a 12-week, double-blind treatment period with a 21-day follow-up period.

The trial was carried out in compliance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation for Good Clinical Practice Guidelines. Before initiation, the trial protocol, patient information sheet, and consent form were reviewed and approved by each participating institution's review board. Before participation in the trial, written, informed consent was received from each patient.

Study population

Eligible patients were aged 18-75 years, had a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥60% and ≤90% of predicted normal at screening, had a history of asthma of 3 months or more at study enrollment with initial diagnosis before the age of 40 years, and were symptomatic at screening and randomization (defined by mean 7-question Asthma Control Questionnaire [ACQ-7] total score of ≥1.5). Patients had never smoked, or were ex-smokers with less than 10 pack-years who stopped smoking at least 1 year before enrollment.

Asthma was confirmed at screening (FEV_1 reversibility of ≥12% and ≥200 mL 15-30 minutes after 400 μg salbutamol [albuterol]) and was mild and symptomatic despite current maintenance with low- to medium-dose ICS (200-400 μg budesonide or equivalent dose), that is, asthma was uncontrolled at GINA step 2,[1] for 4 weeks or more before screening.

Key exclusion criteria included a diagnosis of chronic obstructive pulmonary disease, serious coexisting illness, concurrent use of anticholinergic bronchodilators, and LABA therapy within 4 weeks before enrollment.

Randomization and treatment

Patients were randomized 1:1:1 in blocks of 6 to either tiotropium 5 μg, tiotropium 2.5 μg, or placebo, all administered via the Respimat Soft Mist inhaler once daily in the evening as add-on to low- to medium-dose ICS maintenance treatment. They were required to stop taking short-acting β_2-agonists at least 8 hours before visit 1 and continued to take their usual ICS asthma medication throughout the study. Randomization was achieved using a validated, pseudo-random number generator and a supplied seed number in a manner that was reproducible and nonpredictable. Each patient inhaled 2 puffs from the Respimat Soft Mist inhaler once daily in the evening. Medication was dispensed in a double-blind fashion; the 2 different doses of tiotropium and placebo were identical in appearance. Salbutamol (metered-dose inhaler; 100 μg per puff) was dispensed as rescue medication.

Study endpoints

The primary efficacy endpoint was peak FEV_1 within 3 hours of dosing (peak $FEV_{1(0\text{-}3h)}$) response, where response was defined as the change from baseline at week 12. Peak $FEV_{1(0\text{-}3h)}$ was defined as the maximum value of the FEV_1 measurements within 3 hours after evening dosing. FEV_1 measurements were performed 10 minutes before study drug administration (baseline), and at 30 minutes, 1 hour, 2 hours, and 3 hours after dosing.

Secondary endpoints included trough FEV_1 (key secondary endpoint) and FEV_1 area under the $curve_{(0\text{-}3h)}$ ($AUC_{(0\text{-}3h)}$) responses determined by the change in each parameter from baseline at week 12. Trough FEV_1 was defined as FEV_1 measured at the end of the dosing interval (24 hours after administration) and 10 minutes before administration of the trial medication. FEV_1 $AUC_{(0\text{-}3h)}$ was calculated using the trapezoidal rule, divided by the observation time (3 hours) to report in liters; trough values were assigned to time 0.

Use of salbutamol rescue medication was analyzed as the number of puffs of rescue medication used during the daytime and nighttime and per day (ie, the full 24-hour period) on a weekly basis during the 12-week treatment period and during the last 7 days before visit 5 at week 12, and was recorded as a weekly mean response from baseline. ACQ-7 total score at week 12 and morning and evening pre-bronchodilator mean peak expiratory flow (PEF_{AM} and PEF_{PM}) responses (change from baseline at week 12) were also assessed. *Post hoc* subgroup analyses of responses by gender, smoking history, and baseline FEV_1 % of predicted normal were performed.

All efficacy evaluations were conducted at baseline and subsequently at week 4, week 8, week 12 (double-blind treatment period), and week 15 (follow-up visit). Baseline and visits at weeks 4-12 were conducted in the evening. Baseline was defined as the respective pretreatment value measured at the randomization visit, 10 minutes before administration of the first dose of trial medication.

At the time of screening, 12-lead electrocardiogram, physical examination, and laboratory tests were performed. The safety and tolerability of tiotropium Respimat were determined by the incidence and intensity of adverse events (AEs) and changes in vital signs measured at baseline (randomization visit) and at weeks 12 and 15. AEs were monitored throughout the study.

Statistical analyses

The efficacy and safety analyses were performed on the treated set, defined as all randomized patients who received at least 1 documented dose of trial drug. The full analysis set was identical to the treated set.

The primary objective of the trial was to demonstrate the superiority of tiotropium Respimat over placebo as add-on to low- to medium-dose ICS maintenance therapy after 12 weeks of treatment. The null hypotheses were tested in a stepwise manner to control the probability of a type I error. First, the null hypothesis that mean peak $FEV_{1(0\text{-}3h)}$ response at week 12 in the group receiving tiotropium Respimat 5 μg is not higher than in the group receiving placebo was tested. If this hypothesis was rejected, then a similar null hypothesis for the tiotropium Respimat 2.5 μg dose versus placebo was tested. The second hypothesis was to be considered confirmatory only if the previous null hypothesis could not be rejected; that is, if the superiority of treatment with tiotropium Respimat 5 μg over placebo could not be established, analysis of the second hypothesis was considered to be descriptive only.

The primary endpoint, peak $FEV_{1(0\text{-}3h)}$ response, was analyzed using restricted maximum likelihood-based mixed-effects model repeated measures. The model included the fixed, categorical effects of "treatment," "center (pooled)," "visit," and "treatment-by-visit interaction," as well as the continuous, fixed covariates of "baseline value" and "baseline value-by-visit-interaction." The "center (pooled)" variable represents the fact that centers and, if necessary, countries with fewer than 5 treated patients were pooled until the pool contained 6 or more patients. "Patient" was included as a random effect in the model. An autoregressive (order 1) (co)variance structure for equally spaced visits was used to model the within-patient errors in the primary analysis. Significance tests were based on least-squares means using a 2-sided $\alpha = 0.05$ (2-sided 95% confidence intervals).

