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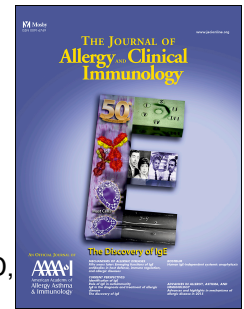
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A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma

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Abstract

Background: Studies in adults and adolescents have demonstrated that tiotropium is efficacious as an add-on therapy to inhaled corticosteroids (ICS) with or without other maintenance therapies in patients with moderate or severe symptomatic asthma.

Objective: To assess the efficacy and safety of once-daily tiotropium Respimat add-on therapy to high-dose ICS with 1 or more controller medications, or medium-dose ICS with 2 or more controller medications, in the first phase III trial of tiotropium in children with severe symptomatic asthma.

Methods: In this 12-week, double-blind, placebo-controlled, parallel-group trial, 401 participants aged 6-11 years were randomized to receive once-daily tiotropium 5 µg (2 puffs of 2.5 µg) or 2.5 µg (2 puffs of 1.25 µg), or placebo (2 puffs), administered through the Respimat device as add-on to background therapy.

Results: Compared with placebo, tiotropium 5 µg add-on therapy, but not 2.5 µg, improved the primary endpoint, peak forced expiratory volume in 1 second (FEV₁) within 3 hours after dosing (5 µg, 139 mL [95% CI, 75-203; $P < 0.001$]; 2.5 µg, 35 mL [95% CI, -28-99; $P = 0.27$]), and the key secondary endpoint, trough FEV₁ (5 µg, 87 mL [95% CI, 19-154; $P = 0.01$]; 2.5 µg, 18 mL [95% CI, -48-85; $P = 0.59$]). The safety and tolerability of tiotropium were comparable with those of placebo.

Conclusion: Once-daily tiotropium Respimat 5 µg improved lung function and was well tolerated as add-on therapy to ICS with other maintenance therapies in children with severe symptomatic asthma.

ClinicalTrials.gov no. NCT01634152

Clinical implications

Once-daily tiotropium Respimat 5 µg improves lung function, with safety and tolerability comparable with those of placebo, in children with severe symptomatic asthma.

Capsule summary

Once-daily tiotropium Respimat 5 µg as add-on therapy to ICS with other maintenance therapy has been shown for the first time to provide improved lung function in children with severe symptomatic asthma.

Key words: *Anticholinergic drug, asthma, asthma control, children, efficacy, FEV₁, lung function, Respimat, safety, tiotropium*

Abbreviations used

ACQ-IA: Interviewer-administered Asthma Control Questionnaire

AE: Adverse event

FEF_(25-75%): Forced expiratory flow between 25% and 75% of the forced vital capacity

FEV₁: Forced expiratory volume in 1 second

FEV_{1(0-3h)}: Forced expiratory volume in 1 second within 3 hours after dosing

FVC: Forced vital capacity

FVC_(0-3h): Forced vital capacity within 3 hours after dosing

ICS: Inhaled corticosteroids

LABA: Long-acting β_2 -agonist

LTRA: Leukotriene receptor antagonist

PEF: Peak expiratory flow

QD: Once daily

SD Standard deviation

SE Standard error

INTRODUCTION

Asthma is one of the most prevalent chronic diseases in children and adolescents,¹ affecting approximately 1 in 11 children in the UK² and 10% of adolescents in the USA.³

The once-daily long-acting anticholinergic bronchodilator tiotropium, delivered through the Respimat Soft Mist inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany), has demonstrated efficacy as an add-on therapy to inhaled corticosteroids (ICS) with or without other maintenance therapies in adults and adolescents. Based on this comprehensive clinical evidence, tiotropium is approved in several countries for the treatment of symptomatic asthma in adults⁴⁻⁹ and in the USA for the treatment of children aged ≥ 12 years.¹⁰⁻¹² Furthermore, the current Global Initiative for Asthma recommendations include tiotropium add-on therapy as part of steps 4 and 5 of the stepwise approach for patients aged ≥ 12 years.¹³

In children aged 6-11 years, the current Global Initiative for Asthma strategy recommends treatment with low-dose ICS, followed by a stepwise increase in ICS dose and/or additional (or second class of) maintenance therapy, such as a long-acting β_2 -agonist (LABA) or leukotriene receptor antagonist (LTRA), if control has not been achieved.¹³ However, treatment according to guidelines has been reported to result in sufficient asthma control in only around 50% of pediatric patients.^{3,14,15} This may be explained in most cases by low adherence to asthma treatment, which is of general concern in asthma patients and is notably poor in the pediatric population.¹⁶⁻²¹ Prescribing physicians may also not adhere consistently to treatment guidelines and may fail to prescribe appropriate therapy or provide adequate education for pediatric asthma patients, compounding the issue of poor asthma control.^{22,23} However, a proportion of patients have asthma that remains unstable or suffer from frequent exacerbations despite adhering to therapy and after addressing any comorbidities.²⁴⁻²⁶

Asthma exacerbations are linked with high morbidity, risk of mortality, and high treatment costs.²⁷ The risk of an asthma exacerbation increases with decreasing lung function, and recurring exacerbations may lead to the development of persistent asthma in children²⁸⁻³⁰ and significantly poorer lung function,²⁸ leading to a potentially higher risk of developing chronic obstructive pulmonary disease in adulthood.^{31,32} Pediatric patients with asthma also have higher rates of comorbidities, including depression and behavioral disorders, which rise further with increasing asthma severity.³³ Children with poorly controlled asthma are at a higher risk of suffering from sleep interference and nighttime awakenings, and may miss school days as a result.^{3,34-36} Overall, therefore, there is a need to improve adherence through better communication strategies,³⁷ and for additional options for the treatment of suboptimally controlled asthma.¹⁶ Safety considerations are particularly relevant in younger patients, and it is important that potential new therapies are both efficacious and well tolerated.

Here we present results from the first completed phase III study of once-daily tiotropium Respimat add-on therapy in children with asthma, in which the 5 µg and 2.5 µg doses were administered over 12 weeks in participants aged 6-11 years with severe symptomatic asthma.

METHODS

Study design

This was a 12-week, phase III, randomized, double-blind, placebo-controlled, parallel-group study (VivaTinA-asthma; NCT01634152) in children aged 6-11 years with severe symptomatic asthma. The study design is the same as that of the PensieTinA-asthma study in adolescents (aged 12-17 years) with severe symptomatic asthma¹² (Fig 1A), and is part of a larger pediatric investigational program that is linked to the investigational program of tiotropium conducted in adult and adolescent asthma patients. The trial was conducted at 92 sites in 17 countries (Argentina, Australia, Belgium, Brazil, Canada, Czech Republic, Germany, Guatemala, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Ukraine, and the USA).

Study population

Eligible participants were aged 6-11 years with at least a 6-month documented history of asthma at enrollment, and were symptomatic at screening and before randomization, defined as an interviewer-administered Asthma Control Questionnaire (ACQ-IA)³⁸ mean score of at least 1.5. Participants were required to: have been receiving maintenance therapy with ICS either at a stable high dose in combination with 1 or more controller medications (e.g. LABA or LTRA) or at a stable medium dose in combination with 2 or more controller medications (e.g. LABA and/or LTRA and/or sustained-release theophylline) for at least 4 weeks before screening; and have a prebronchodilator forced expiratory volume in 1 second (FEV₁) of 60-90% of predicted normal at screening, FEV₁ reversibility of 12% or more 15-30 minutes after 200 µg salbutamol (albuterol), and variability of absolute FEV₁ values from screening to randomization within ±30%.

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

Study procedures

Following a 4-week screening period, participants were randomized 1:1:1 to once-daily tiotropium 5 µg (2 puffs of 2.5 µg) or 2.5 µg (2 puffs of 1.25 µg), or placebo (2 puffs), administered through the Respimat Soft Mist inhaler over 12 weeks, with a 3-week follow-up period after the last dose of treatment (Fig 1A). Participants were required to show compliance of 80% or more (recorded with the AM3 asthma monitor device [electronic peak flow meter and eDiary; eResearch Technology, Höchberg, Germany]) at randomization to continue with the trial. Randomization was performed using a pseudo-random number generator with a supplied seed number, with a block size of 6.

Study treatments were administered as add-on to high-dose ICS maintenance therapy (>400 µg budesonide or equivalent) with 1 or more controller medications (e.g. LABA and/or LTRA) or medium-dose ICS (200-400 µg budesonide or equivalent) with 2 or more controller medications (e.g. LABA and/or LTRA and/or sustained-release theophylline). Participants self-administered medication once daily in the evening between 4 PM and 7 PM, taking ICS therapy first (if usually administered in the evening), then other controller therapies, followed by trial medication. Open-label salbutamol hydrofluoroalkane metered-dose inhalers (100 µg per actuation) were provided as rescue medication during the screening, treatment, and follow-up periods. Permitted concomitant medications for the treatment of acute asthma exacerbations included: temporary increases in the dose of ICS; temporary addition of systemic corticosteroids, short-acting theophylline preparations, systemic β_2 -agonists, or inhaled short-acting anticholinergics; and antibiotics.

