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Tiotropium Respimat® add-on therapy to inhaled corticosteroids in patients with symptomatic asthma improves clinical outcomes regardless of baseline characteristics

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Abstract

Background: Despite currently available therapies and detailed treatment guidelines, many patients with asthma remain symptomatic. Tiotropium delivered by the soft mist inhaler Respimat®, as add-on therapy to medium-dose inhaled corticosteroids (ICS), has been shown to improve lung function and asthma control in patients with symptomatic moderate asthma.

Objective: To determine whether the efficacy of tiotropium Respimat® in asthma differs by patients' study baseline characteristics.

Methods: Two replicate Phase III, randomized, double-blind, placebo-controlled, parallel-group studies (MezzoTinA-asthma®; NCT01172808 and NCT01172821) of once-daily tiotropium Respimat 5 µg and 2.5 µg add-on to ICS were conducted in patients with symptomatic asthma despite treatment with medium-dose ICS with or without additional controllers. Subgroup analyses of peak forced expiratory volume in 1 second (FEV_1), trough FEV_1, risk of severe asthma exacerbation and Asthma Control Questionnaire responder rate were performed to determine whether results were influenced by patients' baseline characteristics.

Results: In this analysis, 523 patients received placebo while 517 and 519 patients received the 5 µg and 2.5 µg dose of tiotropium Respimat, respectively. The magnitude of the improvements in lung function and asthma control, as well as the reduced risk of severe exacerbation with both doses of tiotropium Respimat versus placebo, was independent of a broad range of baseline characteristics.

Conclusions: Once-daily tiotropium Respimat as add-on to ICS is a beneficial treatment option for patients with asthma who remain symptomatic despite at least medium-dose ICS, regardless of baseline characteristics.

Keywords: Tiotropium; FEV_1; Respimat; exacerbation; Asthma Control Questionnaire

Lay summary

Up to half of people with asthma still suffer from symptoms despite treatment. A drug that relaxes the smooth muscle in the airways, called tiotropium, reduces symptoms of asthma when it is added on top of other asthma drugs. Asthma patients are diverse. We wanted to see whether the drug works across different patients. To test this, we studied just over 1500 people with symptomatic moderate asthma. Some were given the drug tiotropium at one dose (5 µg) and some were given the drug at a lower dose (2.5 µg), once a day, on top of other asthma drugs. Other patients were given a placebo (a substance with no effect) or a drug called salmeterol, but here we focus on the tiotropium and placebo groups. We measured their symptoms and breathing before and after giving them the different drugs. We found that tiotropium improves asthma symptoms and control compared with the placebo across the different patient types.

Abbreviations

ACQ-7	7-question Asthma Control Questionnaire
AE	adverse event
BMI	body mass index
CI	confidence interval
FEV_1	forced expiratory volume in 1 second
$FEV_{1(0–3h)}$	FEV_1 from baseline 0–3 hours post-dose
FVC	forced vital capacity
GINA	Global Initiative for Asthma
HR	hazard ratio
ICS	inhaled corticosteroid
IgE	immunoglobulin E
OR	odds ratio
LABA	long-acting β_2-agonist
LTRA	leukotriene receptor antagonist
MMRM	mixed model repeated measures
PEF	peak expiratory flow
T2	type 2
TALC	Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid

Introduction

Despite currently available therapies and detailed treatment guidelines, up to 50% of patients with asthma remain symptomatic [1–3]. One option to improve asthma control in patients who remain symptomatic despite treatment with low or medium doses of inhaled corticosteroids (ICS; Global Initiative for Asthma [GINA] Steps 2 and 3) is to add another controller [1]. The clinical efficacy and safety of treatment with tiotropium, a long-acting anticholinergic delivered by the soft mist inhaler Respimat®, as add-on to standard ICS maintenance treatment, with or without a long-acting β_2-agonist (LABA), has been demonstrated in a large clinical program involving close to 6000 patients aged 6–75 years with varying severities of symptomatic asthma [4–13]. Consequently, once daily tiotropium Respimat® is approved for treatment in patients aged 6 years and older in the European Union and United States [14,15].

