

Tiotropium add-on therapy in adolescents with moderate asthma: A 1-year randomized controlled trial

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Background: Results from phase III clinical trials in adults and phase II clinical trials in children and adolescents demonstrate that tiotropium is an effective treatment when added to inhaled corticosteroid (ICS) maintenance therapy.

Objective: We sought to assess the efficacy and safety of once-daily tiotropium Respimat added to ICSs with or without a leukotriene receptor antagonist in a phase III trial in adolescent patients with moderate symptomatic asthma.

Methods: In this 48-week, double-blind, placebo-controlled, parallel-group study, 398 patients aged 12 to 17 years were randomized to receive 5 µg (2 puffs of 2.5 µg) or 2.5 µg (2 puffs of 1.25 µg) of once-daily tiotropium or placebo (2 puffs)

administered through the Respimat device every evening, each as add-on treatment to ICS background therapy, with or without a leukotriene receptor antagonist; long-acting β₂-agonist therapy was not permitted during the study.

Results: Improvement in peak FEV₁ within 3 hours after dosing at 24 weeks (primary end point) was statistically significant with both tiotropium doses compared with placebo: 5 µg of tiotropium, 174 mL (95% CI, 76-272 mL); 2.5 µg of tiotropium, 134 mL (95% CI, 34-234 mL). Significant improvements in trough FEV₁ at week 24 (a secondary end point) were observed with the 5-µg dose only. Trends for improvement in asthma control and health-related quality of life over the 48-week treatment period were observed.

Conclusions: Once-daily tiotropium significantly improved lung function and was safe and well tolerated when added to at least ICS maintenance therapy in adolescent patients with moderate symptomatic asthma. Larger responses were observed with the 5-µg tiotropium dose. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: Adolescent, anticholinergic drug, asthma, asthma control, efficacy, FEV₁, lung function, Respimat, safety, tiotropium

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Asthma is a heterogeneous condition characterized by chronic airway inflammation and intermittent symptoms that affects approximately 300 million persons worldwide¹ and is the most prevalent chronic disease in children and adolescents.² At least 40% of patients experience asthma symptoms and exacerbations despite treatment with inhaled corticosteroids (ICSs) administered as monotherapy or in combination with a long-acting β₂-agonist (LABA).³⁻⁵ Frequent exacerbations contribute to high treatment costs and are associated with an increased risk of persistent asthma in children.^{6,7} Therefore, limiting the rate of exacerbations and achieving asthma control are the main goals of asthma treatment, especially in this age group.

As in adults, ICSs are viewed as the most efficacious first-line therapy and are recommended for adolescents with persistent asthma, with other controllers added in a stepwise manner if patients continue to experience symptoms or asthma exacerbations.^{1,8} Clinical studies in adults have demonstrated that tiotropium administered through the Respimat Soft Mist inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) is an effective and well-tolerated add-on treatment to at least ICS maintenance therapy in patients with mild, moderate, or severe symptomatic asthma.⁹⁻¹⁶ The 2015 revision of the Global Initiative for Asthma strategy includes 5 µg of tiotropium administered through the Respimat device as an option for addition to ICS plus a LABA treatment at steps 4 and 5 in adults with a history of

Abbreviations used

ACQ-6:	6-question Asthma Control Questionnaire
ACQ-7:	7-question Asthma Control Questionnaire
AQLQ(S)+12:	Asthma Quality of Life Questionnaire with Standardized Activities (≥ 12 years)
AUC:	Area under the curve
AUC _(0-3h) :	Area under the curve within 3 hours after dosing
FVC:	Forced vital capacity
FVC _(0-3h) :	Forced vital capacity within 3 hours after dosing
ICS:	Inhaled corticosteroid
LABA:	Long-acting β_2 -agonist
LTRA:	Leukotriene receptor antagonist
PEF:	Peak expiratory flow

exacerbations.¹ Phase II studies in adolescents and children have shown similar lung function benefits to those observed in adults when tiotropium Respimat is added to at least ICSs.^{17,18}

We present results from a 1-year phase III study designed to examine the efficacy and safety of 2 doses (5 and 2.5 μg) of once-daily tiotropium Respimat compared with placebo when added to background treatment with ICS maintenance therapy with or without a leukotriene receptor antagonist (LTRA) in adolescents with moderate symptomatic asthma.

METHODS**Study design**

This was a 1-year, phase III, randomized, double-blind, placebo-controlled, parallel-group study (NCT01257230) in adolescent patients (aged 12–17 years) with moderate symptomatic asthma. The trial was conducted at 65 sites in 12 countries (Germany, Spain, Hungary, Italy, Slovakia, Latvia, Ukraine, Russia, Korea, Mexico, Chile, and the United States).

Population

Eligible patients were aged 12 to 17 years with a documented history of asthma of more than 3 months at enrollment and were symptomatic at screening and before randomization, which was defined as a 7-question Asthma Control Questionnaire (ACQ-7) mean score of at least 1.5. Patients were required: to have been receiving maintenance therapy with ICSs with or without a LABA or an LTRA for 4 or more weeks before screening; to have a prebronchodilator FEV₁ of 60% to 90% of predicted normal value at screening, FEV₁ reversibility of 12% or greater and 200 mL or greater 15 to 30 minutes after 400 μg of salbutamol (albuterol), and variability of absolute FEV₁ values from screening to randomization within $\pm 30\%$; and never to have smoked or to have stopped smoking 1 or more years before enrollment (parental smoking was also recorded).

A key exclusion criterion was a diagnosis of any significant lung disease other than asthma.

Procedures

After a 4-week screening period, patients were randomized in a 1:1:1 ratio to receive 5 μg (2 puffs of 2.5 μg) or 2.5 μg (2 puffs of 1.25 μg) of once-daily tiotropium or placebo (2 puffs) in the evening (between 5 and 7 PM) delivered through the Respimat Soft Mist inhaler (Boehringer Ingelheim) over 48 weeks. Patients were followed up for a further 21 days to assess safety (see Fig E1 in this article's Online Repository at www.jacionline.org). Randomization was performed with a pseudo-random number generator with a supplied seed number and fixed block sequence, with a block size of 6.

Study treatment (tiotropium or placebo) was taken as add-on therapy to background ICS maintenance treatment with or without an LTRA. Permitted doses of ICS maintenance therapy were 200 to 800 μg of budesonide or equivalent for patients aged 12 to 14 years and 400 to 800 μg of budesonide or

equivalent for patients aged 15 to 17 years. These were continued unaltered for the duration of the study. Patients were required to stop LABA therapy at least 72 hours before screening (visit 1) but were permitted to continue LTRAs at the same dose throughout the study. Open-label salbutamol (albuterol) hydrofluoroalkane metered-dose inhalers (100 μg per actuation) were provided as rescue medication during the screening and treatment periods.

The study complied with the principles of the Declaration of Helsinki and the International Conference on Harmonisation for Good Clinical Practice Guidelines. The trial protocol, patient information sheet, and consent form were reviewed and approved by each participating institution's review board. Before participation in the study, written, informed consent was obtained from each patient and the patients' parents or guardians, according to local requirements.

Analysis

The primary efficacy end point was change from baseline (response) in peak FEV₁ within 3 hours after dosing (peak FEV_{1(0-3h)}) at week 24. Blinded efficacy and safety monitoring continued to week 48.

Secondary end points included trough FEV₁ (measured at the end of the dosing interval at 10 minutes before administration of the next dose of study medication), FEV₁ area under the curve (AUC) within 3 hours after dosing (FEV₁ AUC_(0-3h)), peak forced vital capacity (FVC) within 3 hours after dosing (FVC_(0-3h)), trough FVC, FVC AUC_(0-3h), and mean forced expiratory flow between 25% and 75% of FVC, all measured after 24 weeks of treatment.

