

Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma

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Clinical Implications

- This clinical trial in children aged 6 to 11 years with symptomatic moderate asthma demonstrates the efficacy and safety of tiotropium Respimat in this population and supports its use as an add-on treatment option to inhaled corticosteroids.

TO THE EDITOR:

The Global Initiative for Asthma strategy recommendations for children aged 6–11 years with asthma include treatment with low-dose inhaled corticosteroids (ICS), followed by a stepwise increase in ICS dose plus addition of further maintenance therapy if control is not achieved.¹ Children are particularly challenging to treat, and therapeutic options in this age group are more limited than in adolescents and adults.¹ There is, therefore, a need for therapeutic options, as an alternative to a long-acting β_2 -agonist (LABA) or increasing ICS dose that will not only improve lung function and/or asthma control but also meet the safety standards required in younger patients.

The efficacy and safety of the once-daily long-acting anticholinergic bronchodilator, tiotropium Respimat (Boehringer Ingelheim, Ingelheim am Rhein, Germany) add-on therapy has been investigated in a large clinical program in more than 6000 patients aged 1 to 75 years across the different severities of asthma. Comparable safety and tolerability with placebo combined with improved lung function versus placebo have been demonstrated in adults, adolescents, and children.^{2–4} Data in adults also demonstrate benefits in asthma control and exacerbation risk.^{5–7}

Szefer et al⁴ recently reported data from a 12-week, phase III study of tiotropium Respimat in children aged 6 to 11 years with symptomatic severe asthma. Here we present data from a phase III, 48-week study examining the efficacy and safety of once-daily tiotropium Respimat as add-on to usual maintenance therapy in children aged 6 to 11 years with symptomatic moderate asthma, thus providing longer-term safety data and efficacy data in a different population.

We report a phase III, 48-week, randomized, double-blind, placebo-controlled, parallel-group study conducted at 79 sites in 16 countries (CanoTinA-asthma; NCT01634139) (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Patients aged 6 to 11 years were randomized

(1:1:1) to receive tiotropium 5 or 2.5 μ g or placebo (Figure E2, available in this article's Online Repository at www.jaci-inpractice.org), administered as 2 puffs once-daily via Respimat, as add-on to maintenance therapy of ICS at a stable medium dose (200–400 μ g budesonide or equivalent) either alone or with a leukotriene receptor antagonist (LTRA).

The primary end point was change from baseline in peak forced expiratory volume in 1 second within 3 hours after dosing ($FEV_{1(0-3h)}$) and the key secondary efficacy end point was trough FEV_1 response, both measured at week 24. Other secondary end points included peak $FEV_{1(0-3h)}$ and trough FEV_1 responses at week 48, peak and trough forced vital capacity responses, asthma control and responder rate (using interviewer-administered Asthma Control Questionnaire [ACQ-IA]), and asthma symptoms using patients' electronic diaries, all assessed at weeks 24 and 48. Safety analysis was based on treatment-emergent adverse events (AEs) and serious AEs occurring between first drug intake and 30 days after the last dose.

Efficacy analyses were performed on the full analysis set, comprising all patients who received at least 1 dose of trial medication. Safety analyses were descriptive. The trial was not powered for inferential analysis of secondary and further end points, and the *P* values presented for these should be considered nominal at the 5% alpha level. Additional methodology details are described in this article's Online Repository at www.jaci-inpractice.org.

Of 403 patients randomized, 401 were treated and 382 (95.3%) completed the 48-week treatment period. Baseline patient demographics and disease characteristics were representative for the population and disease under study and were generally balanced between treatment groups (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Both doses of tiotropium provided statistically significant improvements in peak $FEV_{1(0-3h)}$ response, measured as change from baseline, versus placebo at week 24 (Table 1), with an adjusted mean difference versus placebo for tiotropium 5 μ g of 164 mL (95% confidence interval [CI], 103–225; *P* < .001) and 170 mL for tiotropium 2.5 μ g (95% CI, 108–231; *P* < .001). Statistically significant improvements were also seen in trough FEV_1 at week 24 for both doses: the adjusted mean difference from placebo was 118 mL for the 5 μ g dose (95% CI, 48–188; *P* = .001) and 116 mL for the 2.5 μ g dose (95% CI, 46–186; *P* = .001) (Table 1). Improvements in peak $FEV_{1(0-3h)}$ and trough FEV_1 responses observed at week 24 were sustained to week 48, with *P* values < .05 for each comparison (Figure E3, available in this article's Online Repository at www.jaci-inpractice.org).

Similarly, improvements in ACQ-IA score versus placebo were seen with tiotropium; more than 80% of patients receiving tiotropium were considered ACQ-IA responders (ACQ-IA improvement of at least 0.5) at week 24 (tiotropium 5 μ g, 87.4%; tiotropium 2.5 μ g, 80.0%; placebo, 74.0%). Results from further efficacy end points are described in more detail in Table E2, Table E3, and Figure E4, available in this article's Online Repository at www.jaci-inpractice.org.