All continuous secondary endpoints were analyzed using restricted maximum likelihood-based mixed-effects model repeated measures as described above for the primary endpoint, unless stated otherwise. Adjusted mean values as well as treatment contrasts were calculated, together with the 95% confidence intervals. All calculated *P* values were to serve an exploratory function. No adjustment for multiplicity was done, and all analyses were evaluated using $\alpha = 0.05$.

Sample size. Sample-size calculations determined that 150 patients per treatment group were required. Using a 2-sided test with a type I error of 0.05 (ie, α) and assuming an observed standard deviation of 370 mL, this trial had a power of approximately 80% to detect a difference of 120 mL between treatments in the change from baseline of peak FEV_1.

RESULTS

Between April 2011 and April 2012, 686 patients were enrolled at 65 trial sites in 12 countries (Argentina, Austria, Croatia, Estonia, Guatemala, Hungary, India, Italy, Korea, Latvia, Poland, and Slovakia). Of these, 465 patients were randomized to receive either tiotropium 5 μg (n = 155), tiotropium 2.5 μg (n = 154), or placebo (n = 156) (Figure 1). The discontinuation rate was low (1.9%), and 464 patients were treated.

Overall, baseline patient demographics were generally balanced across the treatment groups, with a few exceptions (Table I). The mean age of the overall study population was 42.9 years. The median duration of asthma in each treatment group was 15.0 years (range, 4.0 months to 61.0 years). No patients currently smoked, and 17.7% were ex-smokers, although the latter proportion was higher in the tiotropium 5 μg group.

Although the overall majority of patients were female, there was a higher proportion of males in the tiotropium 2.5 μg group compared with the 5 μg and placebo groups. Baseline characteristics by gender are shown in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org).

Efficacy

Primary endpoint. Both doses of tiotropium were superior to placebo with regard to the primary endpoint of peak $FEV_{1(0\text{-}3h)}$ response at week 12 (adjusted mean difference from placebo: 5 μg, 128 mL, $P < .001$; 2.5 μg, 159 mL, $P < .001$) (Table II; Figure 2).

Secondary endpoints. Both doses of tiotropium were also superior to placebo after 12 weeks with regard to the key secondary endpoint of adjusted mean trough FEV_1 response (adjusted mean difference from placebo: 5 μg, 122 mL, $P = .001$; 2.5 μg, 110 mL, $P = .003$) (Table II).

For other endpoints, both doses of tiotropium significantly improved FEV_1 $AUC_{(0\text{-}3h)}$, PEF_{AM}, and PEF_{PM} responses (Table II).

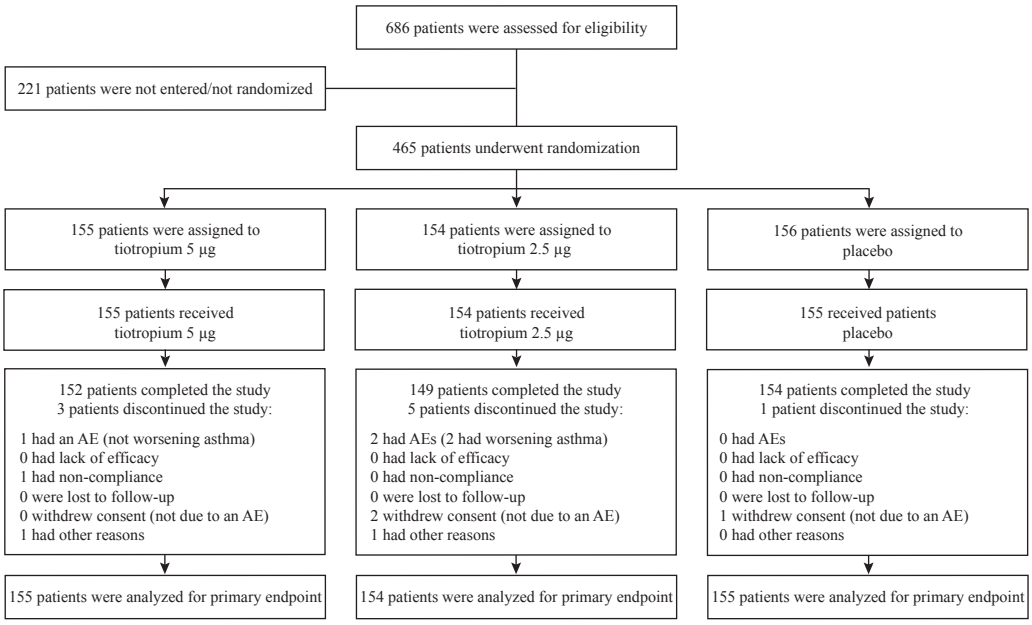

FIGURE 1. Patient disposition. *AE*, adverse event.