Other secondary efficacy end points included time to first episode of asthma worsening (prespecified as exacerbation) and time to first severe asthma exacerbation evaluated over the 48-week treatment period. An episode of asthma worsening was defined as a progressive increase in 1 or more asthma symptoms that were outside a patient's usual day-to-day variation and lasting for 2 or more consecutive days and/or a decrease in a patient's best morning peak expiratory flow (PEF) of 30% or more from their mean morning PEF for 2 or more consecutive days; these were recorded as described below. A severe asthma exacerbation was defined as an episode of asthma worsening that required treatment with systemic corticosteroids for 3 or more consecutive days.

The number of puffs of rescue medication during the daytime, nighttime, and entire 24-hour period was measured by the patients at home by using the AM3 asthma monitor device (electronic peak flow meter and eDiary; eResearch Technology, H ochberg, Germany) and expressed as mean weekly values. Asthma control was assessed by using the 6-question Asthma Control Questionnaire (ACQ-6) and ACQ-7 and expressed as a responder rate after 24 weeks of treatment. Patients were classified as responders if they achieved the minimal clinically important difference of a 0.5-point or greater reduction in ACQ scores.¹⁹ For completeness of data, *post hoc* analyses of ACQ-6 and ACQ-7 scores at week 48 were also performed.

Additional end points included the Asthma Quality of Life Questionnaire with Standardized Activities (≥ 12 years; AQLQ[S]+12) total score and responder rate after both 24 and 48 weeks of treatment. Patients were classified as responders if they reached the minimal clinically important difference of an increase from baseline of 0.5 points or more.²⁰ Weekly mean predose morning and evening PEF responses were measured with the AM3 device.

Post hoc analyses of peak and trough FEV₁ at week 24 were performed in patients aged 12 to 14 years and 15 to 17 years to determine whether responses in lung function after tiotropium add-on therapy differed significantly between patients in early and late adolescence.

Adverse events were monitored throughout the treatment and follow-up periods to assess safety and tolerability.

Statistical analyses

Efficacy analyses were performed on the full analysis set, which was the same as the treated set. Safety analyses were performed on the treated set, which was defined as all randomized patients who had received at least 1 dose of study medication.

The null hypotheses were tested in a stepwise manner to control the probability of a type I error (1-sided $\alpha = .025$). First, the superiority of 5 μg of

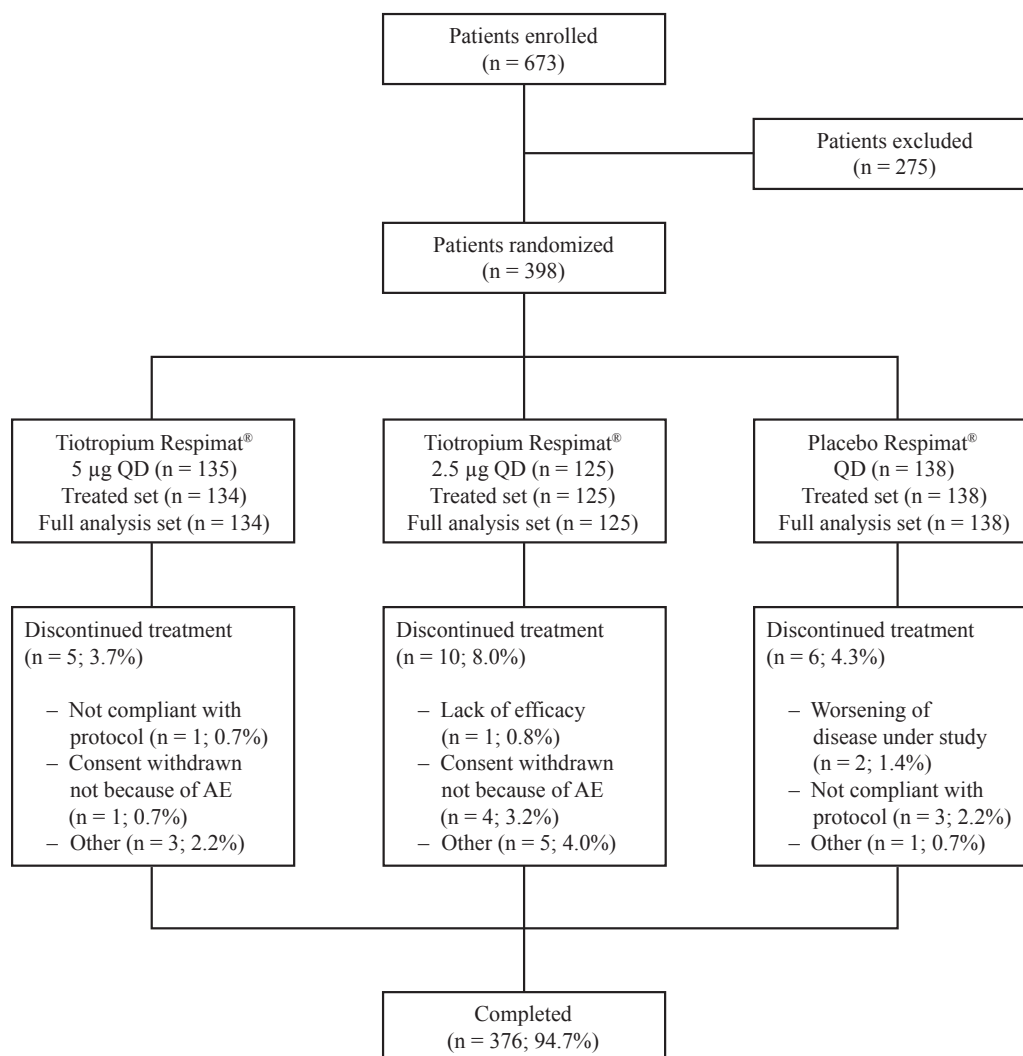


FIG 1. CONSORT diagram. Of the patients screened, the main reasons for noninclusion were as follows: adverse event ($n = 3$), consent withdrawn ($n = 11$), violation of inclusion or exclusion criteria ($n = 243$), lost to follow-up ($n = 3$), and other ($n = 15$). Of those randomized, 1 patient randomized to 5 μg of tiotropium administered through the Respimat device was not treated. AE, Adverse event; QD, once daily.

tiotropium versus placebo for peak $\text{FEV}_{1(0-3\text{h})}$ response at week 24 was tested. If the corresponding null hypothesis was rejected, the same null hypothesis for the 2.5- μg dose was tested. If the superiority of treatment with 5 μg of tiotropium over placebo could not be established, testing of the second hypothesis was considered descriptive only.

The primary end point, peak $\text{FEV}_{1(0-3\text{h})}$ response, was analyzed by using a restricted maximum likelihood-based mixed-effects model with repeated measures. The model included the fixed, categorical effects of “treatment,” “country,” “visit,” and “treatment-by-visit interaction,” as well as the covariates of “baseline value” and “baseline value-by-visit interaction.” “Patient” was included as a random effect in the model. Adjusted means and treatment contrasts were calculated, together with 95% CIs and 2-sided P values. The level of significance was set to .05.

All continuous secondary end points were analyzed by using a maximum likelihood-based mixed-effects model with repeated measures. Adjusted mean values and treatment contrasts were calculated, together with 95% CIs. All calculated P values were to serve an exploratory function. There was no adjustment for multiplicity, and all analyses were evaluated at an α level of .05. For time to first severe exacerbation and time to first episode of asthma worsening, analyses were to be performed with the Cox proportional hazards regression model, with “treatment” fitted as an effect.

Sample-size calculations determined that 127 patients per treatment group were required to detect a difference of 120 mL between treatments in the change from baseline of peak $\text{FEV}_{1(0-3\text{h})}$ with a power of approximately 80%, assuming a common SD of 340 mL.

For lung function end points, baseline (visit 2; randomization) was defined as the respective pretreatment value measured 10 minutes before administration of the first dose of study medication.

RESULTS

A total of 398 patients were randomized. Of these, 376 (94.7%) patients completed the 48-week treatment period and 21 (5.3%) prematurely discontinued study medication (Fig 1).