Evidence from three studies suggests that tiotropium Respimat as add-on maintenance therapy to low-dose or medium-dose ICS is effective in patients with asthma, with an efficacy that is similar to that of LABAs [6,16,17]. Firstly, data from the Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC; NCT00565266) study, a randomized, double-blind, three-way crossover trial in patients with inadequately controlled asthma, showed that tiotropium Respimat as add-on to low-dose ICS was associated with improvements in lung function, symptoms and asthma control that were greater than when the dose of ICS was doubled [17]. For most outcomes in this study, tiotropium Respimat was either non-inferior to or better than the LABA salmeterol [17]. Secondly, in a Phase II, parallel group, proof-of-concept trial in B16-Arg/Arg patients with symptomatic asthma who were receiving

medium-dose ICS (NCT00350207), there was an improvement in mean weekly pre-dose morning peak expiratory flow (PEF) after the addition of tiotropium Respimat that was greater than with placebo and non-inferior to salmeterol [6]. Thirdly, data from the Phase III MezzoTinA-asthma® trials (NCT01172808 and NCT01172821) demonstrated that the addition of once-daily tiotropium Respimat to medium-dose ICS significantly improves lung function and asthma control compared with placebo, with an efficacy similar to salmeterol [16].

However, with the growing interest in personalized medicine, it is important to explore patient characteristics that may be used to predict potential treatment responses. To date, there are limited data on predictors of response to tiotropium Respimat. Exploratory analyses from the TALC study found that airway obstruction, as demonstrated by a reduced forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio, and a response to salbutamol (albuterol) were good predictors of clinical response to tiotropium HandiHaler® (both $P<0.001$) [18]. In addition, data are available from a subgroup analysis of the PrimoTinA-asthma® trials (NCT00772538 and NCT00776984), which assessed add-on tiotropium Respimat in patients with symptomatic severe asthma on maintenance therapy with high-dose ICS/LABA [19]. In this subgroup analysis, treatment with tiotropium Respimat 5 µg compared with placebo resulted in improvements in lung function, reduced risk of asthma exacerbations and asthma worsening, and improvements in asthma symptom control [19]. These results were independent of a range of baseline characteristics, including gender, age, body mass index (BMI), disease duration, age at asthma onset and smoking status [19]. Furthermore, a recent exploratory subgroup analysis of the PrimoTinA-asthma and MezzoTinA-asthma trials assessed whether lung function endpoints, exacerbations and

asthma control (assessed by the 7-question Asthma Control Questionnaire [ACQ-7]) were influenced by a type 2 (T2) allergic phenotype status at baseline, as measured by total serum immunoglobulin E (IgE) levels, clinical judgement of allergic asthma and blood eosinophilia [20]. It showed that tiotropium Respimat was efficacious in improving lung function and asthma control, and significantly reduced the risk of severe asthma exacerbations compared with placebo, independent of T2 phenotype status at baseline [20]. These results suggest that patients being considered for add-on tiotropium Respimat therapy for symptomatic asthma and/or for asthma exacerbation prevention at a dose of either 5 µg or 2.5 µg do not require T2 status phenotyping [20].

Building on these data, we present here additional subgroup analyses of data from the two Phase III MezzoTinA-asthma studies performed in patients with symptomatic asthma despite treatment with medium-dose ICS (with or without previous LABA or short-acting β_2-agonist therapy) [16]. The present analysis explored whether there are further characteristics that may be used to predict improvements in lung function and asthma control.

Methods

Study design

The MezzoTinA-asthma studies (NCT01172808 and NCT01172821) were two replicate Phase III, randomized, double-blind, placebo-controlled, parallel-group studies assessing the efficacy and safety of tiotropium Respimat add-on therapy (5 µg and 2.5 µg) in patients with symptomatic moderate asthma on medium-dose ICS [16].

Briefly, patients were randomized 1:1:1:1 following a 4-week screening period to once-daily tiotropium 5 µg (as two puffs in the evening), once-daily tiotropium 2.5 µg (as two puffs in

the evening), twice-daily salmeterol 50 µg (as two puffs in the morning and two puffs in the evening) or placebo in a double-dummy protocol, each as an add-on to medium-dose ICS (400–800 µg budesonide or equivalent) for 24 weeks (Figure 1). Tiotropium was delivered via the soft mist inhaler Respimat (Boehringer Ingelheim Pharma, Ingelheim am Rhein, Germany). Analysis of the salmeterol data is not included here as it is outside of the focus of the current article.