TABLE I. Baseline patient demographics and disease characteristics

	Tiotropium 5 µg (n = 155)	Tiotropium 2.5 µg (n = 154)	Placebo (n = 155)	Total (N = 464)
Age (y)*	41.9 ± 13.0	43.8 ± 14.0	42.8 ± 12.1	42.9 ± 13.0
Gender, n (%)				
Male	59 (38.1)	72 (46.8)	52 (33.5)	183 (39.4)
Female	96 (61.9)	82 (53.2)	103 (66.5)	281 (60.6)
Body mass index (kg/m^2)*	26.8 ± 5.0	26.2 ± 5.6	26.3 ± 5.1	26.4 ± 5.2
Smoking status, n (%)				
Never smoked	122 (78.7)	131 (85.1)	129 (83.2)	382 (82.3)
Ex-smoker	33 (21.3)	23 (14.9)	26 (16.8)	82 (17.7)
Smoking history (pack-years)*	4.4 ± 2.9	4.2 ± 3.3	5.5 ± 2.7	4.7 ± 3.0
Median (range) duration of asthma (y)	15.0 (0.5-49.0)	15.0 (0.3-61.0)	15.0 (0.3-57.0)	15.0 (0.3-61.0)
FEV_1 at screening*				
Actual (L)	2.3 (0.6)	2.3 (0.7)	2.2 (0.6)	2.3 (0.6)
% of predicted	74.9 (8.1)	73.2 (8.6)	73.7 (8.5)	73.9 (8.4)
FEV_1 at baseline (randomization)*				
Actual (L)	2.5 (0.7)	2.4 (0.8)	2.4 (0.7)	2.4 (0.7)
% of predicted	79.6 (11.3)	75.8 (12.3)	77.5 (12.0)	77.7 (11.9)
FVC*				
Actual (L)	3.6 (0.9)	3.6 (1.0)	3.5 (0.9)	3.5 (0.9)
% of predicted	97.4 (13.8)	95.6 (15.4)	96.7 (14.3)	96.6 (14.5)
FEV_1/FVC at baseline (randomization) (%)*	69.7 (10.1)	67.4 (10.9)	68.5 (10.5)	68.5 (10.5)
PEF_{AM} (L/min)*	363.1 (116.5)	350.5 (112.7)	353.7 (114.8)	355.8 (114.5)
PEF_{PM} (L/min)*	377.5 (118.2)	364.1 (110.0)	363.7 (116.7)	369.8 (114.9)
ACQ-7 total score*	2.1 (0.4)	2.1 (0.4)	2.1 (0.4)	2.1 (0.4)
ICS dose of stable maintenance treatment (µg)*,†	376.9 (59.7)	384.4 (93.4)	383.0 (77.1)	381.4 (77.8)

ACQ-7, 7-question Asthma Control Questionnaire; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroids; *PEF_{AM}*, morning peak expiratory flow; *PEF_{PM}*, evening peak expiratory flow.
Common baseline mean (standard deviation), weekly number of puffs of rescue medication: 1.841 (2.059).
*Values are mean ± standard deviation.
†Budesonide or equivalent dose.

Numerical improvements in the adjusted mean ACQ-7 total score were observed across all treatment groups after 12 weeks; however, the differences between each dose of tiotropium versus placebo were not statistically significant (Table II).

The adjusted weekly mean number of puffs of rescue medication used per 24 hours decreased during the trial in all treatment groups (at week 12, the responses were tiotropium 5 µg, −0.848; tiotropium 2.5 µg, −0.594; placebo, −0.815). However, the

TABLE II. FEV_1, PEF_{AM}, and PEF_{PM} responses, and ACQ-7 total score, at week 12

Treatment and parameter	Adjusted* mean (SE)	Active vs placebo		
		Adjusted* mean of difference (SE) (mL)	95% CI	*P* value†
FEV_1 response‡				
Peak $FEV_{1(0\text{-}3h)}$ (mL) (primary endpoint)				
Tiotropium 5 μg (n = 152)	262 (26)	128 (36)	57, 199	<.001
Tiotropium 2.5 μg (n = 151)	293 (26)	159 (36)	88, 230	<.001
Placebo (n = 154)	134 (26)			
Trough FEV_1 (mL)				
Tiotropium 5 μg (n = 152)	137 (27)	122 (37)	49, 194	.001
Tiotropium 2.5 μg (n = 151)	125 (26)	110 (37)	38, 182	.003
Placebo (n = 154)	15 (26)			
FEV_1 $AUC_{(0\text{-}3h)}$ (mL)				
Tiotropium 5 μg (n = 152)	174 (25)	125 (34)	58, 192	<.001
Tiotropium 2.5 μg (n = 151)	198 (24)	149 (34)	82, 216	<.001
Placebo (n = 154)	48 (24)			
Peak $FEV_{1(0\text{-}3h)}$ % predicted				
Tiotropium 5 μg (n = 152)	9.0 (0.8)	4.7 (1.1)	2.5, 6.8	<.001
Tiotropium 2.5 μg (n = 151)	8.5 (0.8)	4.2 (1.1)	2.0, 6.4	<.001
Placebo (n = 154)	4.3 (0.8)			
Trough FEV_1 % predicted				
Tiotropium 5 μg (n = 152)	4.8 (0.8)	4.4 (1.2)	2.1, 6.7	<.001
Tiotropium 2.5 μg (n = 151)	3.0 (0.8)	2.6 (1.2)	0.3, 4.9	.02
Placebo (n = 154)	0.4 (0.8)			
PEF_{AM} response (L/min)‡				
Tiotropium 5 μg (n = 152)	23.0 (3.9)	25.6 (5.4)	14.9, 36.2	<.001
Tiotropium 2.5 μg (n = 150)	23.7 (3.9)	26.3 (5.4)	15.7, 36.9	<.001
Placebo (n = 152)	−2.5 (3.9)			
PEF_{PM} response (L/min)‡				
Tiotropium 5 μg (n = 152)	21.4 (3.8)	27.6 (5.3)	17.2, 38.0	<.001
Tiotropium 2.5 μg (n = 149)	16.2 (3.8)	22.4 (5.3)	12.0, 32.8	<.001
Placebo (n = 153)	−6.2 (3.8)			
ACQ-7 total score§				
Tiotropium 5 μg (n = 152)	1.391 (0.049)	0.014 (0.067)	−0.118, 0.146	.83
Tiotropium 2.5 μg (n = 149)	1.438 (0.049)	0.061 (0.067)	−0.071, 0.194	.36
Placebo (n = 154)	1.377 (0.048)			