The study complied with the principles of the Declaration of Helsinki and the International Conference on Harmonisation for Good Clinical Practice Guidelines. Before trial initiation,

the trial protocol, participant and parent/guardian information sheets, and consent forms were reviewed and approved by the independent ethics committee and/or institutional review board of each participating institution. Before participation in the trial, written, informed consent was received from each participant's parent or guardian, and informed assent suitable for this age group was obtained from participants.

Study endpoints

All primary and secondary efficacy endpoints were analyzed at week 12. The primary efficacy endpoint was change from baseline (response) in peak FEV_1 within 3 hours after dosing ($FEV_{1(0-3h)}$). The key secondary efficacy endpoint was trough FEV_1 response (measured at the end of the dosing interval, 10 minutes before the administration of the next dose of trial medication).

Other secondary efficacy endpoints included: peak forced vital capacity (FVC) response within 3 hours after dosing ($FVC_{(0-3h)}$) and trough FVC response; ACQ-IA score and responder rate; weekly mean asthma symptom-free days response; weekly mean rescue medication use response; and weekly mean evening peak expiratory flow (PEF) response, measured at home.

Further efficacy endpoints included: mean forced expiratory flow between 25% and 75% of the FVC ($FEF_{(25-75\%)}$) response at each time point during the 12-week treatment period; peak $FEV_{1(0-3h)}$ and trough FEV_1 percent predicted responses at week 12; and time to first episode of asthma worsening (prespecified as exacerbation; defined as a progressive increase in 1 or more asthma symptoms that were outside a participant's usual day-to-day variation, lasting for 2 or more consecutive days, and/or a decrease in a participant's best morning PEF of 30% or more from their mean morning PEF for 2 or more consecutive days, recorded as described below) and first severe exacerbation (defined as an episode of asthma worsening that required

treatment with systemic corticosteroids for 3 or more consecutive days) over the 12-week treatment period.

Post hoc analyses were performed on in-clinic trough PEF responses at week 12 and trough FEV₁/FVC responses over 12 weeks.

Adverse events were recorded until 30 days after the last dose of trial medication to assess safety and tolerability.

Study assessments

In-clinic lung function testing was conducted at screening and at every visit during the treatment period. Spirometers met American Thoracic Society and European Respiratory Society criteria.³⁹ At each time point, in-clinic FEV₁ and FVC responses were measured from at least 3 and up to 8 spirometric maneuvers; the highest FEV₁ and FVC responses from an acceptable maneuver were selected, regardless of whether they came from the same or different maneuvers.

The ACQ-IA was completed at screening and at every visit during the treatment period.

Rescue medication use, treatment compliance, and any worsening of asthma symptoms were measured by participants at home using the AM3 device. Home-based FEV₁ and PEF were measured twice daily with the AM3 device.

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, defined as all randomized participants who 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; $\alpha = 0.025$). First, the superiority of tiotropium 5 μg versus placebo for peak $\text{FEV}_{1(0-3\text{h})}$ response at week 12 was tested. If the corresponding null hypothesis was rejected, then the same null hypothesis for the 2.5 μg dose was tested. Testing for the superiority of tiotropium 5 μg , and then 2.5 μg , versus placebo for the key secondary endpoint was then conducted. If at any stage the previous step was not successful, further analyses were considered descriptive, i.e. non-confirmatory, only.

All lung function endpoints, ACQ-IA scores, and endpoints from the AM3 device were analyzed 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”. Baseline was defined as the pretreatment value measured at randomization in the evening 10 minutes before the evening dose of the participant’s usual asthma medication and first dose of trial medication for lung function endpoints, and as the average of the 7 days immediately preceding randomization for endpoints measured using the AM3 device. “Patient” was included as random effect. ACQ-IA responder analyses were performed using the minimal clinically important difference of 0.5.⁴⁰ Time to first severe exacerbation and time to first episode of asthma worsening were analyzed using Cox’s proportional hazards regression model with “treatment” fitted as an effect. Safety analyses were descriptive in nature.

Sample size was determined using a conservative 2-group *t*-test with a power of 80% and a probability of a type I error of 2.5% (1-sided). It was determined that 125 participants per treatment group were required to detect a difference of 150 mL in peak $\text{FEV}_{1(0-3\text{h})}$ response, assuming a common standard deviation (SD) of 420 mL.

RESULTS

A total of 401 participants were randomized; 392 (97.8%) completed the 12-week treatment period, 1 (0.2%) was not treated, and 8 (2.0%) prematurely discontinued study medication (Fig 1B). Mean treatment exposure $\pm$ SD was 86.1 ± 9.1 days, and mean adherence with study medication $\pm$ SD was $82.0 \pm 21.6\%$, recorded with the AM3 device.

Baseline participant demographics and disease characteristics

Overall, baseline demographics and disease characteristics were balanced between treatment groups (Table I). The majority of participants were male (69.8%), 36.3% were aged 6-8 years, and 63.8% were aged 9-11 years, with a mean age $\pm$ SD of 9.0 ± 1.6 years overall. Mean asthma duration $\pm$ SD was 4.9 ± 2.5 years, and 7.8% of participants had been exposed to second-hand smoke. In the 3 months before screening, all participants received treatment with ICS, 78.8% received a LABA, and 85.0% received an LTRA. During the treatment period, 30.2% of participants received ICS plus 1 other controller, 69.8% received ICS plus 2 other controllers, 78.5% received a LABA, and 84.8% received an LTRA.

Efficacy

Primary endpoint

Tiotropium provided a statistically significant improvement versus placebo in the primary endpoint, peak $FEV_{1(0-3h)}$ response at week 12, with the 5 μ g dose (adjusted mean difference: 139 mL; 95% CI, 75-203; $P < 0.001$) but not with the 2.5 μ g dose (adjusted mean difference: 35 mL; 95% CI, -28-99; $P = 0.27$) (Fig 2A and Table II); all subsequent analyses were therefore considered descriptive.

Key secondary endpoint

Improvements in trough FEV₁ response versus placebo after 12 weeks of treatment were statistically significant with the 5 µg dose (adjusted mean difference: 87 mL; 95% CI, 19-154; $P = 0.01$) but not with the 2.5 µg dose (adjusted mean difference: 18 mL; 95% CI, -48-85; $P = 0.59$) (Fig 2B).

Other secondary endpoints

Additional secondary endpoints are presented in Table II. No statistically significant differences compared with placebo were observed for adjusted mean peak FVC_(0-3h) and trough FVC responses at week 12 following treatment with either dose of tiotropium. Changes in adjusted mean ACQ-IA score with both doses of tiotropium at week 12 were similar to those seen with placebo; the majority of participants in all treatment groups were responders (ACQ-IA improvement of at least 0.5) after 12 weeks (tiotropium 5 µg, 80.8%; tiotropium 2.5 µg, 79.4%; placebo, 76.9%). The adjusted mean number of asthma symptom-free days was increased by a similar degree in all treatment groups after 12 weeks, and there was a non-significant difference versus placebo in adjusted mean daytime rescue medication use with both tiotropium doses (Table II). Adjusted mean differences in weekly mean evening PEF responses following tiotropium administration, measured at home using an unsupervised AM3 device (Table II), were inconsistent and did not correlate with the *post hoc* in-clinic trough PEF results (see below). When analyzed by age group, the adjusted mean difference versus placebo in weekly mean evening PEF response with tiotropium was inconsistent (for example, in participants aged 6-8 years: tiotropium 5 µg: 6.58 L/min; 95% CI, -9.04-22.19; $P = 0.41$; tiotropium 2.5 µg: 5.91 L/min; 95% CI, -8.11-19.93; $P = 0.41$; and in participants aged 9-11 years: tiotropium 5 µg: -10.66 L/min; 95% CI, -22.92-1.61; $P = 0.09$; tiotropium 2.5 µg: -2.45 L/min; 95% CI, -15.39-10.49; $P = 0.71$).

Further endpoints

Post hoc analysis of in-clinic trough PEF response at week 12 demonstrated a statistically significant improvement compared with placebo for tiotropium 5 µg (adjusted mean difference versus placebo: 13.80 L; 95% CI, 3.47-24.13; $P = 0.009$); however, the difference was not significant with the 2.5 µg dose (adjusted mean difference versus placebo: 9.55 L; 95% CI, -0.67-19.76; $P = 0.07$).

Adjusted mean differences in $FEF_{(25-75\%)}$ responses between both tiotropium doses and placebo were statistically significant at all time points throughout the study period, with the exception of the 2.5 µg dose at week 8 (Fig 3). Improvements in adjusted mean peak $FEV_{1(0-3h)}$ percent predicted responses were statistically significant compared with placebo for both tiotropium doses at week 12; improvements in adjusted mean trough FEV_1 percent predicted responses were statistically significant with tiotropium 5 µg only (Fig 4). *Post hoc* analyses of adjusted mean trough FEV_1/FVC responses demonstrated statistically significant improvements at all time points versus placebo with both tiotropium doses, with the exception of tiotropium 2.5 µg at week 8 (Fig 5).

Seven participants (5.4%) in the tiotropium 5 µg group, 3 participants (2.2%) in the tiotropium 2.5 µg group, and 8 participants (6.0%) in the placebo group experienced a severe asthma exacerbation during the treatment period. At least 1 episode of asthma worsening was reported for 35 participants (26.9%) receiving tiotropium 5 µg, 29 participants (21.3%) receiving tiotropium 2.5 µg, and 47 participants (35.1%) receiving placebo. The risk of severe asthma exacerbations and episodes of asthma worsening was lower with tiotropium than with placebo (hazard ratios <1); however, this difference was significant only for episodes of asthma worsening with tiotropium 2.5 µg versus placebo ($P = 0.006$).