Full details of the study design, methodologies and main results from the two trials have been published previously [16]. The trials were carried out in accordance with the Declaration of Helsinki and International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice, and all participating patients provided signed, informed consent.

Tiotropium Respimat, placebo or salmeterol was administered as maintenance therapy with ICS as monotherapy or in combination with other controllers; however, LABAs were not allowed. Therefore, patients in the placebo arm not only received placebo, but continued with their own background treatment with medium-dose ICS and potentially other controllers, except LABA. Open-label salbutamol (albuterol) metered-dose inhalers were provided to patients as rescue medication.

Study population

Patients aged 18–75 years with a ≥3-month history of asthma were enrolled. An initial asthma diagnosis before the age of 40 years and symptomatic disease, with an ACQ-7 mean score of ≥1.5 [21], were required. The main exclusion criteria were lung diseases other than asthma (e.g. chronic obstructive pulmonary disease) or serious, unstable coexisting illnesses.

Study endpoints

Co-primary endpoints for lung function in each of the trials were change in peak FEV_1 from baseline 0–3 hours post-dose ($FEV_{1(0–3h)}$) response and trough (pre-dose) FEV_1 response at the end of the 24-week treatment period. For the analysis of pooled data from the trials, the primary endpoint was the ACQ-7 responder rate after week 24. This was analyzed as a secondary endpoint in the individual trials. Secondary endpoints in each study included peak FVC, mean weekly pre-dose morning PEF response and weekly pre-dose evening PEF response at week 24.

Secondary endpoints for the pooled data from both trials included time to first severe asthma exacerbation, time to first asthma exacerbation (subsequently described as asthma worsening), both during the 24-week treatment period, and ACQ-7 total score at all visits.

Safety

The analysis of adverse events (AEs) was based on the concept of treatment-emergent AEs, i.e. all AEs that were reported after the first dose of study medication in the treatment period and within 30 days after the last dose of study medication.

Subgroup analyses

All subgroups were assessed for all co-primary endpoints and secondary endpoints, and included all randomized patients who took at least one dose of trial drug. The subgroups were: age (<40, 40–60, >60, and separately <65 and ≥65 years); gender; smoking status (never smoked and ex-smoker); race (White, Black/African American, Asian or American Indian/Alaska native); ethnicity (Hispanic/Latino or Not Hispanic/Latino); BMI (<20, 20–<25, 25–<30 and ≥30 kg/m^2); age at asthma onset (<18 and ≥18 years); disease duration (<5, 5–<20 and ≥20 years); FEV_1 % predicted at screening (≥60–<80% and ≥80%) and FEV_1

reversibility at screening (<15%, ≥15–≤20% and >20%); leukotriene receptor antagonist (LTRA) use at randomization, and LABA use prior to screening. Allergic status by clinician judgment (Yes or No); serum IgE (≤430 µg/L and >430 µg/L) and blood eosinophilia (≤0.6 × 10^9/L and >0.6 × 10^9/L) have been reported in detail previously [20].

Statistical analysis

We carried out separate Fisher's exact test within each of the above subgroups, and calculated odds ratios (ORs) and 95% confidence intervals (Cis) for each subgroup and treatment.

Peak $FEV_{1(0–3h)}$ and trough FEV_1

Categorical subgroup analyses of peak $FEV_{1(0–3h)}$ and trough FEV_1 were performed using a restricted maximum likelihood-based mixed model repeated measures (MMRM) approach, which included treatment, study, visit and treatment-by-visit as fixed, categorical effects, and baseline and baseline-by-visit as fixed, continuous covariates. Patients were included as a random effect, and a spatial power structure was used to model the within-patient errors. The Kenward–Roger approximation was used to estimate the denominator degrees of freedom [22]. The treatment difference was measured by calculating adjusted means and 95% CIs within subgroup categories. An interaction P-value was obtained via a separate MMRM model that additionally included the fixed categorical effects subgroup and treatment-by-subgroup.

ACQ-7 responder rate

Categorical subgroup analyses of ACQ-7 responder rate were performed using a logistic regression that included treatment and study. Patients were defined as responders if an improvement in ACQ-7 mean score of ≥0.5 (the minimum clinically important difference

[21]) was observed. The treatment effect was measured by calculating ORs and 95% CIs within subgroup categories.