Baseline patient demographics and disease characteristics

Overall, baseline patient demographics were balanced across treatment groups (Table I). There were more male patients (65.0%), the mean age of the overall study population was

TABLE I. Baseline patient demographics and disease characteristics

	Tiotropium Respiat 5 µg QD (n = 134)	Tiotropium Respiat 2.5 µg QD (n = 125)	Placebo Respiat QD (n = 138)
Age (y)*	14.5 ± 1.6	14.2 ± 1.8	14.2 ± 1.7
Age (y), no. (%)			
<12	0	1 (0.8)	0
12-14	67 (50.0)	72 (57.6)	76 (55.1)
15-17	67 (50.0)	52 (41.6)	62 (44.9)
Sex, no. (%)			
Male	89 (66.4)	81 (64.8)	88 (63.8)
Body mass index (kg/m ²)*	21.6 ± 4.0	21.9 ± 5.1	20.6 ± 3.5
Smoking status, no. (%)			
Never smoked	134 (100)	125 (100)	137 (99.3)
Current smoker†	0	0	1 (0.7)
Exposure to second-hand smoke, no. (%)			
No	118 (88.1)	115 (92.0)	120 (87.0)
Yes	16 (11.9)	10 (8.0)	18 (13.0)
Duration of asthma (y)*	8.2 ± 4.2	7.7 ± 4.0	7.7 ± 4.2
Prebronchodilator FEV ₁ at screening*			
Actual (mL)	2624 ± 593	2537 ± 552	2553 ± 616
Percent predicted	77.3 ± 8.6	78.1 ± 7.9	77.6 ± 7.5
Postbronchodilator FEV ₁ at screening*			
Actual (mL)	3313 ± 738	3200 ± 670	3210 ± 754
Percent predicted	97.6 ± 11.1	98.7 ± 10.5	97.7 ± 9.7
FEV ₁ *‡			
Actual (mL)	2821 ± 665	2680 ± 629	2736 ± 686
Percent predicted	83.0 ± 11.2	82.3 ± 10.3	83.0 ± 10.2
FVC*			
Actual (mL)	3639 ± 902	3461 ± 835	3570 ± 845
Percent predicted	93.4 ± 14.4	92.6 ± 12.8	95.0 ± 12.7
FEV ₁ /FVC ratio (%)*	78.5 ± 10.4	78.4 ± 11.3	76.9 ± 9.7
FEF _(25-75%) (L/s)*	2.6 ± 1.0	2.4 ± 0.9	2.4 ± 1.0
Predose morning PEF (L/min)*	341.2 ± 87.4	343.6 ± 93.9	334.6 ± 93.4
Predose evening PEF (L/min)*	362.6 ± 86.0	360.7 ± 91.3	356.7 ± 96.1
ACQ-6 score*	2.0 ± 0.4	2.0 ± 0.5	2.0 ± 0.5
ACQ-7 score*	2.0 ± 0.4	2.1 ± 0.5	2.0 ± 0.4
AQLQ(S)+12 score*	5.3 ± 0.8	5.4 ± 0.9	5.4 ± 0.8
ICS dose of stable maintenance treatment (µg)*‡	536 ± 256	557 ± 346	527 ± 275
Concomitant therapies in the 3 mo before screening, no. (%)			
LABA	41 (30.6)	35 (28.0)	39 (28.3)
LTRA	17 (12.7)	12 (9.6)	18 (13.0)
Concomitant therapies during the treatment period, no. (%)			
LABA	4 (3.0)	0	7 (5.1)
LTRA	15 (11.2)	8 (6.4)	14 (10.1)

The treated set is shown.

FEF_(25-75%), Forced expiratory flow between 25% and 75% of FVC.

*Values are means ± SD.

†Assigned as an important protocol violation.

‡Budesonide or equivalent dose.

14.3 years (54.2% aged 12-14 years and 45.6% aged 15-17 years; 1 patient was aged 11 years at enrollment) with a mean duration of asthma of 7.9 years, and 11.1% of patients reported passive exposure to smoke. In the 3 months before screening, all patients had received maintenance treatment with ICSs, 29.0% had received a LABA, and 11.8% had received an LTRA. During the treatment period, 2.8% of patients received treatment with a LABA (protocol violations) and 9.3% continued treatment with an LTRA.

Efficacy

Primary end point. A statistically significant greater improvement in peak FEV_{1(0-3h)} response was observed after 24 weeks with both doses of tiotropium versus placebo (Fig 2).

The adjusted mean difference in response was greater with the 5-µg dose (174 mL [95% CI, 76-272 mL] vs 134 mL [95% CI, 34-234 mL] for the 2.5-µg dose).

Post hoc analyses demonstrated that improvements in peak FEV_{1(0-3h)} were similar in both younger (12-14 years) and older (15-17 years) patients (treatment-by-subgroup interaction *P* value = .21). This response was numerically higher but not statistically significant with 2.5 µg of tiotropium in the 15- to 17-year age group (see Table E1 in this article's Online Repository at www.jacionline.org).

Secondary end points. A statistically significant improvement in trough FEV₁ versus placebo was observed for 5 µg of tiotropium (Table II). *Post hoc* analyses confirmed that improvements in trough FEV₁ were independent of age group

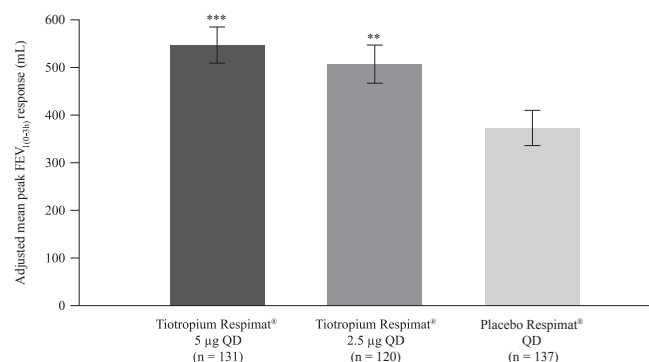


FIG 2. Peak FEV_{1(0-3h)} response at week 24: full analysis set. Results are adjusted for treatment, country, week, baseline, treatment-by-week interaction, and baseline-by-week interaction. Error bars are $\pm$ SEs. Common baseline mean FEV₁ $\pm$ SD is 2747 $\pm$ 662 mL. ** $P < .01$ versus placebo Respimat and *** $P < .001$ versus placebo Respimat. Peak FEV_{1(0-3h)}, Peak FEV₁ within 3 hours after dosing; QD, once daily.

(treatment-by-subgroup interaction P value = .70; see Table E2 in this article's Online Repository at www.jacionline.org).

AUC calculations provide a useful method to demonstrate an average bronchodilatory effect over time. Improvements in FEV₁ AUC_(0-3h) for both the 5- and 2.5- μ g doses compared with placebo were statistically significant (Table II), but the numerically higher values for peak FVC_(0-3h), trough FVC, and FVC AUC_(0-3h) with both tiotropium doses versus placebo did not reach statistical significance (see Table E3 in this article's Online Repository at www.jacionline.org).

Forced expiratory flow between 25% and 75% of FVC treatment differences were statistically significant at all time points with both tiotropium doses compared with placebo, with the exception of 2.5 μ g of tiotropium at 10 minutes before dosing and 30 minutes after dosing (Fig 3).

Overall, 16 patients experienced at least 1 severe asthma exacerbation during the study: 2 (1.5%) in the 5 μ g of tiotropium group, 5 (4.0%) in the 2.5 μ g of tiotropium group, and 9 (6.5%) in the placebo group. At least 1 episode of asthma worsening was reported for 30 (22.4%) patients in the 5 μ g of tiotropium group, 34 (27.2%) in the 2.5 μ g of tiotropium group, and 37 (26.8%) in the placebo group. The median time to first severe asthma exacerbation and time to first episode of asthma worsening were not calculated because events were reported for less than 50% of patients in each treatment group.

The weekly mean number of puffs of rescue medication used during the daytime, nighttime, and entire 24-hour period decreased over the 48-week treatment period but was statistically significant only with the 2.5- μ g dose during the entire 24-hour period at week 48 (see Table E4 in this article's Online Repository at www.jacionline.org).