The percentage of patients reporting any AE was lower in patients receiving tiotropium compared with placebo (Table II);

TABLE I. Clinical end point responses at weeks 24 and 48

Treatment and parameter	Adjusted mean response $\pm$ SE (mL)	Active vs placebo Respimat		
		Adjusted mean of difference $\pm$ SE (mL)	95% CI	P value
Peak FEV _{1(0-3h)} response (mL) at week 24				
Tiotropium Respimat 5 μ g (n = 134)	389 $\pm$ 26	164 $\pm$ 31	103-225	<.001
Tiotropium Respimat 2.5 μ g (n = 131)	395 $\pm$ 26	170 $\pm$ 31	108-231	<.001
Placebo Respimat (n = 126)	225 $\pm$ 27			
Trough FEV ₁ response (mL) at week 24				
Tiotropium Respimat 5 μ g (n = 134)	274 $\pm$ 30	118 $\pm$ 36	48-188	.001
Tiotropium Respimat 2.5 μ g (n = 131)	272 $\pm$ 30	116 $\pm$ 36	46-186	.001
Placebo Respimat (n = 126)	156 $\pm$ 31			
Peak FEV _{1(0-3h)} response (mL) at week 48				
Tiotropium Respimat 5 μ g (n = 130)	477 $\pm$ 26	127 $\pm$ 31	65-188	<.001
Tiotropium Respimat 2.5 μ g (n = 130)	474 $\pm$ 26	124 $\pm$ 31	62-185	<.001
Placebo Respimat (n = 124)	351 $\pm$ 27			
Trough FEV ₁ response (mL) at week 48				
Tiotropium Respimat 5 μ g (n = 130)	365 $\pm$ 31	99 $\pm$ 36	29-170	.006
Tiotropium Respimat 2.5 μ g (n = 130)	337 $\pm$ 30	71 $\pm$ 36	1-142	.048
Placebo Respimat (n = 124)	266 $\pm$ 32			

Full analysis set. Results are adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. CI, Confidence interval; FEV₁, forced expiratory volume in 1 second; SE, standard error.

TABLE II. Overall summary of adverse events

No. (%) [*]	Tiotropium Respimat 5 μ g (n = 135)	Tiotropium Respimat 2.5 μ g (n = 135)	Placebo Respimat (n = 131)
Patients with any AE	82 (60.7)	86 (63.7)	89 (67.9)
Patients with investigator-defined drug-related AEs	0	0	2 (1.5)
Patients with AEs leading to discontinuation	0	0	0
Patients with serious AEs	1 (0.7)	3 (2.2)	6 (4.6)
Fatal	0	0	0
AEs in >5% of patients in any treatment arm, by preferred term [†]			
Asthma [‡]	46 (34.1)	49 (36.3)	57 (43.5)
Decreased peak expiratory flow rate	29 (21.5)	31 (23.0)	27 (20.6)
Nasopharyngitis	12 (8.9)	15 (11.1)	13 (9.9)
Respiratory tract infection	13 (9.6)	11 (8.1)	16 (12.2)
Respiratory tract infection viral	8 (5.9)	8 (5.9)	8 (6.1)
Allergic rhinitis	6 (4.4)	4 (3.0)	8 (6.1)
Rhinitis	2 (1.5)	5 (3.7)	7 (5.3)

Treated set.

AE, Adverse event.

^{*}A patient may be counted in 1 or more categories.

[†]Medical Dictionary for Regulatory Activities version 18.1.

[‡]Represents asthma worsening or exacerbation.

the majority of AEs were mild or moderate in intensity. The number of patients reporting investigator-defined drug-related AEs (2 placebo) and serious AEs (1 tiotropium 5 μ g, 3 tiotropium 2.5 μ g dose, 6 placebo) was low. Patients most frequently reported with AEs with the preferred terms asthma (exacerbations or worsening), decreased peak expiratory flow rate, nasopharyngitis, and respiratory tract infection (see this article's Online Repository at www.jaci-inpractice.org). Safety outcomes were consistent with those seen in other age groups and severities of asthma,²⁻⁴ with no new safety signals identified.

This phase III study of tiotropium Respimat in children aged 6 to 11 years with symptomatic moderate asthma showed

significant improvements in lung function with once-daily tiotropium Respimat as add-on to at least ICS maintenance therapy versus placebo, with a safety profile comparable with placebo. Statistically significant improvements were observed in peak and trough FEV₁ response. Changes in measures of asthma control were observed with both doses of tiotropium versus placebo, at 24 and 48 weeks, which were significant only with tiotropium 5 μ g at week 24.

The lung function improvements and safety findings observed in this trial are consistent with those observed in other clinical trials of tiotropium in other age groups and severities of asthma.²⁻⁶

Given the need for additional therapeutic options in this age group, the statistically significant improvements in lung function with tiotropium that are at least comparable with improvements reported for LABA as well as LTRA add-ons in other trials^{8,9} suggest that tiotropium may provide a viable alternative to these add-on options or to increasing ICS dose in a population for whom the treatment options are currently relatively limited.

In conclusion, our results provide valuable year-long data in children aged 6 to 11 years with symptomatic moderate asthma, corroborating the convincing safety and consistent efficacy profile of tiotropium Respimat that has been reported across different age groups and asthma severities.

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Conflicts of interest: C. Vogelberg has participated as a lecturer and speaker in scientific meetings under the sponsorship of Boehringer Ingelheim, MSD, and Novartis; has participated as a member of advisory boards for Boehringer Ingelheim, MSD, and Novartis; and was an investigator on the pediatric tiotropium studies. M. Engel, O. Schmidt, G. El Azzi, P. Moroni-Zentgraf, and R. Sigmund are employees of Boehringer Ingelheim. J. A. Bernstein has received grants from

AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline; has received consulting fees, honoraria, and travel costs for attending advisory boards and investigator meetings from AstraZeneca and Boehringer Ingelheim; and has been employed by the University of Cincinnati/Veterans Administration Hospital Clinical Research Unit and the Bernstein Clinical Research Unit for his work in clinical trials. The rest of the authors declare that they have no relevant conflicts of interest.

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ONLINE REPOSITORY SUPPLEMENTARY METHODS

Study design

This randomized, double-blind, placebo-controlled, parallel-group study (CanoTinA-asthma; NCT01634139) was conducted at 79 sites in 16 countries.