Time to first severe asthma exacerbation

Subgroup analysis of the time to first severe asthma exacerbation was performed using Cox regression analysis. The regression model included treatment and study as effects. The treatment effect was measured by calculating hazard ratios (HRs) and 95% CIs within subgroup categories. The validity of the proportional hazards assumption, which is presumed in Cox regression, was checked graphically through Kaplan–Meier plots and plots of Schoenfeld residuals. All included patients were analyzed from start of treatment until first occurrence of the event (severe asthma exacerbation). A patient who did not experience an event during the treatment period was censored at the end of the treatment period. An interaction P-value was obtained via a separate Cox regression that additionally included subgroup and treatment-by-subgroup interaction terms. All analyses were done with SAS® v9.4.

Results

Baseline demographics and disease characteristics

A total of 2100 patients were included: 523 in the placebo group, 541 in the salmeterol group, 519 in the 2.5 µg tiotropium Respimat group and 517 in the 5 µg tiotropium Respimat group (Figure 1). Baseline demographics and disease characteristics were balanced between treatment groups (Table 1). The majority of patients were female (~60%); most patients had never smoked (84%). Mean age was 43.1 years. Concomitant leukotriene modifiers had been taken by 10% of patients in the last 3 months before screening.

Efficacy

Peak $FEV_{1(0–3h)}$ and trough FEV_1

Peak $FEV_{1(0–3h)}$ and trough FEV_1 responses were significantly improved with tiotropium Respimat versus placebo after 24 weeks' treatment, with treatment differences for the pooled trials of 185 mL and 223 mL for peak $FEV_{1(0–3h)}$ in the tiotropium 5 µg and 2.5 µg groups, respectively, and 146 mL and 180 mL for trough FEV_1 for tiotropium 5 µg and 2.5 µg, respectively [16]. This indicates that the effects of both tiotropium Respimat doses were similar on these endpoints across the pooled trial data.

The results of the different subgroup analyses showed that these improvements in lung function with tiotropium Respimat versus placebo were independent of the patient baseline characteristics assessed (Figures 2 and 3). In addition, the subgroup analyses results were similar between the two doses of tiotropium Respimat.

ACQ-7 responder rate

Significant improvements in ACQ-7 responder rate (a co-primary endpoint) were observed with tiotropium Respimat 5 µg and 2.5 µg after week 24 versus placebo; OR 1.32 (95% CI 1.02–1.71; P=0.035) and OR 1.33 (95% CI 1.03–1.72; P=0.031), respectively [8]. The improvements in ACQ-7 responder rate with tiotropium Respimat compared with placebo were not significantly influenced by patients' baseline characteristics except for the following: Hispanic/Latino ethnicity (for tiotropium Respimat 5 µg); BMI <20 kg/m^2 and FEV_1 reversibility at screening <15% (both for tiotropium Respimat 2.5 µg; Figure 4).

Time to first severe asthma exacerbations

The time to first severe asthma exacerbations was reduced with tiotropium Respimat versus placebo, with overall HRs of 0.5 (95% CI 0.30–0.84) for the 2.5 µg dose and 0.72 (95% CI

0.45–1.14) for the 5 µg dose (Figure 5). Categorical subgroup analyses demonstrated that this was largely independent of patients' baseline characteristics. The responses from the following subgroups showed trends that favored tiotropium Respimat across both doses: age <65 years; sex (male and female); smoking status (ex-smoker and never smoked); race (all); ethnicity (Not Hispanic/Latino); BMI (20–<25 and 25–<30 kg/m^2); age of onset (<18 and ≥18); duration of asthma (5–<20, ≥20 years); LABA use prior to screening (Yes); FEV_1 % predicted at screening (60–<80% and ≥80%), and FEV_1 reversibility at screening (<15% and >20%); and leukotriene modifiers at randomization (yes and no).

Safety

Full safety data have been presented previously [16]. In summary, the numbers of patients reporting AEs were comparable between treatment arms, with asthma, decreased PEF rate and nasopharyngitis being the most frequently reported AEs (Table S1). The number of patients reporting serious AEs was similar across the treatment groups, with the most frequently reported being asthma. There were no deaths in the study.