Safety and tolerability

The overall incidence of adverse events was lower with tiotropium 5 µg (n = 56; 43.1%) and 2.5 µg (n = 59; 43.4%) compared with placebo (n = 66; 49.3%). The majority of adverse events were mild or moderate in intensity and the most frequently reported adverse events, by preferred term, included asthma, decreased PEF rate, nasopharyngitis, and respiratory tract infection (Table III). Investigator-defined drug-related adverse events were reported for 3 participants: tiotropium 5 µg, n = 1 (dizziness); placebo, n = 2 (cough, n = 1; asthma, cough, decreased appetite, fatigue, and metabolic cardiomyopathy, n = 1). Adverse events leading to discontinuation were reported for 4 participants receiving tiotropium 5 µg (asthma, n = 2) or placebo (cough, n = 1; metabolic cardiomyopathy, n = 1). Eight participants reported serious adverse events, none of which was considered to be related to the study drug: tiotropium 5 µg, n = 4 (asthma, n = 3; appendicitis, n = 1); tiotropium 2.5 µg, n = 2 (asthma, n = 1; epilepsy, n = 1); placebo, n = 2 (asthma, n = 1; asthmatic crisis, n = 1). No deaths occurred during the trial.

DISCUSSION

In this phase III study in children aged 6-11 years with severe symptomatic asthma, once-daily tiotropium Respimat add-on to ICS plus 1 or more controller medications improved lung function compared with placebo. Statistically significant improvements in the primary endpoint, peak $FEV_{1(0-3h)}$ response, were observed with tiotropium 5 µg only so all subsequent analyses, including those for the key secondary endpoint of trough FEV_1 response, were considered descriptive. Likewise, improvements in the key secondary endpoint, trough FEV_1 response, were statistically significant with tiotropium 5 µg only. Peak $FVC_{(0-3h)}$ and trough FVC responses with tiotropium were not statistically significant. The safety and tolerability of tiotropium were comparable with those of placebo, consistent with previously published data in adults and adolescents.^{9,11,12}

The significant improvements in peak and trough FEV_1 responses observed with tiotropium in this study of children with severe symptomatic asthma are consistent with published data in adults and adolescents with comparable asthma severity, suggesting that consistent findings are generally observed across the tiotropium trial program in both adult and pediatric asthma patients. In the PrimoTinA-asthma studies in adults with severe symptomatic asthma, tiotropium 5 µg led to significant improvements in both peak and trough FEV_1 responses at weeks 24 and 48.⁹ The PensieTinA-asthma study in adolescents with severe symptomatic asthma demonstrated improvements with tiotropium versus placebo in several domains of lung function, including peak and trough FEV_1 responses, $FEF_{(25-75\%)}$ responses, and morning and evening PEF responses; however, findings were not statistically significant as the trial did not meet the primary endpoint of peak $FEV_{1(0-3h)}$ response at week 12.¹²

Changes in ACQ-IA score in this study were similar between tiotropium and placebo, with more than 75% of participants in all treatment arms showing an ACQ response (improvement

of at least 0.5). These responder rates are similar to those observed in adolescent patients^{11,12} and greater than those observed in adults.⁵ These data are in line with findings that studies of a second or third controller added on to ICS are unlikely to achieve the minimum important difference (0.5) in ACQ score versus placebo; this may be attributable to improved adherence with background medication in the trial setting, resulting in improvements from baseline in all treatment arms.⁴¹ Interestingly, despite improvements being observed in asthma control in all treatment arms, a reduction in respiratory adverse events (asthma and decreased PEF rate) was observed with tiotropium compared with placebo, which may be indicative of improved asthma control, as respiratory adverse events can be considered both a safety and an efficacy parameter.

Statistically significant improvements in FEF_(25-75%) response were observed versus placebo with tiotropium across the trial duration (with the exception of tiotropium 2.5 µg at week 8). FEF_(25-75%) is a reflection of small airway function,^{42,43} and these improvements in conjunction with the observed improvements in FEV₁ support the efficacy of tiotropium in children with severe symptomatic asthma.

Children with severe asthma have been reported to maintain similar levels of lung function to children with less severe asthma, despite having frequent asthma symptoms.⁴⁴ However, in the present study, we observed statistically significant improvements with tiotropium in relation to spirometry but no significant improvements in asthma symptoms. Furthermore, it has been shown that FEV₁/FVC significantly decreases as asthma severity increases in children,⁴⁴ and that decreases in FEV₁/FVC ratio are linked to an increased risk of exacerbations,⁴⁵ suggesting that the improvements in FEV₁/FVC with tiotropium versus placebo observed in our study may be of importance.

In-clinic data demonstrated a significant improvement in trough PEF response with tiotropium 5 µg, whereas analysis of home-based, unsupervised measurements of evening PEF using the AM3 device revealed no significant differences between tiotropium and placebo, overall and by age group. This is in contrast to the significant improvements versus placebo seen in home-based measurements of evening PEF in adolescents with tiotropium 5 µg¹² and in adults with tiotropium 5 µg and 2.5 µg.⁵ Comparison with these other phase III data suggest that the young participants in the current trial may have experienced difficulty obtaining accurate PEF measurements at home in the absence of supervision by a medical professional.⁴⁶

Data on the efficacy and safety of ICS plus tiotropium compared with the combination of ICS plus LABA are becoming available.^{5,47,48} The MezzoTinA-asthma study in adults with moderate symptomatic asthma demonstrated that tiotropium shows efficacy and tolerability comparable with those of the LABA salmeterol⁵; however, data on the efficacy of ICS plus LABA versus ICS plus anticholinergic drugs in children are lacking. Surveillance studies have provided further reassuring information in relation to the safety and tolerability of ICS plus LABA in pediatric patients.⁴⁹⁻⁵²

Poor medication adherence is a common issue in children, leading to suboptimal asthma control.^{53,54} Once-daily dosing with other asthma medications has been shown to improve adherence versus twice-daily dosing.⁵⁵ Once-daily dosing of tiotropium may therefore be of benefit in the stepwise addition of treatments for uncontrolled asthma in children aged 6-11 years with severe symptomatic asthma,¹³ particularly when a LABA is unsuitable or ineffective.^{56,57} The RespiMat Soft Mist inhaler may provide further benefits for pediatric patients with asthma, since it is easy to use and delivers a dose independent of a patient's variable inspiratory flow, which facilitates superior lung deposition compared with

alternative inhaler devices.⁵⁸ However, effective and repeated instruction on inhaler technique remains of considerable importance, particularly in pediatric patients.^{59,60}

The results of this trial should be interpreted in the light of certain limitations. Improved adherence to background medication in the clinical trial environment can lead to a marked placebo response.⁴¹ Additionally, the short duration of the study limits the analysis of severe or seasonal exacerbations, asthma worsening, and asthma control endpoints, and may have affected the lung function endpoints. Lung function is the most sensitive assessment for bronchodilator medications, and was therefore selected as the primary endpoint of this study. However, as a result, this trial was not fully powered for the analysis of FEV₁/FVC, which may provide a more accurate reflection of asthma severity in children than FEV₁.⁴⁴ Similarly, this trial was not powered for the analysis of important patient-reported outcomes such as ACQ score or exacerbations, which require larger, long-term studies to assess. Furthermore, although smaller, short-term studies can provide valuable information over a short time-frame, they may overestimate the magnitude of treatment effects and can require validation from larger confirmatory studies.⁶¹

Nevertheless, the relatively large participant population in this trial increases the reliability of the study findings. These data add to the body of evidence from trials in adults and adolescents that demonstrates the efficacy, safety, and tolerability of tiotropium Respimat in asthma, and provides insight into its real-world efficacy, as tiotropium was studied as an add-on to participants' usual background therapy.

In conclusion, once-daily tiotropium Respimat 5 µg improves lung function and is a well-tolerated bronchodilator when added to ICS plus 1 or more controller medications in children aged 6-11 years with severe symptomatic asthma.

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References

1. Masoli M, Fabian D, Holt S, Beasley R, Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59:469-78.
2. Asthma UK. Asthma facts and FAQs. 2014. Available at: <http://www.asthma.org.uk/asthma-facts-and-statistics>. Accessed May 19, 2016.
3. Schmier JK, Manjunath R, Halpern MT, Jones ML, Thompson K, Diette GB. The impact of inadequately controlled asthma in urban children on quality of life and productivity. *Ann Allergy Asthma Immunol* 2007;98:245-51.
4. Paggiaro P, Halpin DM, Buhl R, Engel M, Zubek VB, Blahova Z, et al. The effect of tiotropium in symptomatic asthma despite low- to medium-dose inhaled corticosteroids: a randomized controlled trial. *J Allergy Clin Immunol Pract* 2016;4:104-13.e2.
5. Kerstjens HAM, Casale TB, Bleecker ER, Meltzer EO, Pizzichini E, Schmidt O, et al. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. *Lancet Respir Med* 2015;3:367-76.
6. Beeh KM, Moroni-Zentgraf P, Ablinger O, Hollaenderova Z, Unseld A, Engel M, et al. Tiotropium Respimat[®] in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma. *Respir Res* 2014;15:61.
7. Timmer W, Moroni-Zentgraf P, Cornelissen P, Unseld A, Pizzichini E, Buhl R. Once-daily tiotropium Respimat[®] 5 µg is an efficacious 24-h bronchodilator in adults with symptomatic asthma. *Respir Med* 2015;109:329-38.