Study population

Patients aged 6 to 11 years were randomized if they had at least a 6-month documented history of asthma at enrolment; were symptomatic at screening and before randomization (defined as an interviewer-administered Asthma Control Questionnaire [ACQ-IA] mean score of at least 1.5); were receiving maintenance therapy with inhaled corticosteroids (ICS) at a stable moderate dose (200–400 µg budesonide or equivalent) either alone or in combination with one or more controller medications (eg, long-acting β_2 -agonist [LABA] or leukotriene receptor antagonist [LTRA]) for at least 4 weeks before screening; had a prebronchodilator forced expiratory volume in 1 second (FEV₁) 60% to 90% of predicted normal at screening, FEV₁ reversibility 12% or more 15 to 30 minutes after 200 µg salbutamol (albuterol), and variability of absolute FEV₁ values from screening to randomization within $\pm 30\%$; and were not diagnosed with any significant disease other than asthma.

Randomization and masking

After screening (4 weeks), patients were randomized 1:1:1, using a pseudorandom number generator with a supplied seed number, to once-daily tiotropium 5 or 2.5 µg or placebo, as 2 puffs via the Respimat Soft Mist inhaler over 48 weeks, with a 3-week follow-up period (Figure E1). All trial medications were administered in a double-blind fashion; patients, parents/legal representative/caregivers, and investigators were unaware of the identity of the assigned treatment. The 2 doses of tiotropium and placebo were identical in appearance to safeguard blinding in this trial.

Study procedures

Study treatments were administered as add-on to medium-dose ICS (200–400 µg budesonide or equivalent) either alone or with an LTRA; LABA treatment was to be stopped at least 24 hours before the 4-week run-in period (visit 1), and treatment with sustained-release theophylline was not allowed. Patients self-administered medication once daily between 16:00h and 19:00h in the following order: ICS therapy (if usually administered in the evening); any other controller therapies; then trial medication. Open-label salbutamol hydrofluoroalkane metered-dose inhalers (100 µg per puff) were provided as rescue medication. 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 was performed in accordance with the Declaration of Helsinki and International Conference on Harmonisation for Good Clinical Practice Guidelines. The trial protocol and patient 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. Written, informed consent was received from each patient's

parent or guardian, and informed assent suitable for this age group was obtained from patients before enrolment in the study.

Outcomes

The primary end point was change from baseline (response) in peak FEV₁ within 3 hours after dosing (FEV_{1(0-3h)}), and the key secondary efficacy end point was trough FEV₁ response (measured at the end of the dosing interval, 10 minutes before the administration of the next dose of trial medication), both measured at week 24.

Other secondary end points included peak FEV_{1(0-3h)} and trough FEV₁ responses at week 48, peak (within 3 hours after dosing) and trough forced vital capacity (FVC) responses, asthma control and responder rate (as assessed using ACQ-IA), and asthma symptoms as assessed by patients' electronic diaries, all assessed at weeks 24 and 48.

Further end points included peak and trough in-clinic peak expiratory flow (PEF) responses at weeks 24 and 48, forced expiratory flow at 25% to 75% of FVC (FEF_{25-75%}) response at weeks 12, 24, and 48, and time to first episode of asthma worsening (defined as a progressive increase in ≥ 1 asthma symptoms that were outside a patient's usual day-to-day variation, lasting for ≥ 2 consecutive days, and/or a decrease in a patient's best morning PEF of $\geq 30\%$ from their mean morning PEF for ≥ 2 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 consecutive days) over the 48-week treatment period. The *post hoc* analysis of the FEV₁/FVC ratio at weeks 24 and 48 was also performed.

Study assessments

FEV₁ and FVC responses were measured from at least 3 and up to 8 spirometric maneuvers at each time point; 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.

Patients used the AM3 asthma monitor device (electronic peak flow meter and eDiary; eResearch Technology, Höchberg, Germany) to monitor rescue medication usage, treatment adherence, and any worsening of asthma symptoms at home, measuring FEV₁ and PEF twice daily.

Statistical analyses

The null hypotheses were tested in a stepwise manner to control the probability of a type I error (1-sided; $\alpha = 0.025$). If the null hypothesis for superiority of tiotropium 5 µg versus placebo for peak FEV_{1(0-3h)} response at week 24 was rejected, the same null hypothesis for the 2.5 µg dose was tested, followed by testing for superiority of tiotropium 5 µg, and then 2.5 µg, versus placebo for the key secondary end point. If at any stage the previous step was not successful, further analyses were considered descriptive only.

Baseline was defined as the pretreatment value measured at randomization in the evening 10 minutes before the evening dose of the patient's usual asthma medication and first dose of trial medication for lung function end points, and as the average of the 7 days immediately preceding randomization for end points measured using the AM3 device.

To detect a difference of 120 mL in peak $FEV_{1(0-3h)}$ response between treatment groups with a power of 80% and a probability of a type I error of 2.5% (1-sided), 127 patients per group were required, using a conservative 2-group *t*-test and assuming a common standard deviation (SD) of 340 mL.

Efficacy and safety analyses were performed on the full analysis set, which comprised all patients who received at least 1 dose of trial medication (treated set). Efficacy analyses used a restricted maximum likelihood-based mixed effects model with repeated measures, including terms for “treatment,” “country,” “visit,” “baseline,” “treatment-by-visit interaction,” and “baseline-by-visit interaction,” and “patient” as a random effect.

The minimal clinically important difference used to define responders for the ACQ-IA responder analyses was 0.5.²² Safety analyses were descriptive.

Missing data at a given visit were imputed by the available data from the patient at that visit. For missing diary data, lowest values were used, as appropriate.