Discussion

Tiotropium Respimat (5 µg and 2.5 µg) was shown to be an effective therapeutic agent with a good safety profile, providing improvements in lung function and asthma control irrespective of baseline characteristics in patients with symptomatic asthma receiving medium-dose ICS maintenance treatment. The subgroup analyses presented here show that the efficacy of both doses of once-daily tiotropium Respimat add-on therapy is independent of a broad range of baseline characteristics as follows: age, gender, smoking status, race, ethnicity, BMI, age at onset of asthma, disease duration, LABA use prior to screening, FEV_1

reversibility at screening and LTRA use at randomization. Overall, there were similar findings between the 5 µg and 2.5 µg doses for the measured baseline characteristics.

The heterogeneity of asthma means that patients may respond differently to targeted therapies. Our findings add to the body of evidence that supports the use of tiotropium Respimat without the need for phenotyping [19]. Our findings also build on the previously published subgroup analysis of the PrimoTinA-asthma and MezzoTinA-asthma trials, where tiotropium Respimat was found to be efficacious regardless of baseline T2 phenotype status [20]. In contrast, other treatment options have been shown to have differences in efficacy in particular patient populations. For example, patients with asthma with higher sputum or blood eosinophils are known to respond better to systemic corticosteroids and ICS compared with those who have lower levels [23,24]. Obesity is a common comorbidity of asthma, and obese asthma patients tend to have poorer asthma control and increased hospitalizations compared with lean patients [25,26]. Obese asthma patients also exhibit a blunted response to ICS, and generally do not respond as well to controller medications [27]. Furthermore, BMI has been shown as an important determinant of response to active treatment [28]. Animal studies have shown that the hyperinsulinemia that accompanies obesity potentiates vagally-induced bronchoconstriction due to a loss of inhibitory M2 receptor function, leading to increased acetylcholine release in overweight and obese patients with asthma [29]; therefore, long-acting muscarinic antagonism may be particularly beneficial for these patients. The findings of this present study show that tiotropium Respimat at doses of 5 µg and 2.5 µg is of benefit in patients with symptomatic moderate asthma, regardless of their BMI. Smokers with asthma can also pose a therapeutic challenge, as this group of patients tend to be resistant to treatment with ICS [30–32].

Improvements in lung function with tiotropium Respimat were shown to be independent of patient smoking status.

ACQ-7 responder rate and time to first severe asthma exacerbation were largely independent of patients' baseline characteristics, including age, sex, smoking status and ethnicity. The only exceptions to this were Hispanic/Latino ethnicity (for tiotropium Respimat 5 µg), BMI <20 kg/m^2 and FEV_1 reversibility at screening <15% (both for tiotropium Respimat 2.5 µg) for ACQ-7 responder rate. However, in these subgroups, patient numbers were relatively small in comparison with the other subgroups and showed wide CI ranges, thus making it difficult to draw a definitive conclusion. Analysis of the rate ratio of severe exacerbations was not performed since time to first severe asthma exacerbation was largely independent of baseline characteristics and the numbers of exacerbations were low.

Our findings extend the recommendations in the GINA report, which include tiotropium Respimat as an add-on therapy option in patients with a history of asthma exacerbations at Step 4 or 5, with no requirement for prior phenotyping, and suggest that they may be added successfully in patients on Step 3 who remain symptomatic [1]. Furthermore, the subgroups included in this analysis examine the baseline characteristics that clinicians can easily evaluate when considering which therapy best meets a patient's needs. Therefore, it is noteworthy that, when deciding on the most appropriate asthma therapy, the use of tiotropium Respimat is not ruled out by any of the baseline characteristics evaluated in this study.

These results also reflect those of the TALC study, although a lower dose of ICS was used in that study than in our study [17]. In the TALC study, baseline characteristics such as ethnicity, gender, atopy, IgE, sputum eosinophils, asthma duration and BMI were found to

be non-predictive of a clinical response to tiotropium when administered by HandiHaler [18]. However, response to a short-acting bronchodilator, magnitude of airway obstruction and higher cholinergic tone (defined as a lower resting heart rate) were found to be predictors of a response to tiotropium HandiHaler in the TALC population [18]. In our study, the response to tiotropium Respimat is independent of a response to a short-acting bronchodilator (FEV_1 reversibility at screening >15%, ≥15–≤20% and >20%) and airway obstruction (FEV_1 % predicted at screening ≥60–<80% and ≥80%). We did not assess the effect of cholinergic tone on response to tiotropium Respimat.