ACQ-7, 7-question Asthma Control Questionnaire; *AUC*, area under the curve; *CI*, confidence interval; *FEV_1*, forced expiratory volume in 1 second; *peak $FEV_{1(0\text{-}3h)}$*, peak forced expiratory volume in 1 second within 3 hours of dosing; *PEF_{AM}*, morning peak expiratory flow; *PEF_{PM}*, evening peak expiratory flow; SE, standard error.
Common baseline mean (standard deviation), mL, at visit 2: FEV_1, 2420 (711); trough FEV_1, 2422 (712). Common baseline mean ACQ-7 total score (standard deviation), 2.101 (0.415).
*Adjusted for treatment, center, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction.
†Versus placebo.
‡Difference between each parameter at 12 weeks and the baseline (measured 10 minutes before the first dose of trial medication at randomization).
§ACQ-7 total score is an absolute value; lower ACQ-7 score represents better control of asthma symptoms.

adjusted mean difference from placebo in weekly mean number of puffs of rescue medication used per 24 hours was not significant for both tiotropium 5 μg ($P = .80$) and tiotropium 2.5 μg ($P = .09$) at week 12. Weekly puffs of rescue medication in the 2.5 μg dose group tended to be higher compared with placebo during the latter weeks of the trial and were significantly higher than placebo at night-time at weeks 8-11 ($P = .03$ to .045; data not shown) and at week 8 for 24-hour use ($P = .03$; Table E2, available in this article's Online Repository at www.jaci-inpractice.org), but there was no monotonic trend over time.

Significant differences were observed in adjusted weekly mean PEF_{AM} and PEF_{PM} for tiotropium 5 μg and 2.5 μg versus placebo at each week (Table II; Figure 3). There was a dose-ordering pattern for PEF_{PM}, a pre-bronchodilator measurement that represents a true 24-hour value, with tiotropium 5 μg demonstrating higher PEF values than 2.5 μg.

***Post hoc* efficacy analyses.** *Post hoc* subgroup analyses of peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 responses were performed by gender, smoking history, and baseline airway obstruction (FEV_1 % of predicted normal). Tiotropium improved adjusted mean lung function parameter responses from baseline to week 12 for both genders, nonsmokers, ex-smokers, and those with a baseline FEV_1 of 60% to <80% or ≥80% of predicted normal post-bronchodilator (Table III).

The absolute differences from placebo in peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 responses associated with tiotropium (both doses) were greater in male patients than in female patients. Tiotropium

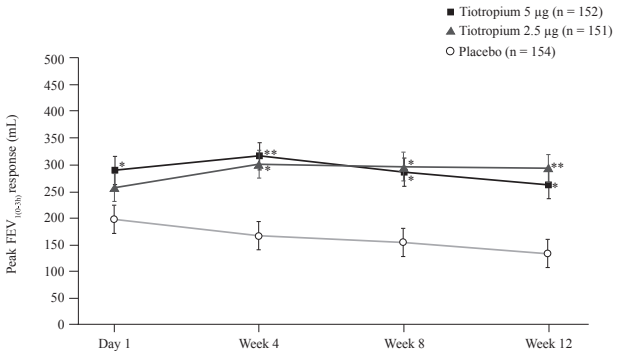

FIGURE 2. Adjusted mean peak $FEV_{1(0\text{-}3h)}$ response over the 12-week study period. $*P < .05$; $**P < .001$. Response defined as a difference from the baseline value at randomization. Error bars are ± standard error. Baseline mean (standard deviation) FEV_1, mL, at visit 2: 2420 (711). Adjusted for treatment, center, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. *FEV_1*, forced expiratory volume in 1 second; *peak $FEV_{1(0\text{-}3h)}$*, peak forced expiratory volume in 1 second within 3 hours of dosing.

was associated with statistically significant peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 responses versus placebo in those who had never smoked. Similar numerical differences were observed in ex-smokers but were not statistically significant, probably due to the small number of ex-smokers analyzed (Table III). In patients with baseline FEV_1 60% to <80% of predicted normal post-bronchodilator, statistically significant peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 responses versus placebo were observed with the tiotropium 5 µg dose, but not with the 2.5 µg dose. In the ≥80% of predicted subgroup, statistically significant responses versus placebo were observed with both tiotropium doses.

Safety and tolerability

The percentage of patients reporting AEs was similar across the treatment groups (Table IV). The most frequently reported events included asthma worsening (tiotropium 5 µg, 11.0%; tiotropium 2.5 µg, 15.6%; placebo, 12.9%), decreased PEF rate (tiotropium 5 µg, 3.9%; tiotropium 2.5 µg, 5.8%; placebo, 3.9%), and upper respiratory tract infection (tiotropium 5 µg, 4.5%; tiotropium 2.5 µg, 1.3%; placebo, 4.5%).

Most AEs were mild or moderate in intensity (Table IV). Two patients (1.3%) in each treatment group were reported with AEs that were considered to be drug-related by the investigator: headache and dysphonia in the tiotropium 5 µg group, asthma and hematuria in the tiotropium 2.5 µg group, and dry mouth and hematuria in the placebo group.

AEs leading to discontinuation and serious AEs were infrequently reported. The serious AE (breast cancer *in situ*) for the patient in the tiotropium 5 µg group required hospitalization; the serious AE (severe asthma exacerbation) for the patient receiving placebo was reported as an immediately life-threatening serious AE and required prolonged hospitalization. Neither serious AE was considered to be related to the study drug. There were no deaths during this trial.

DISCUSSION

In this first study of the efficacy and safety of tiotropium Respimat in patients with symptomatic mild to moderate asthma (uncontrolled at GINA step 2[1]), a significant improvement in lung function was observed with tiotropium (5 and 2.5 µg) compared with placebo after a 12-week treatment period. Both doses of tiotropium achieved the primary endpoint of superiority in peak $FEV_{1(0\text{-}3h)}$ response versus placebo, and also significantly improved trough FEV_1, FEV_1 $AUC_{(0\text{-}3h)}$, PEF_{AM}, and PEF_{PM} responses.