Adjusted mean ACQ-6 and ACQ-7 scores at week 24 in patients treated with tiotropium were numerically lower than those in patients treated with placebo: -0.054 (95% CI, -0.235 to 0.127) and -0.097 (95% CI, -0.263 to 0.069) points, respectively, with 5 μ g of tiotropium and -0.147 (95% CI, -0.333 to 0.038) and -0.160 (95% CI, -0.330 to 0.010) points, respectively, with 2.5 μ g of tiotropium. The proportion of patients who achieved the minimal clinically important difference for both the ACQ-6 and ACQ-7 was higher with both tiotropium doses at week 24 compared with placebo, but the differences were not

statistically significant (ACQ-6, Wilcoxon rank sum test: $P = .51$ for 5 μ g of tiotropium and $P = .14$ for 2.5 μ g of tiotropium; ACQ-7, Wilcoxon rank sum test: $P = .12$ for 5 μ g of tiotropium and $P = .08$ for 2.5 μ g of tiotropium; see Fig E2 in this article's Online Repository at www.jacionline.org).

Post hoc analyses at week 48 demonstrated further improvements (score reductions) in adjusted mean ACQ-6 and ACQ-7 scores (adjusted mean compared with placebo: -0.079 and -0.127 , respectively, for 5 μ g of tiotropium and -0.162 and -0.191 , respectively, for 2.5 μ g of tiotropium). The proportion of patients who were responders increased between weeks 24 and 48 for both the ACQ-6 (Wilcoxon rank sum test: $P = .40$ for 5 μ g of tiotropium and $P = .28$ for 2.5 μ g of tiotropium vs placebo at week 48) and ACQ-7 (Wilcoxon rank sum test: $P = .17$ for 5 μ g of tiotropium and $P = .04$ for 2.5 μ g of tiotropium vs placebo at week 48) and was higher in the 2 tiotropium treatment groups (see Fig E2).

Additional end points. The adjusted mean AQLQ(S)+12 score improved during the 48-week treatment period in all 3 treatment groups, but the treatment differences were not statistically significant between either tiotropium dose and placebo at week 24 or 48 (0.079 [95% CI, -0.087 to 0.245] and 0.030 [95% CI, -0.138 to 0.198], respectively, for 5 μ g of tiotropium and 0.135 [95% CI, -0.036 to 0.306] and 0.140 [95% CI, -0.034 to 0.314], respectively, for 2.5 μ g of tiotropium). The proportion of patients who were responders increased between weeks 24 and 48 in all 3 treatment groups and was highest in the 5 μ g of tiotropium group (Wilcoxon rank sum test: $P = .02$ for 5 μ g of tiotropium and $P = .17$ for 2.5 μ g of tiotropium vs placebo at week 24; $P = .15$ for 5 μ g of tiotropium and $P = .58$ for 2.5 μ g of tiotropium vs placebo at week 48; Fig 4).

Predose morning and evening PEF responses (analyzed as weekly means) tended to be larger in the 5 μ g of tiotropium group compared with those in the 2.5 μ g of tiotropium group and were higher in both tiotropium treatment groups than in the placebo group. Over the 48-week treatment period, the differences in adjusted mean predose morning and evening PEF responses between 5 μ g of tiotropium and placebo were statistically significant at almost all weeks, including week 24 ($P = .02$ and $P = .01$ for predose morning and evening PEF, respectively) and week 48 ($P = .005$ and $P = .008$ for predose morning and evening PEF, respectively). However, in the 2.5 μ g of tiotropium treatment group, statistical significance in the weekly mean difference from placebo was less consistent and observed at some weeks only (week 24: $P = .17$ and $P = .08$ for predose morning and evening PEF, respectively; week 48: $P = .0504$ and $P = .03$ for predose morning and evening PEF, respectively; Fig 5 and see Fig E3 in this article's Online Repository at www.jacionline.org).

Safety and tolerability

The overall incidence of adverse events was comparable across the 3 treatment groups (Table III). There was a low incidence of drug-related adverse events, and most adverse events were mild or moderate in intensity. Serious adverse events, none of which was considered drug-related, were reported for 7 patients: 3 (2.2%) receiving 5 μ g of tiotropium (1 patient with an asthma exacerbation, 1 with upper abdominal pain, and 1 with an anaphylactic reaction after a plant sting), 2 (1.6%) receiving 2.5 μ g of tiotropium (1 patient with multiple injuries after an

TABLE II. Secondary FEV₁ efficacy end point responses at week 24

Treatment and parameter	Adjusted mean ± SE (mL)	Active versus placebo Respimat		
		Adjusted mean of difference ± SE (mL)	95% CI	P value
Trough FEV ₁ (mL)				
Tiotropium Respimat 5 µg QD (n = 131)	400 ± 41	117 ± 54	10 to 223	.03
Tiotropium Respimat 2.5 µg QD (n = 119)	367 ± 44	84 ± 56	−25 to 194	.13
Placebo Respimat QD (n = 137)	283 ± 40			
FEV ₁ AUC _(0-3h) (mL)				
Tiotropium Respimat 5 µg QD (n = 131)	463 ± 36	181 ± 48	88 to 275	<.001
Tiotropium Respimat 2.5 µg QD (n = 119)	411 ± 38	130 ± 49	34 to 225	.008
Placebo Respimat QD (n = 137)	281 ± 35			

The full analysis set is shown. Results are adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. The common baseline mean FEV₁ $\pm$ SD is 2747 $\pm$ 662 mL.

QD, Once daily.

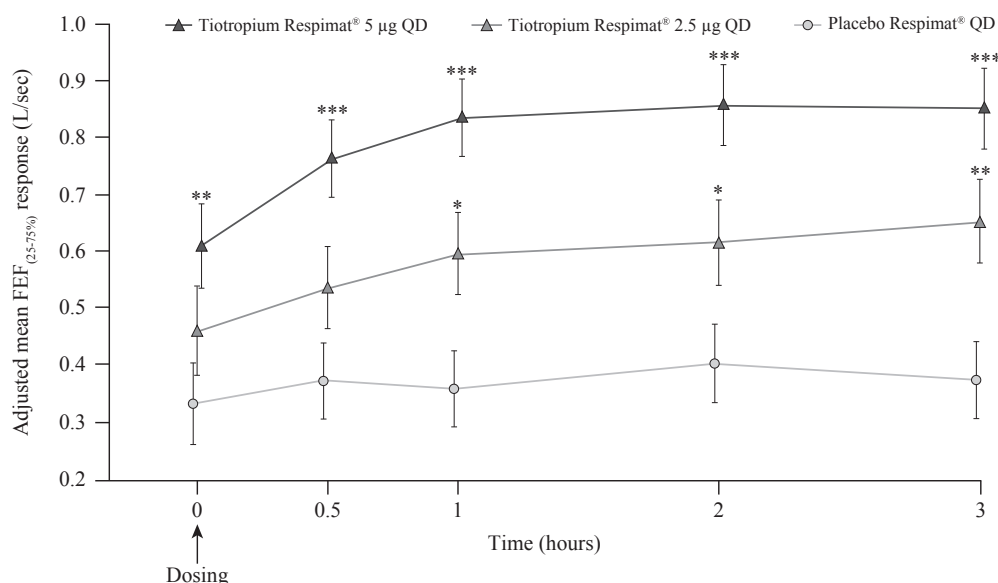


FIG 3. Forced expiratory flow between 25% and 75% of FVC (FEF_{25-75%}) response at week 24: full analysis set. Results are adjusted for treatment, country, week, baseline, treatment-by-week interaction, and baseline-by-week interaction. Common baseline mean $\pm$ SD is 2.48 $\pm$ 0.97 L/s. **P* < .05 versus placebo Respimat, ***P* < .01 versus placebo Respimat, and ****P* < .001 versus placebo Respimat. QD, Once daily.

accident and 1 with appendicitis), and 2 (1.4%) receiving placebo (1 patient with gastroenteritis and 1 with teratoma). There were no deaths during the study.