SUPPLEMENTARY RESULTS

The most frequent reasons for screening failure were violations of the following inclusion and exclusion criteria:

- All patients had to have a prebronchodilator $FEV_1 \geq 60\%$ and $\leq 90\%$ of predicted normal at visit 1.
- Variation of absolute FEV_1 values of visit 1 (prebronchodilator, considered as 100%) as compared with visit 2 (predose) had to be within $\pm 30\%$.
- All patients had to confirm the diagnosis of asthma by bronchodilator reversibility at visit 1, resulting in an increase in FEV_1 of $\geq 12\%$, 15 to 30 minutes after administration of 200 μ g salbutamol/albuterol.
- Patients had to be able to perform all trial-related procedures, including technically acceptable pulmonary function tests and use of electronic diary/peak flow meter (diary compliance of at least 80% was required).
- Patients with any acute asthma exacerbation or respiratory tract infection in the 4 weeks before visit 1 and/or in 4 weeks before visit 2 were excluded. In case of an asthma deterioration occurring in the 4 weeks before visit 1 and/or in the 4 weeks before visit 2, the visit had to be postponed.

Levels of discontinuation were 3.7% for both doses of tiotropium and 6.9% for placebo, and were primarily due to consent withdrawn for reasons other than adverse events (AEs). No patients discontinued medication because of AEs (Figure E2). Mean $\pm$ SD treatment exposure was 330.7 ± 39.2 days, and mean adherence with study medication was $78.6\% \pm 21.1\%$.

Baseline patient demographics and disease characteristics

Baseline patient demographics and disease characteristics were generally balanced between treatment groups (Table E1). The majority of patients were male (65.8%), with a mean $\pm$ SD age of 8.9 ± 1.6 years overall (40.1% aged 6–8 years; 59.9% aged 9–11 years). The mean $\pm$ SD asthma duration was 4.2 ± 2.4 years, and 7.2% of patients had been exposed to second-hand smoke. In the 3 months before screening, all patients received treatment with ICS, 73.3% received ICS alone, 18.0% received a LABA,

and 30.4% received an LTRA. During the treatment period, 26.7% of patients received ICS plus an LTRA and 73.3% ICS alone in addition to the trial medication.

Additional efficacy end points

Weekly mean evening PEF responses measured at home using an unsupervised AM3 device provided some inconsistencies in the readings; hence, in-clinic trough PEF results were analyzed (see below).

The *post hoc* analysis of in-clinic PEF response at weeks 24 and 48 indicated statistically significant responses versus placebo for tiotropium 5 and 2.5 μ g at both time points (see Table E2).

Adjusted mean differences in $FEF_{25-75\%}$ responses between both doses of tiotropium and placebo were statistically significant at all individual time points analyzed at week 24, with similar results observed at week 48 (Figure E4).

The number of asthma worsening was lower in both tiotropium groups compared with placebo. The number of patients reporting asthma worsening during the 48-week treatment period was 57 (42.2%) for tiotropium 5 μ g, 63 (46.7%) for tiotropium 2.5 μ g, and 65 (50.4%) for placebo. Severe exacerbations were reported at similar frequencies in all 3 treatment groups during the treatment period (7 patients each [5.2%] in the tiotropium 5 and 2.5 μ g groups, and 6 patients [4.6%] in the placebo group).

Weekly mean use of rescue medication was reduced in all treatment groups at weeks 24 and 48, with larger reductions observed in patients treated with tiotropium versus placebo that were statistically significant with tiotropium 5 μ g for daytime and night-time puffs at week 24, and for daytime puffs at week 48 (see Table E3).

The *post hoc* analyses of trough FEV_1 /FVC ratio responses at weeks 24 and 48 revealed statistically significant improvements for both tiotropium doses versus placebo at week 24 and for tiotropium 5 μ g at week 48.

The number of patients reporting any AE was lower in patients receiving tiotropium compared with those receiving placebo; the majority of AEs were mild or moderate in intensity (Table II). The number of investigator-defined drug-related AEs reported was low: none were reported for either dose of tiotropium, with 2 (1.5%) reported in patients receiving placebo. The number of patients reporting serious AEs was also low, being reported in 1 patient receiving the 5 μ g dose (0.7%; appendicitis and paralytic ileus), 3 patients receiving the 2.5 μ g dose (2.2%; 2 patients with asthma worsening and 1 with appendicitis), and 6 patients receiving placebo (4.6%; 2 reports of asthma worsening, 1 of paranasal sinus hematoma, 1 of gastroenteritis, 1 of renal abscess, 1 of anaphylactic shock, and 1 of concussion, fall, and skull fracture). No AEs or serious AEs led to discontinuation of study medication, all patients recovered, and there were no life-threatening AEs or deaths.

Patients were most frequently reported with AEs with the preferred terms: asthma (exacerbations or worsening), decreased PEF rate, nasopharyngitis, and respiratory tract infection, with reporting of preferred terms generally balanced across treatment arms (Table II). There were no reports of dry mouth, an AE commonly associated with anticholinergic drugs.

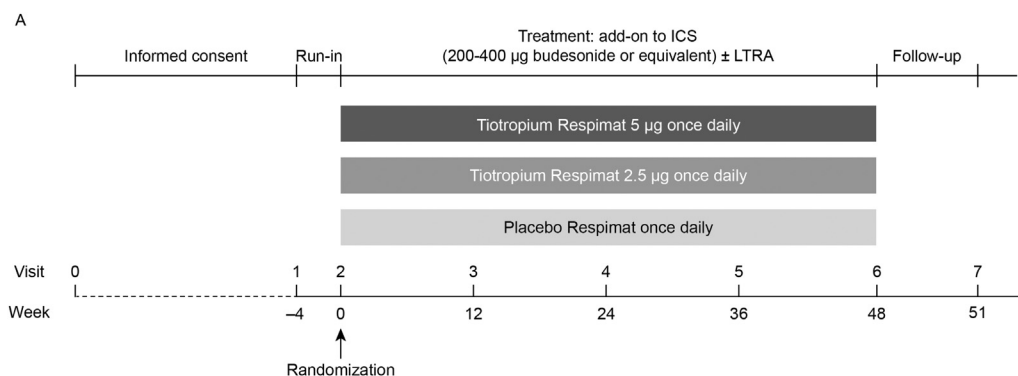


FIGURE E1. Study design. *ICS*, Inhaled corticosteroids; *LTRA*, leukotriene receptor antagonist.