The study enrolled patients with inadequately controlled asthma at GINA step 2; these patients would thus be candidates for treatment with a LABA, such as salmeterol or formoterol, added on to low- to medium-dose ICS.[1] Evidence from previous active-comparator trials has indicated that tiotropium add-on to at least ICS is comparable with add-on salmeterol for improving lung function in patients with symptomatic asthma.[5,9,10] The current study has demonstrated that tiotropium also improves lung function parameters in patients with not fully controlled, mild to moderate asthma, when added on to low- to medium-dose ICS. Furthermore, the airflow improvements seen here with tiotropium appear to be of at least the same magnitude as the addition of salmeterol or formoterol observed in other studies,[11-13] which suggests that tiotropium may have potential as an alternative to LABA when added on to ICS of different dose levels. Further investigation of tiotropium as an alternative to LABA may be informative in this population, because the current study did not include a LABA treatment arm.

A considerable improvement in lung function parameters was observed in all treatment arms of this study between screening and randomization; for example, FEV_1 % predicted improved from 74.9% to 79.6% in the tiotropium 5 µg group, from 73.2% to 75.8% in the tiotropium 2.5 µg group, and from 73.7% to 77.5% in the placebo group. This suggests that patients may have been ICS-naïve or noncompliant to ICS therapy before baseline, and improvements in lung function in the treatment period may reflect greater adherence to ICS treatment during that period. This fact may explain the apparent modest bronchodilation conferred by tiotropium (from randomization to the end of the 12-week treatment period) compared with the acute bronchodilation observed with salbutamol at the screening visit.

Differences in treatment effect size between the 2 tiotropium doses investigated were small; the trial was not powered to demonstrate any statistical differences between the 2 doses of tiotropium. The trend towards numerically greater responses for some spirometry endpoints, particularly peak $FEV_{1(0\text{-}3h)}$ response, with the 2.5 µg dose compared with the 5 µg dose was further investigated and may be explained by baseline imbalances in gender in each group. A higher proportion of male patients was randomized to the 2.5 µg dose group than to the 5 µg dose group and placebo group. Men tend to be taller than women, and height correlates with lung volume, which may, in part, explain the observed differences in response. The expected dose ordering was observed in the 60% to <80% of predicted normal post-bronchodilator subgroup, a measure that takes into account differences related to the patient's gender. With regard to PEF response, a dose-ordering pattern was observed for PEF_{PM}, with tiotropium 5 µg demonstrating higher PEF_{PM} values than the 2.5 µg dose. In this study, the PEF_{PM} assessment measured the 24-hour bronchodilatory effect of tiotropium, because the drug was administered in the evening. The benefits of the 5 µg dose have been widely reported in other studies, including 3 randomized trials that demonstrated that tiotropium Respimat 5 µg

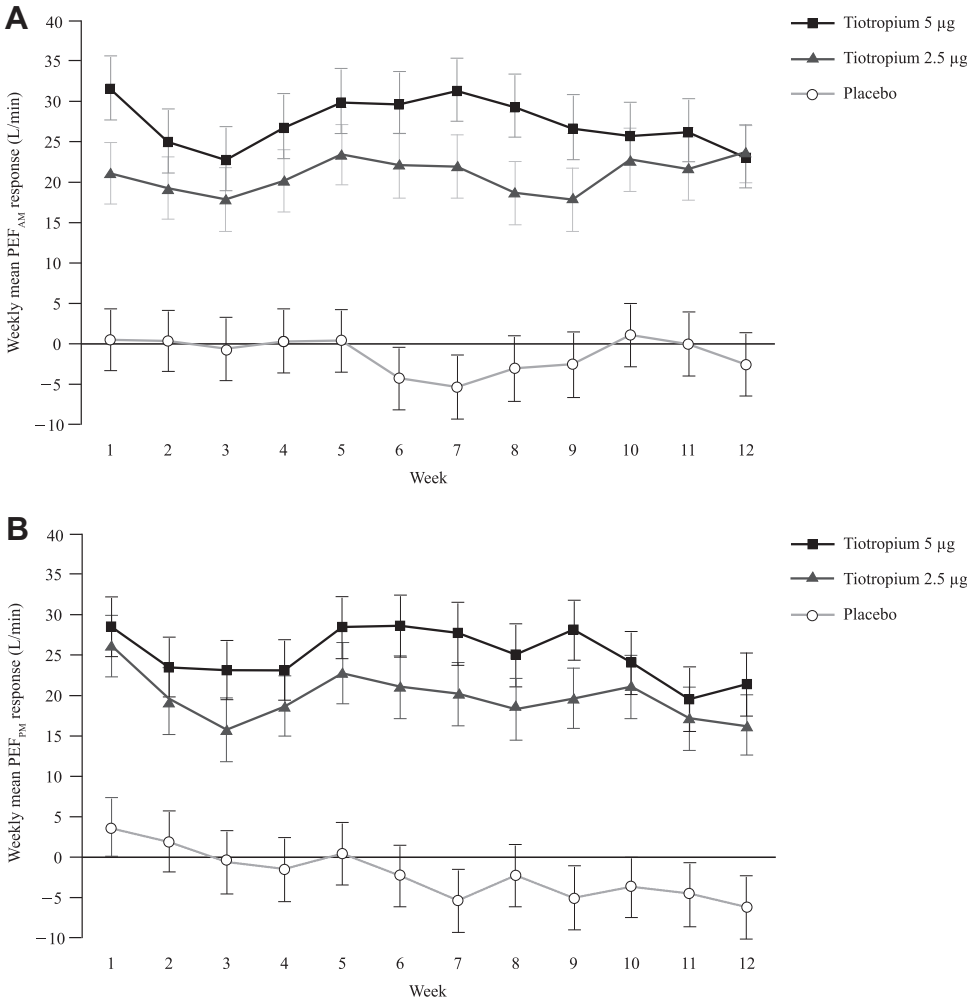

FIGURE 3. Adjusted mean weekly morning PEF (**A**) and adjusted mean weekly evening PEF (pre-bronchodilator) (**B**). $P < .05$ vs placebo for both tiotropium doses at all time points. Response defined as a difference from the baseline value at randomization. Error bars are ± standard error. Baseline mean (standard deviation) PEF, L/min, at visit 2: morning, 355.8 (114.5); evening, 369.8 (115.0). *PEF*, peak expiratory flow.