DISCUSSION

This phase III study examining the efficacy and safety of addition of 5 and 2.5 μ g of tiotropium to background treatment with ICSs with or without an LTRA in adolescent patients with moderate symptomatic asthma confirms that the addition of tiotropium provides significant improvements in lung function. These results are consistent with the improvements in lung function observed in previously published phase II studies in adolescents¹⁷ and phase III studies in adults^{13,21} with moderate symptomatic asthma. Improvements in asthma control, measured based on ACQ-6 and ACQ-7 scores, were positive but not statistically significant. Overall, the efficacy improvements confirmed consistently greater benefit with the 5- μ g dose of tiotropium, which is in line with previously reported dose ordering in adult

phase II dose-ranging studies.^{10,12} Safety and tolerability were comparable with those of background therapy during this relatively large 48-week study, which is consistent with previously published data in adults and adolescents.

The primary lung function end point at week 24 was met, and the continued blinded assessment up to 48 weeks demonstrated that these improvements were sustained. Weekly predose PEF responses followed a similar pattern. Although there is no established minimum clinically important difference for FEV₁ responses, the observed effect sizes are comparable with those seen with LABAs and in other studies of tiotropium in asthmatic patients, in which improvements in clinically relevant measures of asthma control were also observed.^{13,22} Therefore, the bronchodilatory effects of tiotropium might manifest in improved asthma control, and achieving and maintaining improved lung function is important, particularly in the adolescent age group, because reduced lung function can be a marker associated with increased risk of future asthma exacerbations and reduced asthma control.²³⁻²⁵ Over the 48-week treatment period, the incidences of

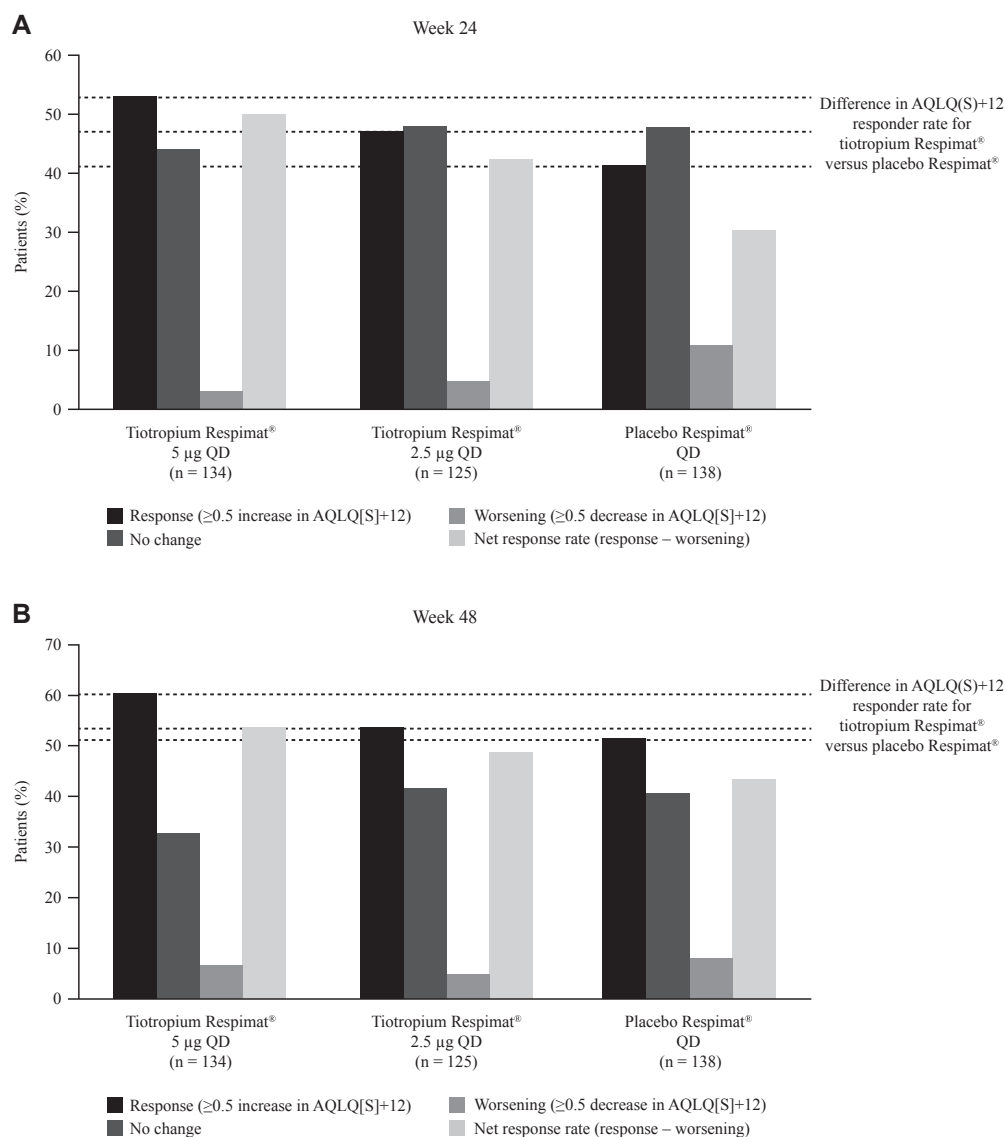


FIG 4. AQLQ(S)+12 responder rate at week 24 (A) and week 48 (B): full analysis set. Results are adjusted for treatment, country, week, baseline, treatment-by-week interaction, and baseline-by-week interaction. Common baseline mean $\pm$ SD is 5.4 ± 0.8 . QD, Once daily.

severe exacerbations and episodes of asthma worsening were relatively low, which was not unexpected because this patient population had moderate asthma, which is not associated with a high rate of exacerbations. Improvements in ACQ-6, ACQ-7, and AQLQ(S)+12 scores were observed but were not statistically significant compared with those in patients receiving placebo; however, the study was not powered for these end points. Furthermore, in a network analysis of results from a large number of asthma trials in which ACQ and AQLQ scores were assessed, Bateman et al²⁶ reported that the minimal clinically important difference (expressed as mean improvements between treatment arms) is seldom achieved and unlikely in studies like ours, in which a second or third controller is added in combination with ICSs.

A limitation of our study might be the relatively large response observed in the placebo group. Outside of the clinical trial environment, adherence to asthma treatment in the adolescent

population is notably poor.^{27–29} It is likely that patients became more adherent to background ICS therapy during the course of the trial, a well-known phenomenon in clinical trials in this age group.²⁶

The results of our study add to the body of evidence that supports the inclusion of tiotropium as an option in the stepwise addition of treatment for uncontrolled asthma in adolescents. According to current guidelines, the addition of a LABA should be considered in adolescent patients with mild or moderate asthma not fully controlled by ICS monotherapy, with a higher dose of ICS or the addition of an LTRA as acceptable alternatives.¹ Studies comparing the responses of individual patients to long-acting anticholinergic bronchodilators and LABAs confirm marked heterogeneity, with similar proportions of patients demonstrating response or nonresponse to both therapeutic options.^{9,13,21} Consistent with this observation, a crossover study performed in 182 children with uncontrolled