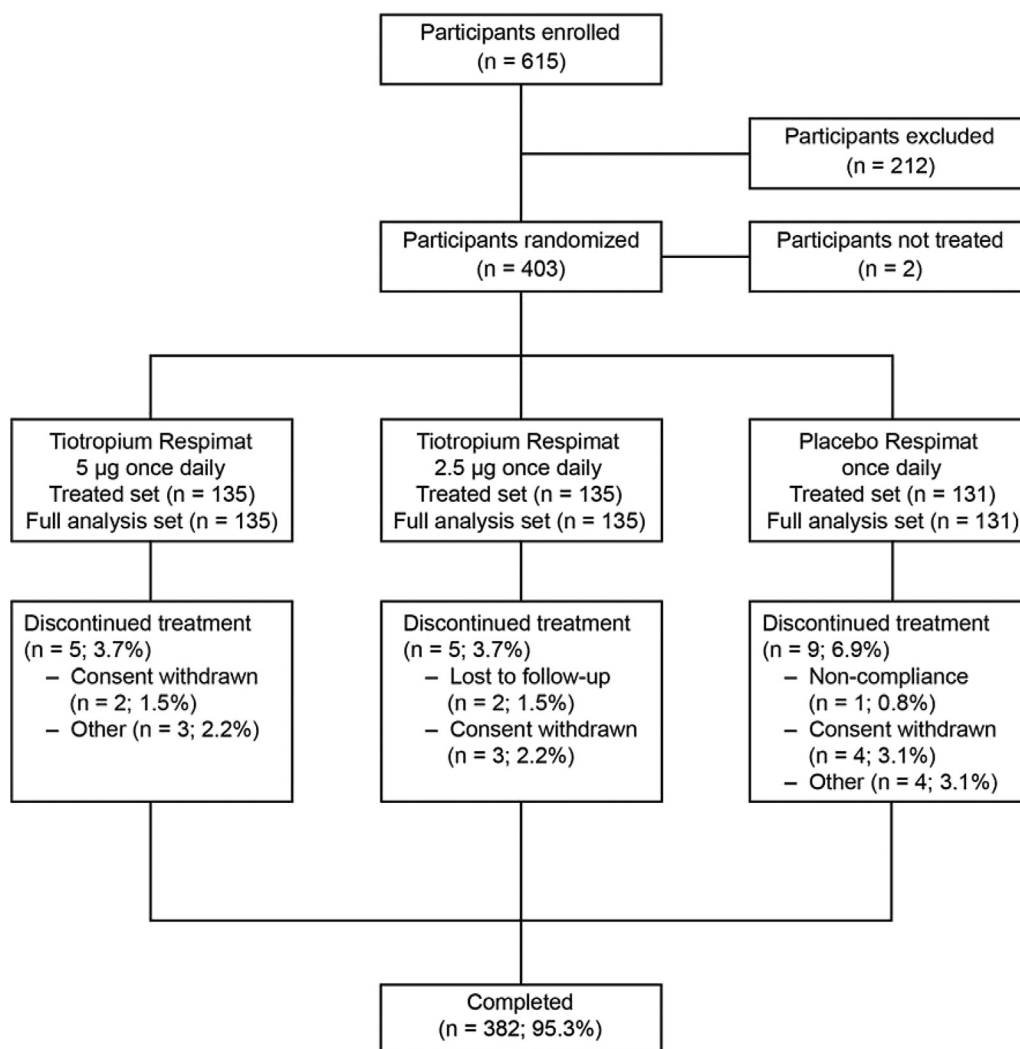


FIGURE E2. Patient disposition CONSORT diagram.