add-on to ICS significantly improved lung function versus placebo in patients with symptomatic moderate to severe asthma,[5-7] and was noninferior to salmeterol. In addition, a phase II dose-ranging study in patients with moderate symptomatic asthma indicated that tiotropium 5 µg produced better FEV_1 and PEF responses than tiotropium 2.5 µg or 1.25 µg.[8] From our data, tiotropium 5 µg and 2.5 µg may be equally efficacious in mild to moderate asthma. However, taking into account data from previous studies across a range of asthma severities, tiotropium 5 µg can be considered the preferred dose for use as add-on to ICS maintenance therapy to improve lung function in patients with asthma that is not fully controlled.

Previous studies have highlighted smoking history and level of airflow obstruction as factors that can impact on response to treatment.[14,15] Although the subgroup analyses presented here were exploratory in nature and contained limited numbers of patients per group, it is valuable to note that tiotropium appeared to elicit responses in all patients regardless of gender, smoking history, or baseline FEV_1 % predicted of normal. Importantly, peak $FEV_{1(0\text{-}3h)}$ and trough FEV_1 responses versus placebo in the 60% to <80% of predicted normal post-bronchodilator subgroup were greater with tiotropium 5 µg than with 2.5 µg. In the ≥80% subgroup, these responses versus placebo were more similar between the 2 doses, although they were numerically greater with tiotropium 2.5 µg. However, it should be remembered that there is limited room for improvement in this subgroup, making dose discrimination particularly difficult.

At baseline, the mean total ACQ-7 score was 2.1 in each treatment group, which indicated that asthma was uncontrolled. After 12 weeks of treatment, all treatment groups recorded an improvement in asthma control (ie, a decrease in score); however, mean scores in each group still remained in the "partially controlled asthma" range (between 0.75 and 1.5). Furthermore, neither dose of tiotropium achieved a difference from placebo that was considered to reach minimum clinical importance (0.5). However, the decrease in ACQ-7 for the placebo group was higher than expected (>0.7), in contrast to a systematic review and meta-analysis that observed an estimated mean decrease in

TABLE III. *Post hoc* efficacy analyses at week 12 by gender, smoking history, and FEV_1 % of predicted post-bronchodilator

		Active vs placebo		
Treatment and parameter	**Adjusted* mean (SE) (mL)**	**Adjusted* mean of difference (SE) (mL)**	**95% CI**	***P* value***
Gender				
Peak $FEV_{1(0\text{-}3h)}$ response				
Males				
Tiotropium 5 μg (n = 58)	312 (48)	188 (70)	51, 326	.007
Tiotropium 2.5 μg (n = 71)	367 (43)	244 (67)	113, 375	<.001
Placebo (n = 51)	123 (51)			
Females				
Tiotropium 5 μg (n = 94)	247 (33)	97 (46)	7, 187	.04
Tiotropium 2.5 μg (n = 80)	238 (36)	87 (48)	−7, 182	.07
Placebo (n = 103)	150 (32)			
Trough FEV_1 response				
Males				
Tiotropium 5 μg (n = 58)	180 (48)	191 (71)	52, 330	.007
Tiotropium 2.5 μg (n = 71)	183 (44)	195 (67)	62, 327	.004
Placebo (n = 51)	−11 (51)			
Females				
Tiotropium 5 μg (n = 94)	134 (34)	89 (47)	−4, 181	.06
Tiotropium 2.5 μg (n = 80)	95 (37)	50 (49)	−46, 147	.31
Placebo (n = 103)	45 (32)			
Smoking history				
Peak $FEV_{1(0\text{-}3h)}$ response				
Never smoked				
Tiotropium 5 μg (n = 120)	281 (32)	132 (44)	45, 219	.003
Tiotropium 2.5 μg (n = 129)	308 (31)	159 (43)	74, 244	<.001
Placebo (n = 128)	149 (31)			
Ex-smoker				
Tiotropium 5 μg (n = 32)	244 (55)	152 (82)	−10, 314	.07
Tiotropium 2.5 μg (n = 22)	243 (66)	150 (90)	−26, 327	.10
Placebo (n = 26)	92 (61)			
Trough FEV_1 response				
Never smoked				
Tiotropium 5 μg (n = 120)	162 (32)	122 (45)	35, 210	.006
Tiotropium 2.5 μg (n = 129)	142 (31)	102 (43)	17, 188	.02
Placebo (n = 128)	39 (31)			
Ex-smoker				
Tiotropium 5 μg (n = 32)	116 (59)	163 (87)	−10, 335	.06
Tiotropium 2.5 μg (n = 22)	98 (71)	145 (95)	−43, 334	.13
Placebo (n = 26)	−47 (64)			
FEV_1 % of predicted normal post-bronchodilator				
Peak $FEV_{1(0\text{-}3h)}$ response				
60% to <80%				
Tiotropium 5 μg (n = 25)	288 (64)	200 (90)	21, 379	.03
Tiotropium 2.5 μg (n = 30)	230 (58)	142 (86)	−28, 311	.10
Placebo (n = 25)	88 (63)			
≥80%				
Tiotropium 5 μg (n = 127)	269 (31)	119 (43)	34, 204	.006
Tiotropium 2.5 μg (n = 121)	316 (31)	166 (44)	81, 252	<.001
Placebo (n = 129)	150 (30)			
Trough FEV_1 response				
60% to <80%				
Tiotropium 5 μg (n = 25)	213 (67)	275 (95)	86, 463	.005
Tiotropium 2.5 μg (n = 30)	37 (61)	99 (90)	−79, 278	.27
Placebo (n = 25)	−62 (67)			