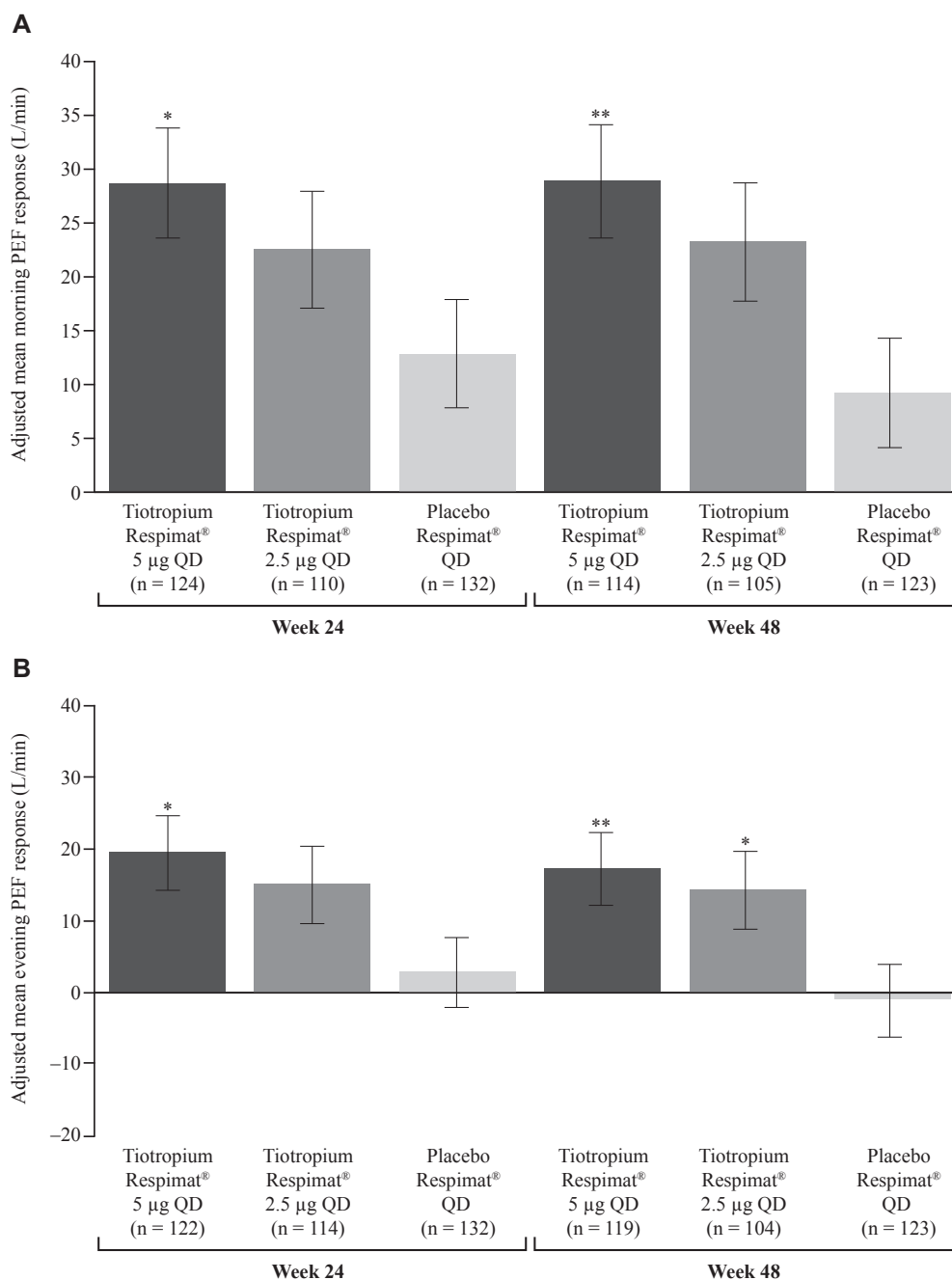


FIG 5. Adjusted mean predose morning (A) and evening (B) PEF responses at weeks 24 and 48: full analysis set. Results are adjusted for treatment, country, week, baseline, treatment-by-week interaction, and baseline-by-week interaction. Common baseline mean predose morning PEF $\pm$ SD is 339.7 ± 91.5 L/min; common baseline predose evening PEF $\pm$ SD is 359.9 ± 91.1 L/min. Adjusted mean predose morning and evening PEF responses versus placebo were as follows: 5 µg of tiotropium, $P = .02$ and $P = .01$, respectively, at week 24 and $P = .005$ and $P = .008$, respectively, at week 48; 2.5 µg of tiotropium, $P = .17$ and $P = .08$, respectively, at week 24 and $P = .0504$ and $P = .03$, respectively, at week 48. * $P < .05$ versus placebo Respimat and ** $P < .01$ versus placebo Respimat.

asthma revealed differential responses to stepping up therapy (a higher dose of ICS or addition of a LABA or an LTRA) in 98% of patients, supporting the need for different treatment options for the management of asthma in children.⁸ Circumstances in which tiotropium might be favored include when a LABA or other controllers do not achieve the desired improvements, when tolerance against the bronchoprotective

effect of a LABA is suspected, or where there are safety concerns about treatment with LABAs.^{30,31} The positive effect of combining tiotropium with LABAs in patients with severe symptomatic asthma has been confirmed in studies in adults.¹¹ Results from similar studies in adolescents and children have been completed (NCT01277523 and NCT01634152), and publication of these results is anticipated.

TABLE III. Overall summary of adverse events

	Tiotropium Respimat 5 µg QD (n = 134)	Tiotropium Respimat 2.5 µg QD (n = 125)	Placebo Respimat QD (n = 138)
Patients with any AE	84 (62.7)	79 (63.2)	82 (59.4)
Patients with severe AEs	2 (1.5)	2 (1.6)	3 (2.2)
Patients with investigator-defined drug-related AEs	4 (3.0)	1 (0.8)	1 (0.7)
Patients with AEs leading to discontinuation of study medication	0	0	2 (1.4)
Patients with serious AEs	3 (2.2)	2 (1.6)	2 (1.4)
AEs in >5% patients by preferred term*			
Asthma†	23 (17.2)	27 (21.6)	32 (23.2)
Nasopharyngitis	20 (14.9)	13 (10.4)	17 (12.3)
Viral respiratory tract infection	10 (7.5)	11 (8.8)	11 (8.0)
Decreased PEF rate	6 (4.5)	9 (7.2)	8 (5.8)
Headache	9 (6.7)	7 (5.6)	2 (1.4)
Viral infection	7 (5.2)	5 (4.0)	6 (4.3)

Values are presented as numbers (percentages). A patient can be counted in more than 1 category. The treated set is shown.

AE, Adverse event; QD, once daily.

*Medical Dictionary for Regulatory Activities, version 16.1.

†Includes asthma worsening and asthma exacerbations.

To date, features that can be used to predict responses to LABAs versus long-acting anticholinergic bronchodilators have not been reported but, if identified, might be of benefit in helping to inform treatment decisions. Peters et al³² have suggested that a positive response to albuterol (salbutamol) and a lower resting heart rate can be used to predict a positive clinical response to tiotropium in adults with asthma; however, these results require confirmation. Further prospective trials in adolescents with poorly controlled asthma might help to identify predictors of response to the different step-up options, including tiotropium.

In conclusion, in adolescent patients with moderate symptomatic asthma, once-daily tiotropium added to at least ICS maintenance treatment significantly improves lung function and demonstrates a trend for improved asthma control and quality of life, with the largest responses observed with the 5-µg dose. Tiotropium also demonstrated safety and tolerability comparable with those of placebo. These data are consistent with findings in adults and support the addition of tiotropium Respimat in the treatment of adolescent patients with moderate symptomatic asthma.

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Clinical implications: Once-daily tiotropium Respimat is an effective add-on treatment to at least ICS maintenance therapy, and its safety and tolerability are comparable with those of placebo, in adolescents with moderate symptomatic asthma.

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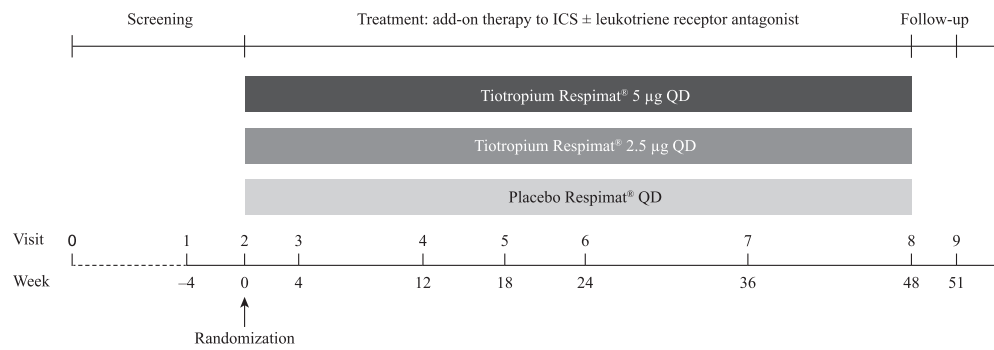


FIG E1. Study design. Patients randomized to placebo received background ICS maintenance treatment with or without an LTRA as active therapy only. In-clinic spirometric evaluations were conducted at baseline (visit 2; randomization) and subsequently at visits 4, 6, and 8 in the evening. *QD*, Once daily.