8. Ohta K, Ichinose M, Tohda Y, Engel M, Moroni-Zentgraf P, Kunimitsu S, et al. Long-term once-daily tiotropium Respimat[®] is well tolerated and maintains efficacy over 52 weeks in patients with symptomatic asthma in Japan: a randomised, placebo-controlled study. *PLoS One* 2015;10:e0124109.
9. Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012;367:1198-207.
10. Vogelberg C, Engel M, Moroni-Zentgraf P, Leonaviciute-Klimantaviciene M, Sigmund R, Downie J, et al. Tiotropium in asthmatic adolescents symptomatic despite inhaled corticosteroids: a randomised dose-ranging study. *Respir Med* 2014;108:1268-76.
11. Hamelmann E, Bateman ED, Vogelberg C, Szeffler SJ, Vandewalker M, Moroni-Zentgraf P, et al. Tiotropium add-on therapy in adolescents with moderate asthma: a 1-year randomized controlled trial. *J Allergy Clin Immunol* 2016;138:441-50.e8.
12. Hamelmann E, Bernstein JA, Vandewalker M, Moroni-Zentgraf P, Verri D, Unseld A, et al. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma. *Eur Respir J* 2016; [Epub ahead of print].
13. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2016. 2016. Available at: <http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed November 7, 2016.
14. Price D, Ryan D, Pearce L, Bawden R, Freeman D, Thomas M, et al. The burden of paediatric asthma is higher than health professionals think: results from the Asthma In Real Life (AIR) study. *Prim Care Respir J* 2002;11:30-3.

15. Gustafsson PM, Watson L, Davis KJ, Rabe KF. Poor asthma control in children: evidence from epidemiological surveys and implications for clinical practice. *Int J Clin Pract* 2006;60:321-34.
16. Anderson WC, III, Szeffler SJ. New and future strategies to improve asthma control in children. *J Allergy Clin Immunol* 2015;136:848-59.
17. Rau JL. Determinants of patient adherence to an aerosol regimen. *Respir Care* 2005;50:1346-56.
18. Weinstein AG. The potential of asthma adherence management to enhance asthma guidelines. *Ann Allergy Asthma Immunol* 2011;106:283-91.
19. Desai M, Oppenheimer JJ. Medication adherence in the asthmatic child and adolescent. *Curr Allergy Asthma Rep* 2011;11:454-64.
20. Hedlin G, Bush A, Lødrup Carlsen K, Wennergren G, De Benedictis FM, Melén E, et al. Problematic severe asthma in children, not one problem but many: a GA²LEN initiative. *Eur Respir J* 2010;36:196-201.
21. de Benedictis D, Bush A. The challenge of asthma in adolescence. *Pediatr Pulmonol* 2007;42:683-92.
22. Montella S, Baraldi E, Bruzzese D, Mirra V, Di Giorgio A, Santamaria F, et al. What drives prescribing of asthma medication to preschool wheezing children? A primary care study. *Pediatr Pulmonol* 2013;48:1160-70.
23. Thomas M, Murray-Thomas T, Fan T, Williams T, Taylor S. Prescribing patterns of asthma controller therapy for children in UK primary care: a cross-sectional observational study. *BMC Pulm Med* 2010;10:29.

24. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJH, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836-44.
25. Demoly P, Paggiaro P, Plaza V, Bolge SC, Kannan H, Sohler B, et al. Prevalence of asthma control among adults in France, Germany, Italy, Spain and the UK. *Eur Respir Rev* 2009;18:105-12.
26. Partridge MR, Dal Negro RW, Olivieri D. Understanding patients with asthma and COPD: insights from a European study. *Prim Care Respir J* 2011;20:315-23.
27. Custovic A, Johnston SL, Pavord I, Gaga M, Fabbri L, Bel EH, et al. EAACI position statement on asthma exacerbations and severe asthma. *Allergy* 2013;68:1520-31.
28. Belgrave DCM, Buchan I, Bishop C, Lowe L, Simpson A, Custovic A. Trajectories of lung function during childhood. *Am J Respir Crit Care Med* 2014;189:1101-9.
29. Teach SJ, Gergen PJ, Szeffler SJ, Mitchell HE, Calatroni A, Wildfire J, et al. Seasonal risk factors for asthma exacerbations among inner-city children. *J Allergy Clin Immunol* 2015;135:1465-73.e5.
30. Fuhlbrigge AL, Kitch BT, Paltiel AD, Kuntz KM, Neumann PJ, Dockery DW, et al. FEV₁ is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol* 2001;107:61-7.
31. Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015;373:111-22.

32. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;374:1842-52.
33. Blackman JA, Gurka MJ. Developmental and behavioral comorbidities of asthma in children. *J Dev Behav Pediatr* 2007;28:92-9.
34. Diette GB, Markson L, Skinner EA, Nguyen TTH, Algatt-Bergstrom P, Wu AW. Nocturnal asthma in children affects school attendance, school performance, and parents' work attendance. *Arch Pediatr Adolesc Med* 2000;154:923-8.
35. Gustafsson D, Olofsson N, Andersson F, Lindberg B, Schollin J. Intervention models on psycho-social health in families with an asthmatic child. *Pediatr Allergy Immunol* 2000;11:241-5.
36. Stores G, Ellis AJ, Wiggs L, Crawford C, Thomson A. Sleep and psychological disturbance in nocturnal asthma. *Arch Dis Child* 1998;78:413-9.
37. Cabana MD, Slish KK, Evans D, Mellins RB, Brown RW, Lin X, et al. Impact of physician asthma care education on patient outcomes. *Pediatrics* 2006;117:2149-57.
38. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
39. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
40. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99:553-8.

41. Bateman ED, Esser D, Chirila C, Fernandez M, Fowler M, Moroni-Zentgraf P, et al. Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire: systematic review and network meta-analysis. *J Allergy Clin Immunol* 2015;136:914-22.
42. Rao DR, Gaffin JM, Baxi SN, Sheehan WJ, Hoffman EB, Phipatanakul W. The utility of forced expiratory flow between 25% and 75% of vital capacity in predicting childhood asthma morbidity and severity. *J Asthma* 2012;49:586-92.
43. Simon MR, Chinchilli VM, Phillips BR, Sorkness CA, Lemanske RF, Jr., Szeffler SJ, et al. Forced expiratory flow between 25% and 75% of vital capacity and FEV₁/forced vital capacity ratio in relation to clinical and physiological parameters in asthmatic children with normal FEV₁ values. *J Allergy Clin Immunol* 2010;126:527-34.e8.
44. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF, Jr., Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med* 2004;170:426-32.
45. Quezada W, Kwak ES, Reibman J, Rogers L, Mastronarde J, Teague WG, et al. Predictors of asthma exacerbation among patients with poorly controlled asthma despite inhaled corticosteroid treatment. *Ann Allergy Asthma Immunol* 2016;116:112-7.
46. Orrell-Valente JK, Jarlsberg LG, Hill LG, Cabana MD. At what age do children start taking daily asthma medicines on their own? *Pediatrics* 2008;122:e1186-e1192.
47. Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol* 2011;128:315-22.

48. Kew KM, Evans DJW, Allison DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta₂-agonists (LABA) for adults with asthma. *Cochrane Database Syst Rev* 2015;6:CD011438.
49. Cates CJ, Oleszczuk M, Stovold E, Wieland LS. Safety of regular formoterol or salmeterol in children with asthma: an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2012;10:CD010005.
50. Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. *N Engl J Med* 2011;364:2473-5.
51. Stempel DA, Szeffler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma. *N Engl J Med* 2016;375:840-9.
52. Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, et al. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. *N Engl J Med* 2016;374:1822-30.
53. Burgess S, Sly P, Devadason S. Adherence with preventive medication in childhood asthma. *Pulm Med* 2011;2011:973849.
54. Navaratnam P, Friedman HS, Urdaneta E. The impact of adherence and disease control on resource use and charges in patients with mild asthma managed on inhaled corticosteroid agents. *Patient Prefer Adherence* 2010;4:197-205.
55. Price D, Robertson A, Bullen K, Rand C, Horne R, Staudinger H. Improved adherence with once-daily versus twice-daily dosing of mometasone furoate administered via a dry powder inhaler: a randomized open-label study. *BMC Pulm Med* 2010;10:1.