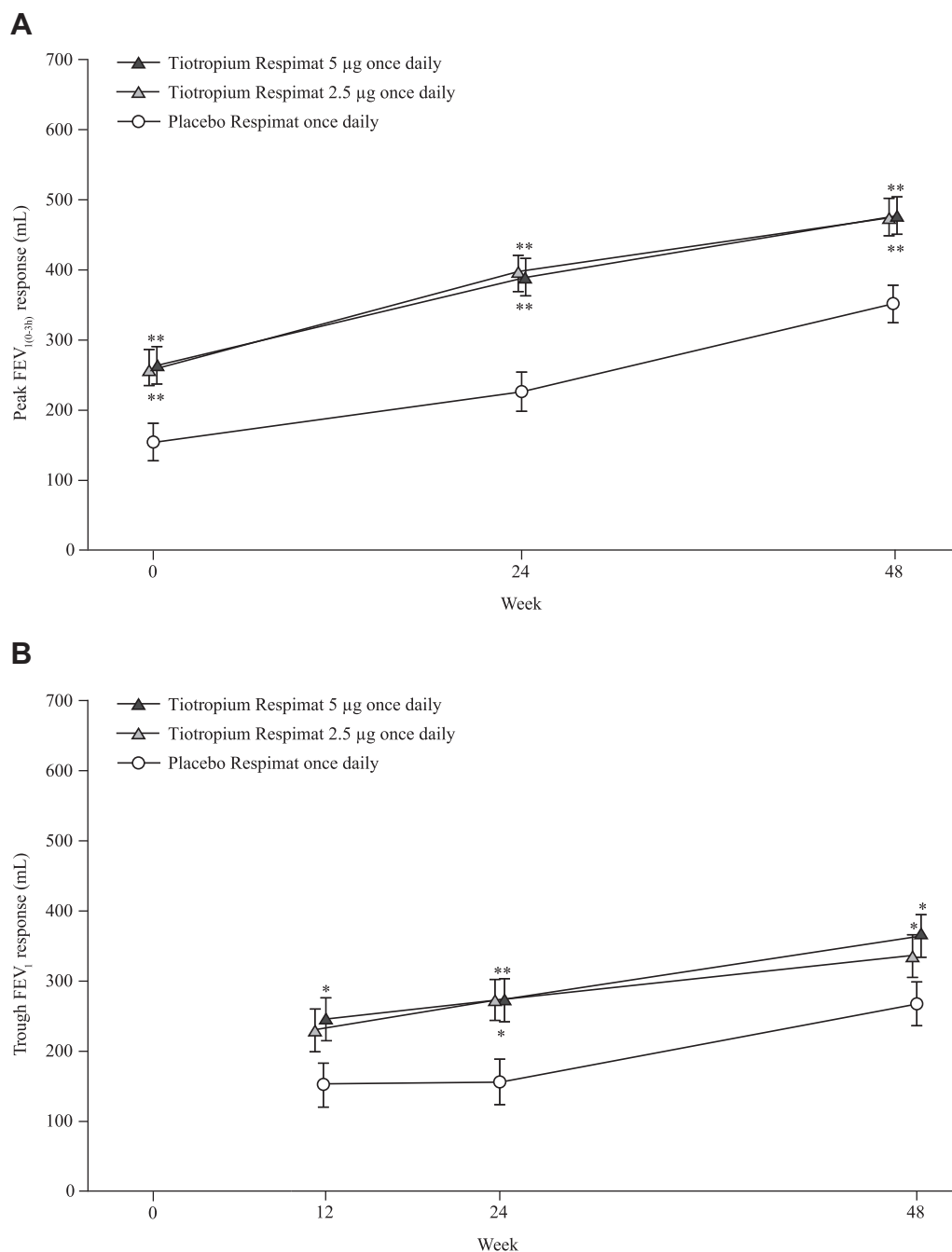


FIGURE E3. A, Peak $FEV_{1(0-3h)}$ responses at weeks 24 and 48. **B,** Trough FEV_1 responses at weeks 12, 24, and 48. Full analysis set. Adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Error bars are $\pm$ standard error. FEV_1 common baseline mean $\pm$ standard deviation = 1629 ± 393 mL. FEV_1 , Forced expiratory volume in 1 second; $FEV_{1(0-3h)}$, forced expiratory volume in 1 second within 3 hours after dosing. * $P < .05$. ** $P \leq .001$ versus placebo Respimat.

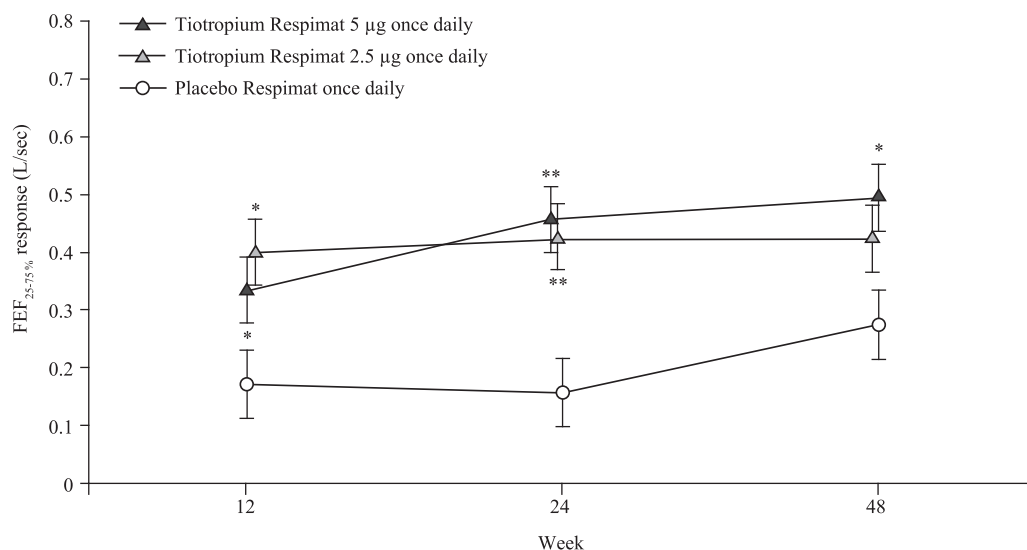


FIGURE E4. $FEF_{25-75\%}$ responses at weeks 12, 24, and 48. Full analysis set. Adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Error bars are $\pm$ standard error. $FEF_{25-75\%}$ common baseline mean $\pm$ standard deviation = 1431 ± 584 mL. $FEF_{25-75\%}$, Forced expiratory flow at 25% to 75% of the forced vital capacity. * $P < .05$. ** $P \leq .001$ versus placebo Respimat.