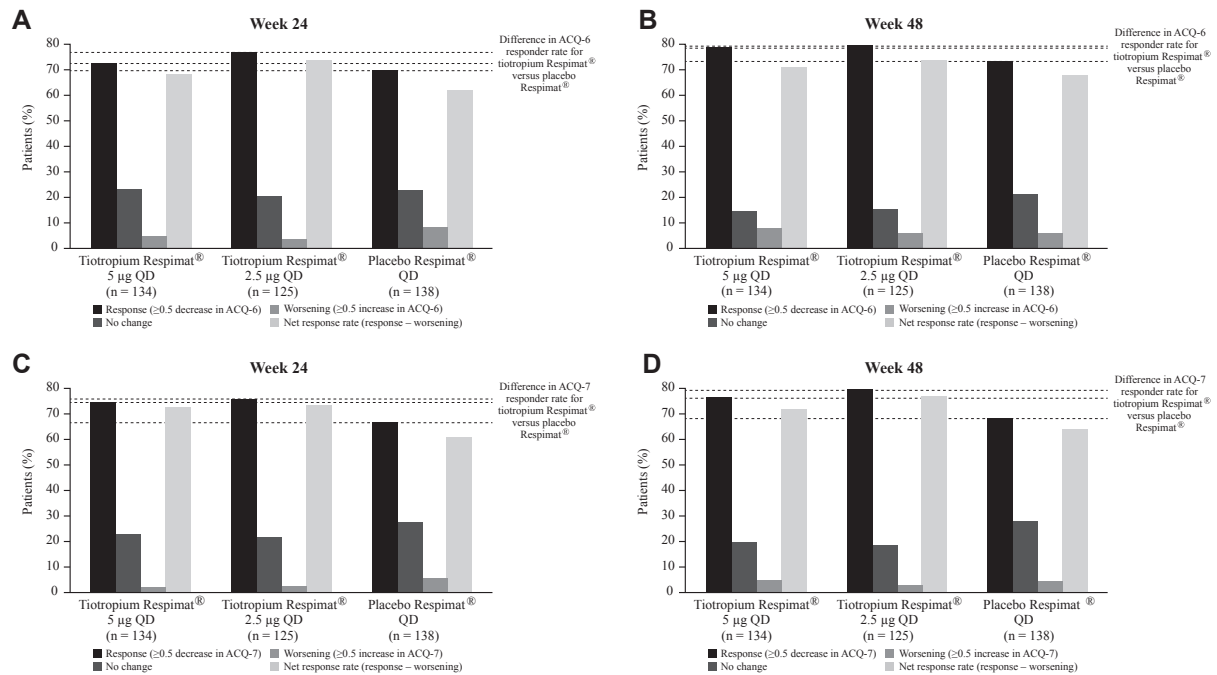


FIG E2. ACQ responder rate analyses: ACQ-6 score at week 24 (A), ACQ-6 score at week 48 (B), ACQ-7 score at week 24 (C), and ACQ-7 score at week 48 (D). The full analysis set is shown. Common baseline mean ACQ-6 score $\pm$ SD is 2.0 ± 0.5 . ACQ-7 score $\pm$ SD is 2.0 ± 0.4 . QD, Once daily.

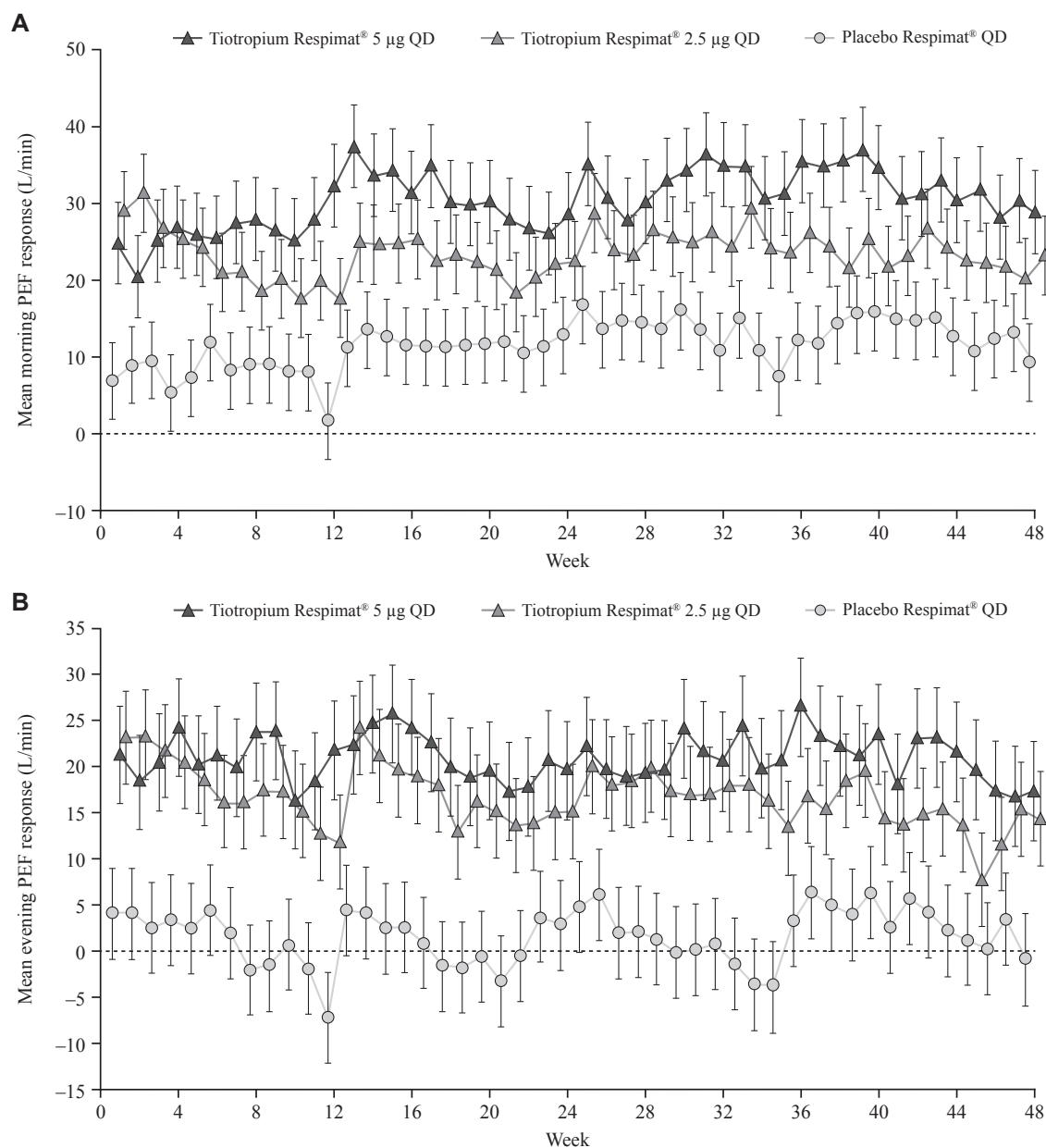


FIG E3. Weekly mean predose morning (A) and evening (B) PEF responses over 48 weeks. The full analysis set is shown. Results are adjusted for treatment, country, week, baseline, treatment-by-week interaction, and baseline-by-week interaction. Common baseline mean predose morning PEF $\pm$ SD is 339.7 ± 91.5 L/min; common baseline mean predose evening PEF $\pm$ SD is 359.9 ± 91.1 L/min. Adjusted mean predose morning and evening PEF response versus placebo is as follows: 5 µg of tiotropium, $P = .02$ and $P = .01$, respectively, at week 24 and $P = .005$ and $P = .008$, respectively, at week 48; 2.5 µg of tiotropium, $P = .17$ and $P = .08$, respectively, at week 24 and $P = .0504$ and $P = .03$, respectively, at week 48. QD, Once daily.