- 526 56. Cates CJ, Wieland LS, Oleszczuk M, Kew KM. Safety of regular formoterol or
527 salmeterol in adults with asthma: an overview of Cochrane reviews. Cochrane Database
528 Syst Rev 2014;2:CD010314.
- 529 57. Simons FER, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of
530 salmeterol in adolescents with exercise-induced asthma using concurrent inhaled
531 glucocorticoid treatment. Pediatrics 1997;99:655-9.
- 532 58. Dalby R, Spallek M, Voshaar T. A review of the development of Respimat[®] Soft Mist[™]
533 Inhaler. Int J Pharm 2004;283:1-9.
- 534 59. Kamps AWA, Brand PLP, Roorda RJ. Determinants of correct inhalation technique in
535 children attending a hospital-based asthma clinic. Acta Paediatr 2002;91:159-63.
- 536 60. Verver S, Poelman M, Bögels A, Chisholm SL, Dekker FW. Effects of instruction by
537 practice assistants on inhaler technique and respiratory symptoms of patients. A
538 controlled randomized videotaped intervention study. Fam Pract 1996;13:35-40.
- 539 61. Hackshaw A. Small studies: strengths and limitations. Eur Respir J 2008;32:1141-3.

TABLE I. Baseline participant demographics and disease characteristics

	Tiotropium 5 µg QD (n = 130)	Tiotropium 2.5 µg QD (n = 136)	Placebo QD (n = 134)
Age (y)*	9.2 ± 1.6	8.8 ± 1.7	9.1 ± 1.6
Age (y), no. (%)			
6-8	36 (27.7)	60 (44.1)	49 (36.6)
9-11	94 (72.3)	76 (55.9)	85 (63.4)
Sex, no. (%)			
Male	90 (69.2)	96 (70.6)	93 (69.4)
Body mass index (kg/m ²)*	18.6 ± 3.7	17.8 ± 3.5	17.9 ± 3.6
Exposure to second-hand smoke, no. (%)			
No	118 (90.8)	126 (92.6)	125 (93.3)
Yes	12 (9.2)	10 (7.4)	9 (6.7)
Duration of asthma (y)*	5.07 ± 2.59	4.96 ± 2.47	4.77 ± 2.39
Prebronchodilator FEV ₁ at screening*			
Actual (mL)	1512 ± 316	1442 ± 314	1469 ± 291
Percent predicted	76.6 ± 8.0	76.8 ± 7.7	76.2 ± 8.1

FEV ₁ reversibility at screening (%)*	27.6 ± 13.1	27.5 ± 13.2	27.1 ± 13.5
FEV ₁ *			
Actual (mL)	1595 ± 353	1569 ± 336	1552 ± 350
Percent predicted	80.9 ± 11.8	83.6 ± 10.9	80.3 ± 11.6
FVC*			
Actual (mL)	2093 ± 474	2057 ± 494	2013 ± 457
Percent predicted	92.0 ± 14.1	94.7 ± 12.9	90.3 ± 13.6
FEF _(25-75%) *			
Actual (L/s)	1.4 ± 0.6	1.4 ± 0.5	1.4 ± 0.6
Percent predicted	60.0 ± 21.9	62.3 ± 23.3	61.6 ± 24.4
Weekly mean evening PEF (L/min)*	235.0 ± 67.7	236.5 ± 58.7	226.3 ± 58.0
ACQ-IA score*	2.0 ± 0.4	1.9 ± 0.3	2.0 ± 0.4
ICS dose of stable maintenance treatment (μg)*†	453 ± 250	439 ± 218	480 ± 240
Concomitant therapies in the 3 months before screening, no. (%)			
LABA	101 (77.7)	113 (83.1)	101 (75.4)
LTRA	114 (87.7)	113 (83.1)	113 (84.3)
Concomitant therapies during the treatment period, no. (%)			

LABA	100 (76.9)	113 (83.1)	101 (75.4)
LTRA	113 (86.9)	113 (83.1)	113 (84.3)

The treated set is shown.

ACQ-IA, Interviewer-administered Asthma Control Questionnaire; *FEF_(25-75%)*, Forced expiratory flow between 25% and 75% of the forced vital capacity; *FEV₁*, Forced expiratory volume in 1 second; *FVC*, Forced vital capacity; *ICS*, Inhaled corticosteroids; *LABA*, Long-acting β_2 -agonist; *LTRA*, Leukotriene receptor antagonist; *PEF*, Peak expiratory flow; *QD*, Once daily.

*Values are means $\pm$ standard deviation.

†Budesonide or equivalent dose.

TABLE II. Primary and other secondary endpoints at week 12

Treatment and parameter	Adjusted mean $\pm$ SE (mL)	Active versus placebo Respimat		
		Adjusted mean of difference $\pm$ SE (mL)	95% CI	<i>P</i> value
Peak FEV _{1(0-3h)} response (mL)				
Tiotropium Respimat 5 μ g QD (n = 128)	391 $\pm$ 26	139 $\pm$ 33	75-203	<0.0001
Tiotropium Respimat 2.5 μ g QD (n = 135)	287 $\pm$ 25	35 $\pm$ 32	−28-99	0.27
Placebo Respimat QD (n = 130)	252 $\pm$ 25			
Peak FVC _(0-3h) response (mL)				
Tiotropium Respimat 5 μ g QD (n = 128)	275 $\pm$ 28	30 $\pm$ 36	−40-101	0.40
Tiotropium Respimat 2.5 μ g QD (n = 135)	201 $\pm$ 27	−43 $\pm$ 36	−113-27	0.23
Placebo Respimat QD (n = 130)	244 $\pm$ 28			
Trough FVC response (mL)				
Tiotropium Respimat 5 μ g QD (n = 128)	150 $\pm$ 30	9 $\pm$ 38	−66-83	0.82
Tiotropium Respimat 2.5 μ g QD (n = 135)	94 $\pm$ 29	−48 $\pm$ 37	−121-26	0.20
Placebo Respimat QD (n = 130)	141 $\pm$ 29			
ACQ-IA score				

Tiotropium Respimat 5 µg QD (n = 126)	0.95 ± 0.06	-0.08 ± 0.08	-0.23-0.08	0.32
Tiotropium Respimat 2.5 µg QD (n = 136)	1.05 ± 0.06	0.02 ± 0.08	-0.13-0.17	0.80
Placebo Respimat QD (n = 130)	1.03 ± 0.06			
Weekly mean asthma symptom-free days response				
Tiotropium Respimat 5 µg QD (n = 127)	0.17 ± 0.03	0.03 ± 0.04	-0.06-0.11	0.55
Tiotropium Respimat 2.5 µg QD (n = 136)	0.13 ± 0.03	-0.02 ± 0.04	-0.10-0.06	0.68
Placebo Respimat QD (n = 128)	0.15 ± 0.03			
Weekly mean daytime rescue medication use response (puffs)				
Tiotropium Respimat 5 µg QD (n = 126)	-0.37 ± 0.06	-0.09 ± 0.08	-0.23-0.06	0.25
Tiotropium Respimat 2.5 µg QD (n = 136)	-0.29 ± 0.06	-0.02 ± 0.07	-0.16-0.13	0.84
Placebo Respimat QD (n = 127)	-0.28 ± 0.06			
Weekly mean evening PEF response measured at home (L/min)				
Tiotropium Respimat 5 µg QD (n = 126)	3.79 ± 3.73	-4.11 ± 4.87	-13.66-5.44	0.40
Tiotropium Respimat 2.5 µg QD (n = 136)	8.46 ± 3.60	0.57 ± 4.81	-8.87-10.00	0.91
Placebo Respimat QD (n = 127)	7.89 ± 3.72			

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 $\pm$ standard deviation: $FEV_1 = 1572 \pm 346$; $FVC = 2.05 \pm 0.48$; weekly mean asthma symptom-free days = 0.27 ± 0.35 ; daytime rescue medication use = 0.70 ± 0.78 ; weekly mean evening PEF = 232.60 ± 61.56 .

ACQ-IA, Interviewer-administered Asthma Control Questionnaire; $FEV_{1(0-3h)}$, Forced expiratory volume in 1 second within 3 hours after dosing; *FVC*, Forced vital capacity; $FVC_{(0-3h)}$, Forced vital capacity within 3 hours after dosing; *PEF*, Peak expiratory flow; *QD*, Once daily.

TABLE III. Overall summary of adverse events

	Tiotropium 5 µg QD (n = 130)	Tiotropium 2.5 µg QD (n = 136)	Placebo QD (n = 134)	Total (n = 400)
Participants with any AE	56 (43.1)	59 (43.4)	66 (49.3)	181 (45.3)
Participants with investigator-defined drug-related AEs	1 (0.8)	0	2 (1.5)	3 (0.8)
Participants with AEs leading to discontinuation	2 (1.5)	0	2 (1.5)	4 (1.0)
Participants with serious AEs	4 (3.1)	2 (1.5)	2 (1.5)	8 (2.0)
AEs in >2% of participants in total, by preferred term*				
Asthma	24 (18.5)	20 (14.7)	30 (22.4)	74 (18.5)
Decreased PEF rate	15 (11.5)	15 (11.0)	20 (14.9)	50 (12.5)
Nasopharyngitis	6 (4.6)	6 (4.4)	11 (8.2)	23 (5.8)
Viral respiratory tract infection	5 (3.8)	2 (1.5)	4 (3.0)	11 (2.8)
Respiratory tract infection	3 (2.3)	1 (0.7)	5 (3.7)	9 (2.3)

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

AE, Adverse event; *PEF*, Peak expiratory flow; *QD*, Once daily.

*Medical Dictionary for Regulatory Activities, version 18.0.