TABLE E1. Baseline patient demographics and disease characteristics

	Tiotropium Respimat 5 µg (n = 135)	Tiotropium Respimat 2.5 µg (n = 135)	Placebo Respimat (n = 131)
Age, y, mean ± SD	8.9 ± 1.7	9.0 ± 1.6	9.0 ± 1.6
Age, no. (%)			
6-8 y	59 (43.7)	53 (39.3)	49 (37.4)
9-11 y	76 (56.3)	82 (60.7)	82 (62.6)
Male, no. (%)	82 (60.7)	97 (71.9)	85 (64.9)
Race, N (%)			
American Indian/Alaska Native	14 (10.4)	15 (11.1)	16 (12.2)
Asian	4 (3.0)	4 (3.0)	2 (1.5)
Black/African American	3 (2.2)	3 (2.2)	1 (0.8)
Hawaiian/Pacific Islander	0	0	0
White	114 (84.4)	113 (83.7)	112 (85.5)
Ethnicity, N (%)			
Non-Hispanic/Latino	116 (85.9)	117 (86.7)	113 (86.3)
Hispanic/Latino	19 (14.1)	18 (13.3)	18 (13.7)
Body mass index, kg/m ² , mean ± SD	17.7 ± 3.2	18.0 ± 3.5	17.7 ± 3.5
Exposure to second-hand smoke, no. (%)			
Yes	7 (5.2)	11 (8.1)	11 (8.4)
Duration of asthma, y, mean ± SD	4.06 ± 2.37	4.42 ± 2.43	4.24 ± 2.30
Prebronchodilator FEV ₁ at screening			
Actual (mL)			
Mean ± SD	1506 ± 359	1490 ± 317	1542 ± 368
Median (range)	1460 (840-2850)	1480 (730-2250)	1470 (780-2640)
% pred.			
Mean ± SD	78.2 ± 7.8	77.0 ± 7.8	78.9 ± 7.1
Median (range)	79.3 (60.1-95.4)	77.3 (60.8-90.7)	79.9 (59.9-90.1)
FEV ₁ *			
Actual			
Mean ± SD	1595 ± 397	1622 ± 381	1673 ± 402
Median (range)	1560 (860-2990)	1620 (910-2880)	1610 (860-2660)
% pred.			
Mean ± SD	82.7 ± 10.9	83.8 ± 11.4	85.7 ± 9.9
Median (range)	82.92 (54.33-106.64)	82.44 (55.11-115.48)	86.05 (59.13-117.64)
FVC*			
Actual			
Mean ± SD	2085 ± 568	2092 ± 515	2187 ± 604
Median (range)	1980 (1120-4750)	2040 (1060-3800)	2070 (1050-4220)
% pred.			
Mean ± SD	93.7 ± 13.4	93.7 ± 15.4	96.8 ± 15.1
Median (range)	94.44 (64.42-43.12)	92.61 (56.79-140.54)	94.72 (68.07-144.78)
FEV ₁ /FVC ratio (%)*			
Mean ± SD	77.5 ± 10.4	78.3 ± 9.7	77.9 ± 10.3
Median (range)	77.42 (39.45-98.77)	79.14 (56.32-99.10)	79.06 (50.47-100.0)
FEF _{25-75%} (L/s)*			
Mean ± SD	1.4 ± 0.6	1.4 ± 0.6	1.5 ± 0.6
Median (range)	1.28 (0.12-3.93)	1.33 (0.13-3.58)	1.45 (0.45-3.30)
PEF (L/min)*			
Mean ± SD	216.3 ± 54.7	222.4 ± 54.2	227.7 ± 54.2
Median (range)	212 (82-384)	225 (101-347)	229 (116-396)
ACQ-IA score*, mean ± SD	1.9 ± 0.3	1.9 ± 0.3	1.9 ± 0.3
ICS dose of stable maintenance treatment, µg*,†, mean ± SD	317 ± 124	312 ± 109	301 ± 102

(continued)

TABLE E1. (Continued)

	Tiotropium Respimat 5 µg (n = 135)	Tiotropium Respimat 2.5 µg (n = 135)	Placebo Respimat (n = 131)
Concomitant therapies in the 3 mo before screening, no. (%)			
LABA	21 (15.6)	31 (23.0)	20 (15.3)
LTRA	40 (29.6)	46 (34.1)	36 (27.5)
Concomitant therapies during the treatment period, no. (%)			
LABA	0	1 (0.7)	1 (0.8)
LTRA	31 (23.0)	41 (30.4)	35 (26.7)

Treated set.

% *pred.*, % Predicted; *ACQ-IA*, interviewer-administered Asthma Control Questionnaire; *FEF_{25-75%}*, forced expiratory flow at 25% to 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; *SD*, standard deviation.

*At randomization, visit 2.

†Budesonide or equivalent dose.