(continued)

TABLE III. *(Continued)*

Treatment and parameter	Adjusted* mean (SE) (mL)	Active vs placebo		
		Adjusted* mean of difference (SE) (mL)	95% CI	*P* value*
≥80%				
Tiotropium 5 μg (n = 127)	140 (31)	99 (43)	13, 184	.02
Tiotropium 2.5 μg (n = 121)	162 (31)	121 (44)	35, 207	.006
Placebo (n = 129)	42 (31)			

CI, Confidence interval; FEV_1, forced expiratory volume in 1 second; *peak* $FEV_{1(0\text{-}3h)}$, peak forced expiratory volume in 1 second within 3 hours of dosing; *SE*, standard error.
*Versus placebo.

TABLE IV. Overall summary of adverse events

n (%)	Tiotropium 5 μg (n = 155)	Tiotropium 2.5 μg (n = 154)	Placebo (n = 155)	Total (N = 464)
Patients with any AE	50 (32.3)	48 (31.2)	45 (29.0)	143 (30.8)
Patients with severe AEs	2 (1.3)	1 (0.6)	2 (1.3)	5 (1.1)
Patients with serious AEs*	1 (0.6)	0	1 (0.6)	2 (0.4)
Breast cancer *in situ*	1 (0.6)	0	0	1 (0.2)
Life-threatening asthma exacerbation	0	0	1 (0.6)	1 (0.2)
Patients with investigator-defined drug-related AEs	2 (1.3)	2 (1.3)	2 (1.3)	6 (1.3)
Patients with AEs leading to discontinuation of study medication	1 (0.6)	2 (1.3)	0	3 (0.6)

AE, Adverse event.
*A patient may be counted in more than 1 category.

ACQ-7 of 0.494 in patients receiving ICS therapy.[16] An additional, unplanned analysis showed that 6-question ACQ (independent of clinician-assessed lung function) results were comparable with those of ACQ-7 (data not shown). Improved compliance to ICS as a result of being a trial participant may have been sufficient to improve asthma control in the placebo group, in this population of patients with mild to moderate asthma. Furthermore, the study was predominantly designed to assess lung function over a relatively short term (12 weeks), and a longer time frame would perhaps be needed to record any differences in clinical outcomes that may exist in patients with such mild disease.

The magnitude of reduction in adjusted weekly mean number of puffs of rescue medication was similar with tiotropium 5 μg and placebo; however, significant improvements with tiotropium versus placebo were not to be expected because of the patient population (mild to moderate asthma) under investigation. Therefore, we believe that the lack of significant improvement in symptoms, as well as in rescue medication use, should not detract from the clinical relevance of the functional improvement observed with tiotropium in this population of patients with mild to moderate asthma.

The incidence of AEs was comparable across the treatment groups, and serious AEs and AEs leading to discontinuation were rare.

Although the short trial duration, the absence of an active comparator, and lack of power to detect clinical symptomatic benefit may be perceived as limitations of this trial, these 3-month data confirm the bronchodilatory effect of tiotropium that has been reported in other trials in patients with asthma that remains uncontrolled despite ICS maintenance therapy.[5-8] The fact that there is no known pathophysiological difference between patients with mild and moderate asthma, coupled with evidence that improvements in lung function translate into clinical benefits,[17] suggest that a different and appropriately powered study design may have detected significant symptomatic outcomes.

This phase III study was a well-controlled, well-conducted clinical trial in a representative population of patients with milder symptomatic asthma than has previously been investigated. The trial was able to confirm that tiotropium add-on therapy improves overall lung function in this group of patients also, further increasing current knowledge of this therapy in different asthma populations receiving various ICS doses. A statistically significant improvement versus placebo in ACQ-7 was not observed over this short study period. This study was not designed to evaluate an effect of tiotropium on asthma exacerbations. However, evidence that improved lung function and control in adults with mild to moderate asthma correlates with reduced risk of future exacerbations,[18] and that low lung function is considered a predictor of future risk of exacerbations,[1] suggests that the observed improvements in airflow could offer clinically relevant benefits to patients in this population.

CONCLUSIONS

Tiotropium Respimat was an efficacious bronchodilator when added to low- to medium-dose ICS maintenance therapy in a population of adult patients with not fully controlled, mild to moderate asthma. Once-daily tiotropium add-on improved lung function after 12 weeks of treatment compared with placebo. The safety and tolerability of tiotropium add-on to ICS maintenance therapy were comparable with those of placebo, and both tiotropium doses were well tolerated over 12 weeks of treatment. The data presented here provide further evidence for tiotropium Respimat as an efficacious alternative bronchodilator therapy when added on to ICS in inadequately controlled asthma.