Figure legends

FIG 1. Study design (A) and CONSORT diagram (B). Usual background therapy is defined as high-dose ICS (>400 μ g budesonide or equivalent) plus 1 or more controller therapies (e.g. a LABA or LTRA) or medium-dose ICS (200-400 μ g budesonide or equivalent) plus 2 or more controller therapies (e.g. a LABA and/or LTRA and/or sustained-release theophylline). ICS, Inhaled corticosteroids; LABA, Long-acting β_2 -agonist; LTRA, Leukotriene receptor antagonist; QD, Once daily.

FIG 2. Peak $FEV_{1(0-3h)}$ (A) and trough FEV_1 (B) responses at week 12: full analysis set. Results are adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Error bars are $\pm$ SEs. Common baseline mean $FEV_1 \pm$ standard deviation is 1572 ± 346 mL. $*P < 0.05$; $**P < 0.001$ versus placebo Respimat. FEV_1 , Forced expiratory volume in 1 second; $FEV_{1(0-3h)}$, Forced expiratory volume in 1 second within 3 hours after dosing; QD, Once daily; SE, Standard error.

FIG 3. $FEF_{(25-75\%)}$ responses over 12 weeks: full analysis set. Results are adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Error bars are $\pm$ SEs. Common baseline mean $FEF_{(25-75\%)} \pm$ standard deviation is 1393 ± 571 mL. $*P < 0.05$; $**P < 0.001$ versus placebo Respimat. $FEF_{(25-75\%)}$, Forced expiratory flow between 25% and 75% of the forced vital capacity; QD, Once daily; SE, Standard error.

FIG 4. Peak $FEV_{1(0-3h)}$ percent predicted (A) and trough FEV_1 percent predicted (B) responses at week 12: full analysis set. Results adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Error bars are $\pm$ SEs. Common baseline mean FEV_1 percent predicted $\pm$ standard deviation is 81.6 ± 11.5 .

* $P < 0.05$; ** $P < 0.001$ versus placebo Respimat. FEV_1 , Forced expiratory volume in 1 second; $FEV_{1(0-3h)}$, Forced expiratory volume in 1 second within 3 hours after dosing; QD, Once daily; SE, Standard error.

FIG 5. Trough FEV_1/FVC responses over 12 weeks: full analysis set. Results are adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Error bars are $\pm$ SEs. Common baseline mean $FEV_1/FVC \pm$ standard deviation is 77.4 ± 10.1 . * $P < 0.05$ versus placebo Respimat. FEV_1 , Forced expiratory volume in 1 second; FVC , Forced vital capacity; QD, Once daily; SE, Standard error.