TABLE E2. Further efficacy end point responses at weeks 24 and 48

Treatment and parameter	Adjusted mean response $\pm$ SE (mL)	Active vs placebo Respimat		
		Adjusted mean of difference $\pm$ SE (mL)	95% CI	P value
Peak FVC _(0-3h) response (mL) at week 24				
Tiotropium Respimat 5 μ g (n = 134)	307 $\pm$ 32	91 $\pm$ 37	18 to 165	.015
Tiotropium Respimat 2.5 μ g (n = 131)	325 $\pm$ 32	110 $\pm$ 38	36 to 184	.004
Placebo Respimat (n = 126)	215 $\pm$ 33			
Trough FVC response (mL) at week 24				
Tiotropium Respimat 5 μ g (n = 134)	206 $\pm$ 34	52 $\pm$ 40	−27 to 131	.20
Tiotropium Respimat 2.5 μ g (n = 131)	246 $\pm$ 34	92 $\pm$ 40	13 to 171	.023
Placebo Respimat (n = 126)	154 $\pm$ 35			
Trough FEV ₁ /FVC ratio response (%) at week 24				
Tiotropium Respimat 5 μ g (n = 134)	82.0 $\pm$ 0.8	3.5 $\pm$ 0.9	1.651 to 5.371	<.001
Tiotropium Respimat 2.5 μ g (n = 131)	80.4 $\pm$ 0.8	2.0 $\pm$ 1.0	0.126 to 3.868	.037
Placebo Respimat (n = 126)	78.4 $\pm$ 0.8			
ACQ-IA score at week 24				
Tiotropium Respimat 5 μ g (n = 134)	0.84 $\pm$ 0.06	−0.182 $\pm$ 0.07	−0.323 to −0.041	.012
Tiotropium Respimat 2.5 μ g (n = 131)	0.90 $\pm$ 0.06	−0.120 $\pm$ 0.07	−0.262 to 0.022	.10
Placebo Respimat (n = 126)	1.02 $\pm$ 0.06			
Peak PEF _(0-3h) measured in clinic (L/min) at week 24				
Tiotropium Respimat 5 μ g (n = 134)	63.22 $\pm$ 4.35	30.51 $\pm$ 5.09	20.51 to 40.51	<.001
Tiotropium Respimat 2.5 μ g (n = 131)	61.23 $\pm$ 4.32	28.54 $\pm$ 5.10	18.54 to 38.55	<.001
Placebo Respimat (n = 126)	32.71 $\pm$ 4.49			
Trough PEF measured in clinic (L/min) at week 24				
Tiotropium Respimat 5 μ g (n = 134)	42.25 $\pm$ 4.87	20.43 $\pm$ 5.72	9.19 to 31.67	<.001
Tiotropium Respimat 2.5 μ g (n = 131)	42.35 $\pm$ 4.86	20.53 $\pm$ 5.73	9.28 to 31.78	<.001
Placebo Respimat (n = 126)	21.82 $\pm$ 5.04			
Peak FVC _(0-3h) response (mL) at week 48				
Tiotropium Respimat 5 μ g (n = 130)	413 $\pm$ 32	52 $\pm$ 38	−22 to 126	.17
Tiotropium Respimat 2.5 μ g (n = 130)	430 $\pm$ 32	69 $\pm$ 38	−5 to 143	.07
Placebo Respimat (n = 124)	361 $\pm$ 33			
Trough FVC response (mL) at week 48				
Tiotropium Respimat 5 μ g (n = 130)	333 $\pm$ 34	53 $\pm$ 40	−26 to 133	.19
Tiotropium Respimat 2.5 μ g (n = 130)	341 $\pm$ 34	62 $\pm$ 40	−17 to 141	.13
Placebo Respimat (n = 124)	280 $\pm$ 35			
ACQ-IA score at week 48				
Tiotropium Respimat 5 μ g (n = 130)	0.72 $\pm$ 0.06	−0.093 $\pm$ 0.07	−0.236 to 0.049	.20
Tiotropium Respimat 2.5 μ g (n = 130)	0.75 $\pm$ 0.06	−0.065 $\pm$ 0.07	−0.208 to 0.078	.37
Placebo Respimat (n = 124)	0.82 $\pm$ 0.06			
Trough FEV ₁ /FVC ratio response (%) at week 48*				
Tiotropium Respimat 5 μ g (n = 130)	81.2 $\pm$ 0.8	2.5 $\pm$ 1.0	0.590 to −4.337	.010
Tiotropium Respimat 2.5 μ g (n = 130)	80.0 $\pm$ 0.8	1.2 $\pm$ 1.0	−0.648 to 3.106	.20
Placebo Respimat (n = 124)	78.7 $\pm$ 0.8			

ACQ-IA, Interviewer-administered Asthma Control Questionnaire; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FVC_(0-3h), forced vital capacity within 3 hours after dosing; PEF_(0-3h), peak expiratory flow within 3 hours after dosing; SE, standard error.

Full analysis set. Results are adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Common baseline mean $\pm$ standard deviation: FVC = 2.12 $\pm$ 0.56; ACQ-IA total score = 1.87 $\pm$ 0.309; FEV₁/FVC: 77.9 $\pm$ 10.1; PEF = 222.09 $\pm$ 54.42.

*Post hoc analysis.

TABLE E3. Use of rescue medication at weeks 24 and 48

Time point	Adjusted mean response $\pm$ SE	Active vs placebo Respimat		
		Adjusted mean of difference $\pm$ SE	95% CI	P value
Week 24				
Daytime puffs				
Tiotropium Respimat 5 μ g (n = 133)	−0.38 $\pm$ 0.05	−0.14 $\pm$ 0.07	−0.269 to −0.013	.031
Tiotropium Respimat 2.5 μ g (n = 130)	−0.35 $\pm$ 0.05	−0.12 $\pm$ 0.07	−0.245 to 0.012	.07
Placebo Respimat (n = 121)	−0.23 $\pm$ 0.06			
Nighttime puffs				
Tiotropium Respimat 5 μ g (n = 130)	−0.30 $\pm$ 0.05	−0.13 $\pm$ 0.06	−0.246 to −0.006	.040
Tiotropium Respimat 2.5 μ g (n = 130)	−0.27 $\pm$ 0.05	−0.1 $\pm$ 0.06	−0.217 to 0.025	.12
Placebo Respimat (n = 122)	−0.18 $\pm$ 0.05			
Week 48				
Daytime puffs				
Tiotropium Respimat 5 μ g (n = 125)	−0.38 $\pm$ 0.05	−0.13 $\pm$ 0.07	−0.260 to −0.002	.046
Tiotropium Respimat 2.5 μ g (n = 123)	−0.37 $\pm$ 0.05	−0.13 $\pm$ 0.07	−0.255 to 0.004	.06
Placebo Respimat (n = 119)	−0.25 $\pm$ 0.06			
Nighttime puffs				
Tiotropium Respimat 5 μ g (n = 125)	−0.30 $\pm$ 0.05	−0.10 $\pm$ 0.06	−0.224 to 0.019	.10
Tiotropium Respimat 2.5 μ g (n = 122)	−0.30 $\pm$ 0.05	−0.10 $\pm$ 0.06	−0.221 to 0.023	.11
Placebo Respimat (n = 119)	−0.20 $\pm$ 0.05			

CI, Confidence interval; SE, standard error.

Full analysis set. Results are adjusted for treatment, country, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. Response based on weekly mean of the last week of treatment preceding week 24 or 48. Common baseline mean $\pm$ standard deviation = daytime puffs: 0.59 $\pm$ 0.75; nighttime puffs: 0.51 $\pm$ 0.74.