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TABLE E1. Baseline patient and disease characteristics by gender

	Tiotropium 5 μg		Tiotropium 2.5 μg		Placebo		Total	
	Male (n = 59)	Female (n = 96)	Male (n = 72)	Female (n = 82)	Male (n = 52)	Female (n = 103)	Male (n = 183)	Female (n = 281)
Baseline								
FEV_1*								
% predicted pre-bronchodilator	73.5 ± 8.0	75.7 ± 8.0	72.8 ± 8.0	73.6 ± 9.1	72.6 ± 7.6	74.3 ± 8.9	73.0 ± 7.9	74.6 ± 8.7
% predicted post-bronchodilator at screening†	91.2 ± 11.2	94.5 ± 13.4	90.1 ± 10.4	92.3 ± 14.8	89.7 ± 11.8	92.3 ± 10.9	90.4 ± 11.0	93.0 ± 13.0
Reversibility (L)†	0.667 ± 0.296	0.499 ± 0.259	0.647 ± 0.292	0.483 ± 0.277	0.648 ± 0.355	0.492 ± 0.251	0.654 ± 0.311	0.492 ± 0.261
Reversibility (%)†	24.4 ± 10.6	25.0 ± 14.7	24.1 ± 10.1	25.8 ± 17.7	23.8 ± 11.5	25.0 ± 13.2	24.1 ± 10.6	25.2 ± 15.1
Predose at baseline (L)‡	2.985 ± 0.647	2.172 ± 0.483	2.837 ± 0.716	2.019 ± 0.599	2.867 ± 0.653	2.129 ± 0.553	2.893 ± 0.676	2.112 ± 0.546
Body mass index (kg/m^2)*	26.5 ± 5.2	27.0 ± 4.9	25.0 ± 4.6	27.3 ± 6.1	26.9 ± 5.7	26.0 ± 4.8	26.0 ± 5.2	26.7 ± 5.2

FEV_1, Forced expiratory volume in 1 second.
*Values are mean ± standard deviation.
†Visit 1 (screening).
‡Visit 2 (randomization).

TABLE E2. Weekly mean number of puffs of rescue medication used per day (response values)

			Active vs placebo		
Time point	**Treatment**	**Adjusted* mean (SE)**	**Adjusted* mean of difference (SE)**	**95% CI**	***P* value†**
Week 1	Tiotropium 5 μg (n = 155)	−0.685 (0.092)	−0.132 (0.129)	−0.385, 0.121	.31
	Tiotropium 2.5 μg (n = 154)	−0.550 (0.093)	0.003 (0.129)	−0.250, 0.256	.98
	Placebo (n = 155)	−0.553 (0.093)			
Week 2	Tiotropium 5 μg (n = 153)	−0.535 (0.093)	−0.008 (0.129)	−0.261, 0.245	.95
	Tiotropium 2.5 μg (n = 154)	−0.464 (0.093)	0.064 (0.129)	−0.189, 0.317	.62
	Placebo (n = 155)	−0.527 (0.093)			
Week 3	Tiotropium 5 μg (n = 152)	−0.570 (0.093)	−0.002 (0.129)	−0.255, 0.252	.99
	Tiotropium 2.5 μg (n = 154)	−0.506 (0.093)	0.062 (0.129)	−0.191, 0.316	.63
	Placebo (n = 154)	−0.568 (0.093)			
Week 4	Tiotropium 5 μg (n = 152)	−0.707 (0.093)	−0.125 (0.129)	−0.379, 0.128	.33
	Tiotropium 2.5 μg (n = 153)	−0.485 (0.093)	0.097 (0.129)	−0.156, 0.350	.45
	Placebo (n = 153)	−0.582 (0.093)			
Week 5	Tiotropium 5 μg (n = 153)	−0.736 (0.093)	−0.047 (0.129)	−0.300, 0.206	.72
	Tiotropium 2.5 μg (n = 152)	−0.613 (0.093)	0.077 (0.129)	−0.177, 0.330	.55
	Placebo (n = 153)	−0.689 (0.093)			
Week 6	Tiotropium 5 μg (n = 153)	−0.736 (0.093)	−0.007 (0.129)	−0.260, 0.247	.96
	Tiotropium 2.5 μg (n = 151)	−0.549 (0.093)	0.180 (0.129)	−0.074, 0.434	.16
	Placebo (n = 154)	−0.729 (0.093)			
Week 7	Tiotropium 5 μg (n = 152)	−0.744 (0.093)	−0.056 (0.129)	−0.309, 0.198	.67
	Tiotropium 2.5 μg (n = 150)	−0.536 (0.093)	0.152 (0.129)	−0.102, 0.405	.24
	Placebo (n = 153)	−0.688 (0.093)			
Week 8	Tiotropium 5 μg (n = 153)	−0.773 (0.093)	−0.010 (0.129)	−0.264, 0.243	.94
	Tiotropium 2.5 μg (n = 152)	−0.489 (0.093)	0.274 (0.129)	0.020, 0.527	.03
	Placebo (n = 154)	−0.763 (0.093)			
Week 9	Tiotropium 5 μg (n = 151)	−0.879 (0.093)	−0.078 (0.129)	−0.332, 0.176	.55
	Tiotropium 2.5 μg (n = 151)	−0.633 (0.093)	0.168 (0.129)	−0.086, 0.422	.19
	Placebo (n = 153)	−0.801 (0.093)			
Week 10	Tiotropium 5 μg (n = 151)	−0.819 (0.093)	−0.032 (0.129)	−0.285, 0.222	.81
	Tiotropium 2.5 μg (n = 150)	−0.621 (0.093)	0.166 (0.129)	−0.088, 0.420	.20
	Placebo (n = 154)	−0.787 (0.093)			
Week 11	Tiotropium 5 μg (n = 152)	−0.789 (0.093)	0.022 (0.129)	−0.232, 0.276	.86
	Tiotropium 2.5 μg (n = 150)	−0.640 (0.093)	0.171 (0.129)	−0.083, 0.425	.19
	Placebo (n = 153)	−0.811 (0.093)			
Week 12	Tiotropium 5 μg (n = 152)	−0.848 (0.093)	−0.033 (0.129)	−0.287, 0.221	.80
	Tiotropium 2.5 μg (n = 150)	−0.594 (0.093)	0.222 (0.129)	−0.032, 0.476	.09
	Placebo (n = 153)	−0.815 (0.093)			

CI, Confidence interval; *SE*, standard error.

Common baseline mean (standard deviation) number of puffs of rescue medication, at week 0: 1.841 (2.059).

*Adjusted for treatment, center, week, baseline, treatment-by-week interaction, and baseline-by-week interaction.

†Versus placebo.