Figure 1A

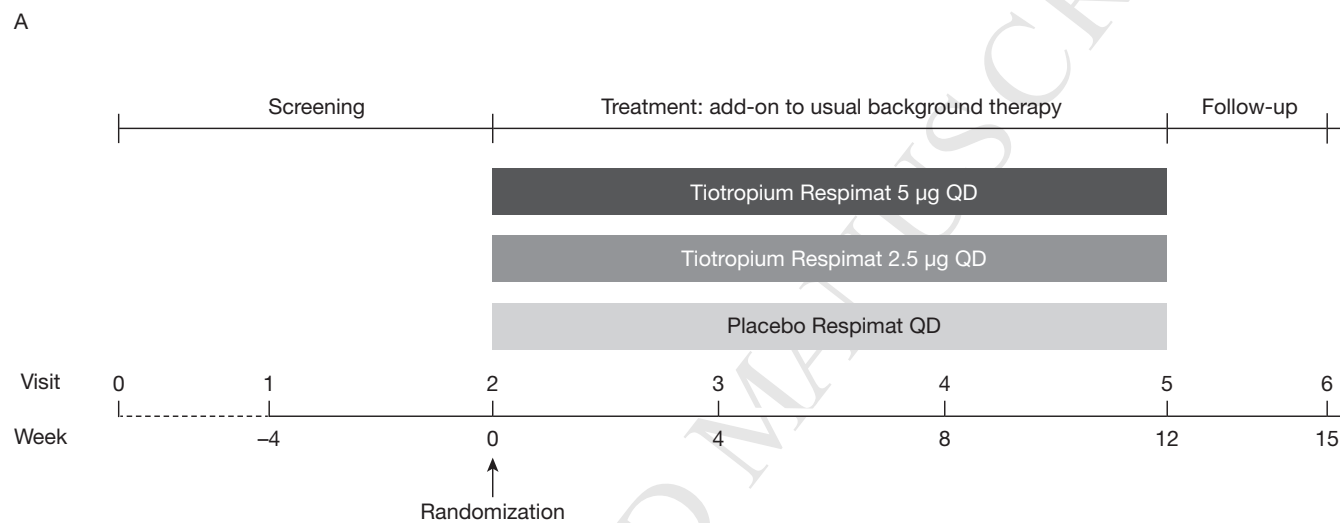


Figure 1B

B

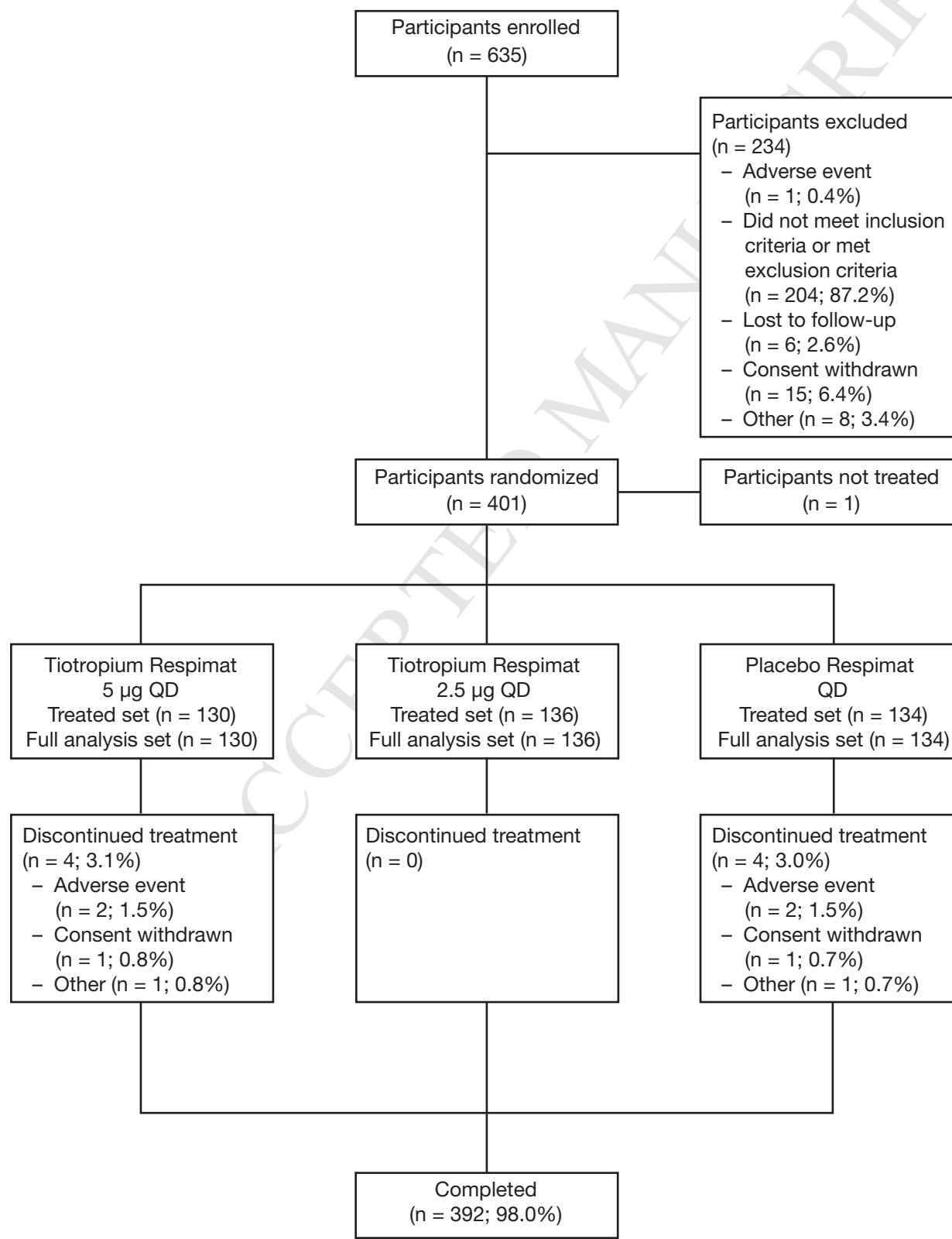


Figure 2A

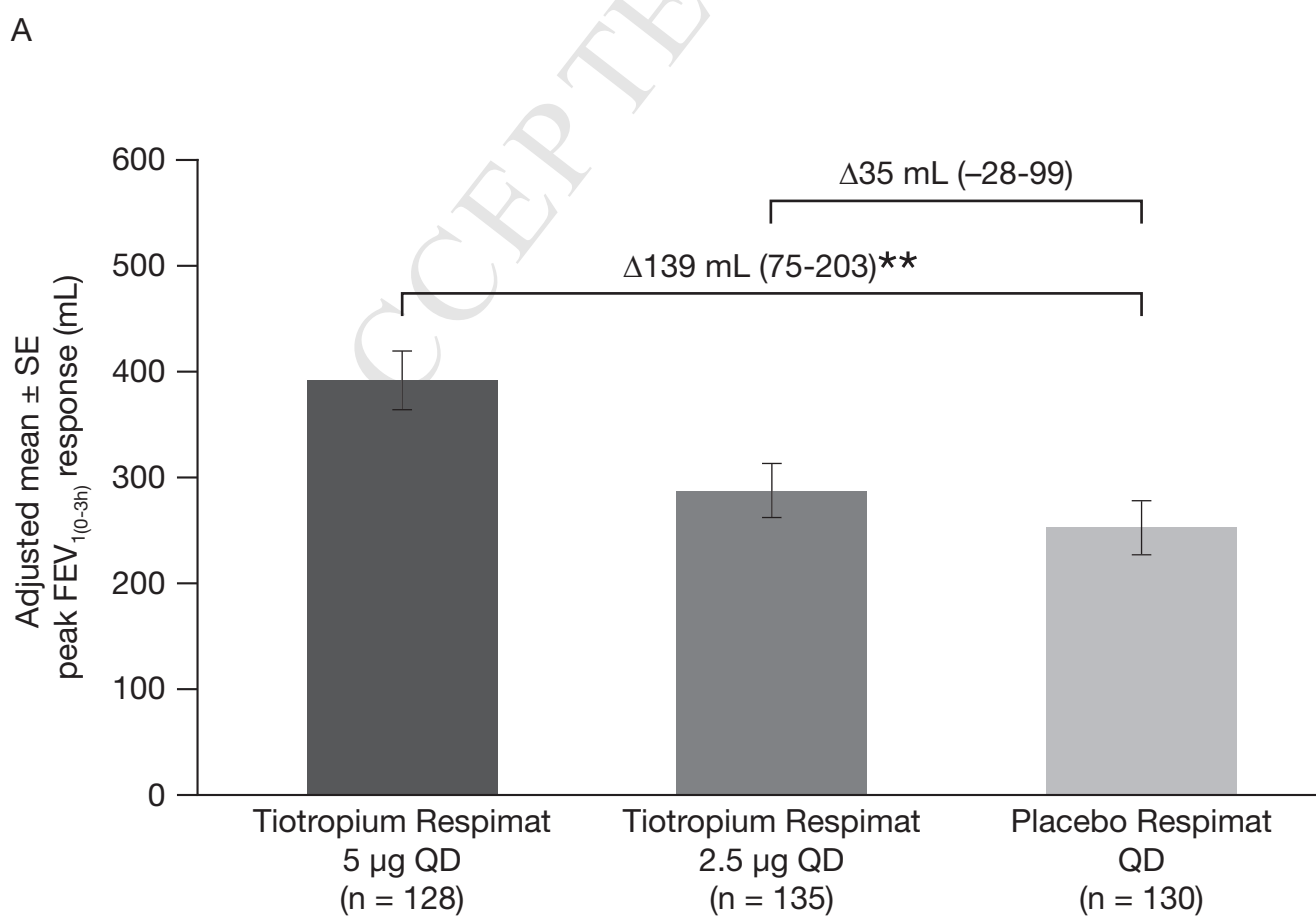


Figure 2B