TABLE E1. *Post hoc* analysis of peak FEV_{1(0-3h)} at week 24 by age group

Treatment	Adjusted mean ± SE (mL)	Active vs placebo Respimat		
		Adjusted mean of difference ± SE (mL)	95% CI	P value
12-14 y				
Tiotropium Respimat 5 µg QD (n = 65)	570 ± 48	139 ± 66	10 to 268	.04
Tiotropium Respimat 2.5 µg QD (n = 72)	584 ± 46	154 ± 64	27 to 280	.02
Placebo Respimat QD (n = 76)	431 ± 45			
15-17 y				
Tiotropium Respimat 5 µg QD (n = 66)	596 ± 54	211 ± 78	58 to 365	.007
Tiotropium Respimat 2.5 µg QD (n = 47)	506 ± 64	121 ± 85	−47 to 289	.16
Placebo Respimat QD (n = 61)	385 ± 56			

The full analysis set is shown. Results are adjusted for treatment, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Subgroup baseline mean FEV₁ is 2452 mL for 12 to 14 years and 3101 mL for 15 to 17 years. Treatment-by-subgroup interaction *P* value = .21.

Peak FEV_{1(0-3h)}, Peak FEV₁ within 3 hours after dosing; *QD*, once daily.

TABLE E2. *Post hoc* analysis of trough FEV₁ at week 24 by age group

Treatment	Adjusted mean ± SE (mL)	Active vs placebo Respimat		
		Adjusted mean of difference ± SE (mL)	95% CI	P value
12-14 y				
Tiotropium Respimat 5 µg QD (n = 65)	410 ± 51	103 ± 70	−35 to 240	.14
Tiotropium Respimat 2.5 µg QD (n = 71)	416 ± 49	109 ± 68	−25 to 243	.11
Placebo Respimat QD (n = 76)	308 ± 47			
15-17 y				
Tiotropium Respimat 5 µg QD (n = 66)	425 ± 59	125 ± 85	−42 to 292	.14
Tiotropium Respimat 2.5 µg QD (n = 47)	360 ± 70	60 ± 94	−124 to 244	.52
Placebo Respimat QD (n = 61)	299 ± 61			

The full analysis set is shown. Results are adjusted for treatment, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Subgroup baseline mean FEV₁ is 2452 mL for 12 to 14 years and 3101 mL for 15 to 17 years. Treatment-by-subgroup interaction *P* value = .70.

QD, Once daily.

TABLE E3. Secondary FVC efficacy end point responses at week 24

Treatment and parameter	Adjusted mean $\pm$ SE (mL)	Active vs placebo Respimat		
		Adjusted mean of difference $\pm$ SE (mL)	95% CI	P value
Peak FVC _(0-3h) (mL)				
Tiotropium Respimat 5 μ g QD (n = 131)	403 $\pm$ 43	72 $\pm$ 56	−37 to 182	.20
Tiotropium Respimat 2.5 μ g QD (n = 120)	419 $\pm$ 45	88 $\pm$ 57	−24 to 200	.12
Placebo Respimat QD (n = 137)	331 $\pm$ 41			
Trough FVC (mL)				
Tiotropium Respimat 5 μ g QD (n = 131)	316 $\pm$ 45	35 $\pm$ 59	−80 to 150	.55
Tiotropium Respimat 2.5 μ g QD (n = 119)	345 $\pm$ 47	63 $\pm$ 60	−55 to 181	.29
Placebo Respimat QD (n = 137)	281 $\pm$ 43			
FVC AUC _(0-3h) (mL)				
Tiotropium Respimat 5 μ g QD (n = 131)	311 $\pm$ 40	71 $\pm$ 53	−32 to 175	.18
Tiotropium Respimat 2.5 μ g QD (n = 119)	330 $\pm$ 42	90 $\pm$ 54	−16 to 196	.10
Placebo Respimat QD (n = 137)	240 $\pm$ 39			

The full analysis set is shown. Results are adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Common baseline mean FVC $\pm$ SD is 3559 $\pm$ 863 mL.

Peak FVC_(0-3h), Peak FVC within 3 hours after dosing; QD, once daily.

TABLE E4. Weekly mean rescue medication use over 48 weeks: weekly mean number of puffs of rescue medication during the daytime, nighttime, and entire 24-hour period

Treatment and parameter	Adjusted mean $\pm$ SE	Active vs placebo Respimat		
		Adjusted mean of difference $\pm$ SE	95% CI	P value
Week 24				
Daytime, no. of puffs				
Tiotropium Respimat 5 μ g QD (n = 122)	−0.215 $\pm$ 0.068	−0.009 $\pm$ 0.090	−0.186 to 0.168	.92
Tiotropium Respimat 2.5 μ g QD (n = 114)	−0.209 $\pm$ 0.071	−0.003 $\pm$ 0.092	−0.184 to 0.178	.98
Placebo Respimat QD (n = 132)	−0.206 $\pm$ 0.066			
Nighttime, no. of puffs				
Tiotropium Respimat 5 μ g QD (n = 124)	−0.032 $\pm$ 0.061	0.112 $\pm$ 0.081	−0.046 to 0.271	.17
Tiotropium Respimat 2.5 μ g QD (n = 110)	−0.122 $\pm$ 0.064	0.023 $\pm$ 0.083	−0.140 to 0.185	.79
Placebo Respimat QD (n = 132)	−0.144 $\pm$ 0.059			
24-h period, no. of puffs				
Tiotropium Respimat 5 μ g QD (n = 125)	−0.480 $\pm$ 0.100	0.044 $\pm$ 0.140	−0.232 to 0.319	.76
Tiotropium Respimat 2.5 μ g QD (n = 117)	−0.556 $\pm$ 0.104	−0.032 $\pm$ 0.143	−0.312 to 0.249	.83
Placebo Respimat QD (n = 135)	−0.524 $\pm$ 0.098			
Week 48				
Daytime, no. of puffs				
Tiotropium Respimat 5 μ g QD (n = 119)	−0.246 $\pm$ 0.068	−0.115 $\pm$ 0.091	−0.294 to 0.064	.21
Tiotropium Respimat 2.5 μ g QD (n = 104)	−0.229 $\pm$ 0.073	−0.098 $\pm$ 0.094	−0.283 to 0.086	.30
Placebo Respimat QD (n = 124)	−0.131 $\pm$ 0.067			
Nighttime, no. of puffs				
Tiotropium Respimat 5 μ g QD (n = 114)	−0.079 $\pm$ 0.062	−0.048 $\pm$ 0.082	−0.210 to 0.113	.56
Tiotropium Respimat 2.5 μ g QD (n = 105)	−0.188 $\pm$ 0.065	−0.157 $\pm$ 0.084	−0.322 to 0.008	.06
Placebo Respimat QD (n = 123)	−0.031 $\pm$ 0.060			
24-h period, no. of puffs				
Tiotropium Respimat 5 μ g QD (n = 123)	−0.648 $\pm$ 0.101	−0.277 $\pm$ 0.142	−0.555 to 0.001	.051
Tiotropium Respimat 2.5 μ g QD (n = 108)	−0.680 $\pm$ 0.106	−0.308 $\pm$ 0.146	−0.593 to −0.022	.04
Placebo Respimat QD (n = 126)	−0.372 $\pm$ 0.099			

The full analysis set is shown. Results are adjusted for treatment, week, baseline, treatment-by-week interaction, and baseline-by-week interaction. Common baseline mean $\pm$ SD is as follows: daytime = 0.757 $\pm$ 1.035; nighttime = 0.596 $\pm$ 0.894; and 24-hour period = 1.268 $\pm$ 1.739.

QD, Once daily.