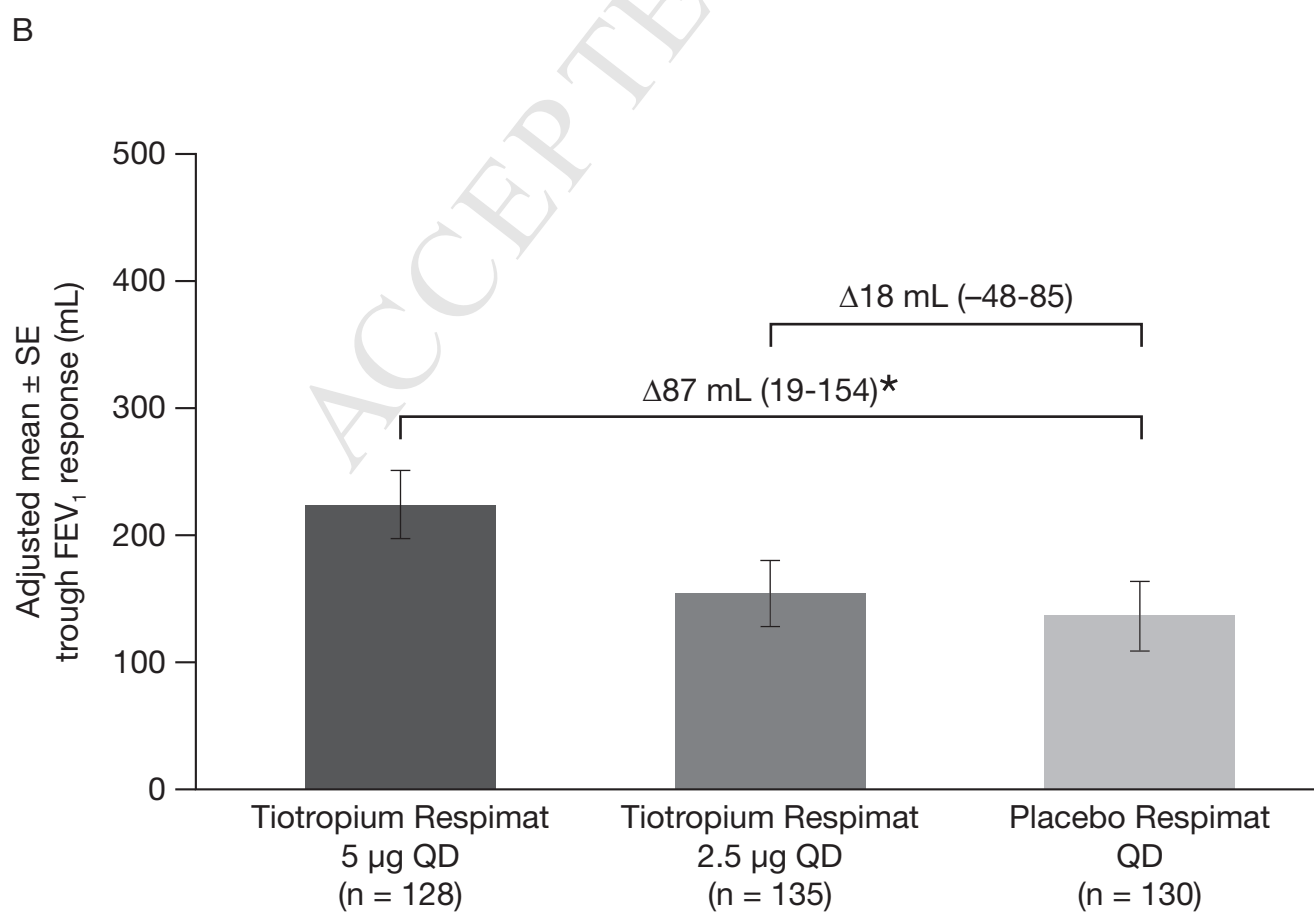


Figure 3

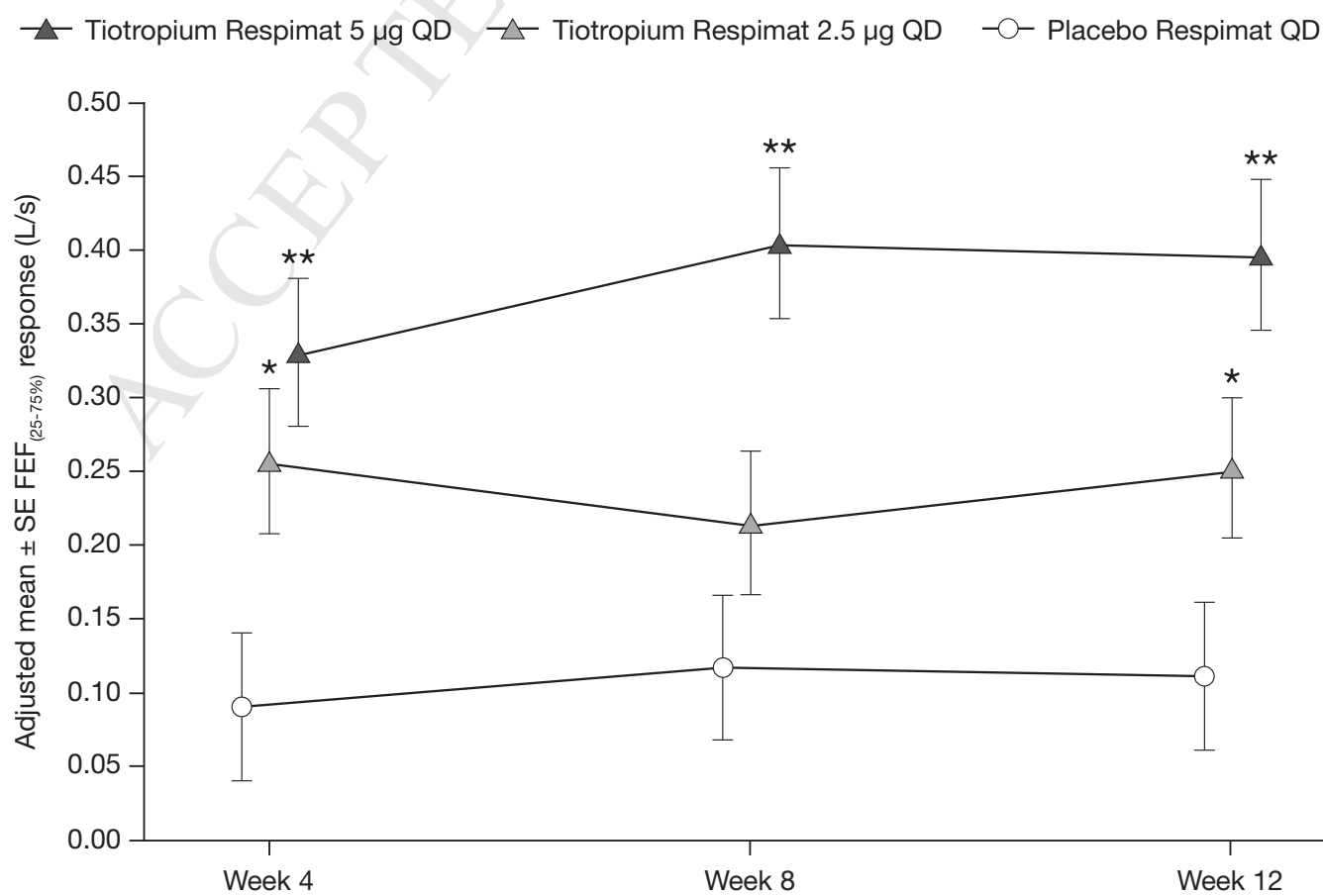


Figure 4A

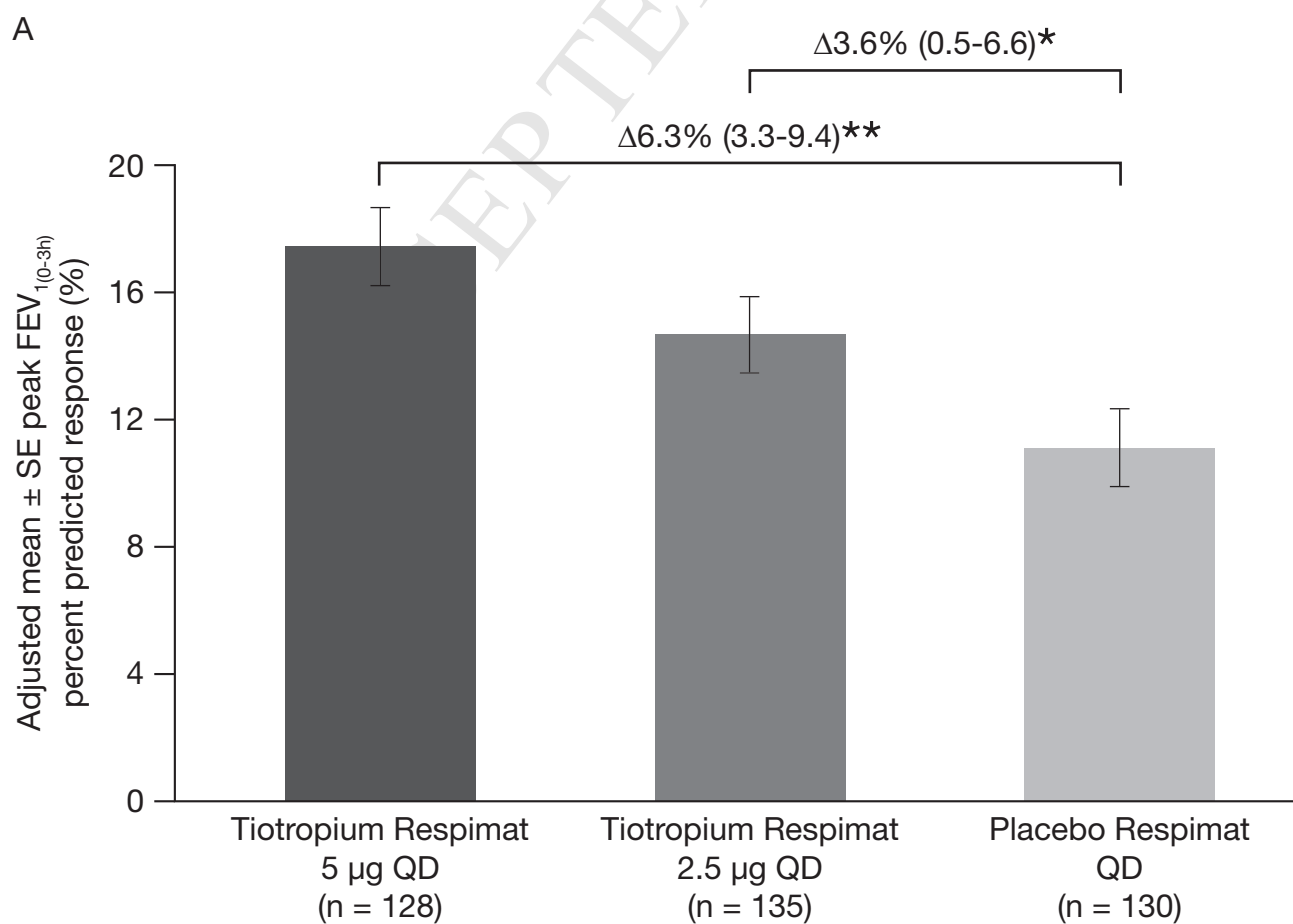


Figure 4B

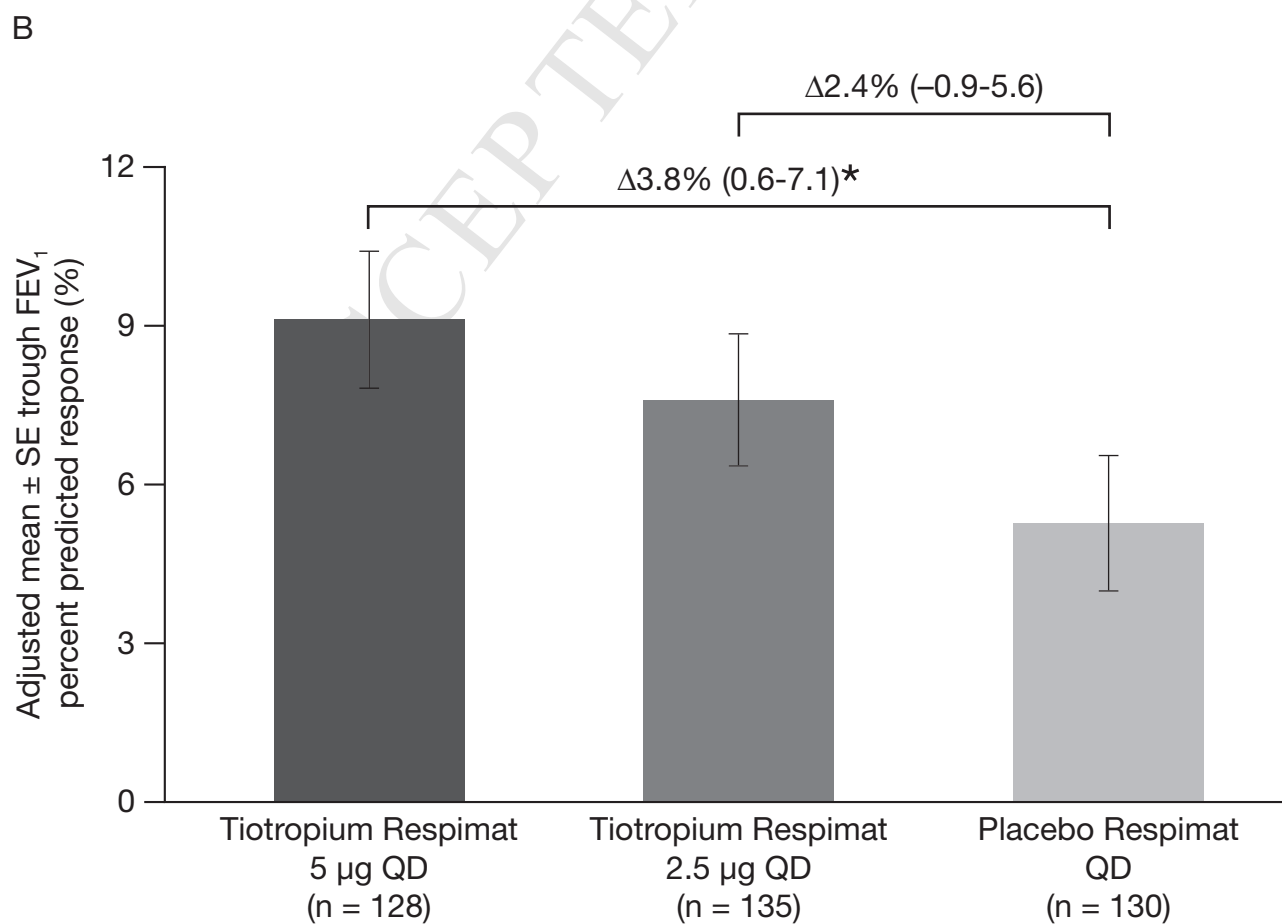


Figure 5