A major strength of this study is that the patient sample is large, allowing investigation of a wide range of baseline characteristics. Our study also has the following limitations. Although the majority of the subgroup analyses were prespecified, the study was not powered for these. In addition, a post hoc analysis was included for two subgroups (LTRA use at randomization and LABA use prior to screening). Another potential limitation is that subgroup analyses were performed by categorization of continuous baseline parameters (such as biomarkers), necessitating the selection of cut-off thresholds.

Conclusions

The results of these subgroup analyses suggest that once-daily tiotropium Respimat as add-on to ICS provides a beneficial treatment option for patients with asthma who remain symptomatic despite medium-dose ICS, regardless of baseline characteristics.

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Conflict of interest

TBC is on the advisory boards for Genentech, Novartis, Sanofi/Regeneron, AstraZeneca, is an investigator on studies funded by Genentech, Novartis, Sanofi/Regeneron and Boehringer Ingelheim, and on the speakers bureau for Genentech.

RA received speaker fees from AstraZeneca, Boehringer Ingelheim and Chiesi.

EOM is a consultant for ALK, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, GossamerBio, Merck and Sanofi/Regeneron, and on the speakers bureau for ALK.

HAMK's institution has received fees for advisory boards from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer and TEVA, unconditional research grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis and TEVA, and per patient fees for participation in trials.

ERB has undertaken clinical trials through his employer, Wake Forest School of Medicine and the University of Arizona. He has also served as a paid consultant outside the submitted work.

LZ-P is contracted by Boehringer Ingelheim. AdlH is employed by Boehringer Ingelheim.

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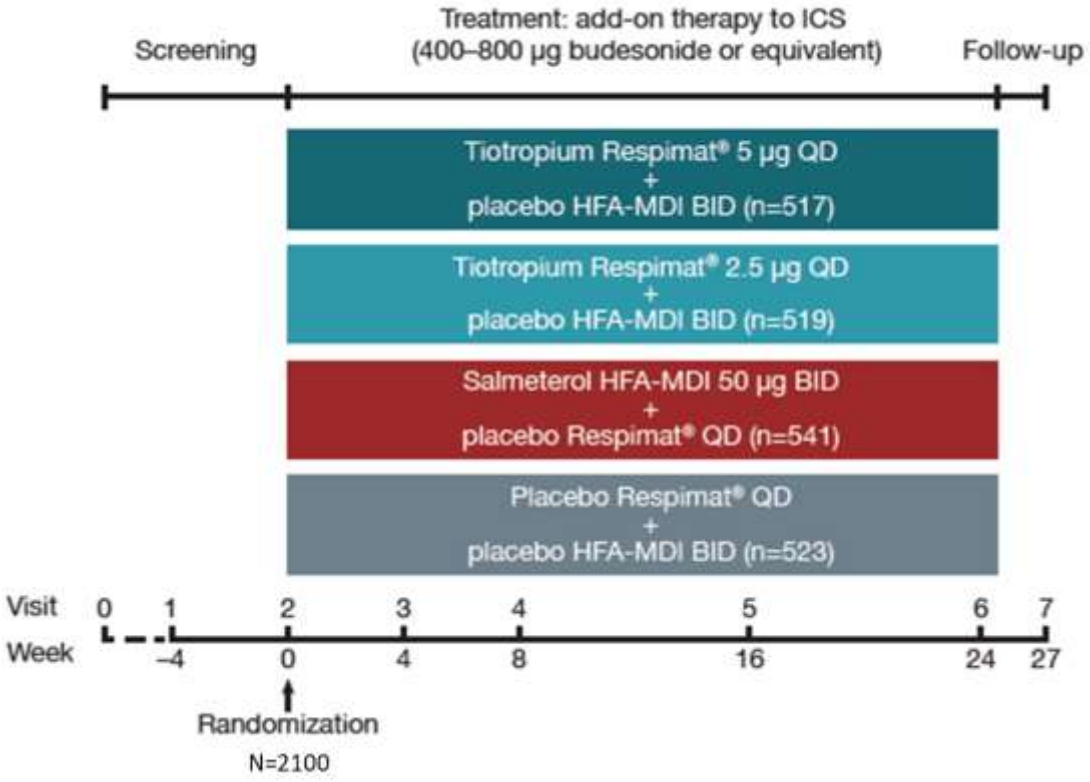
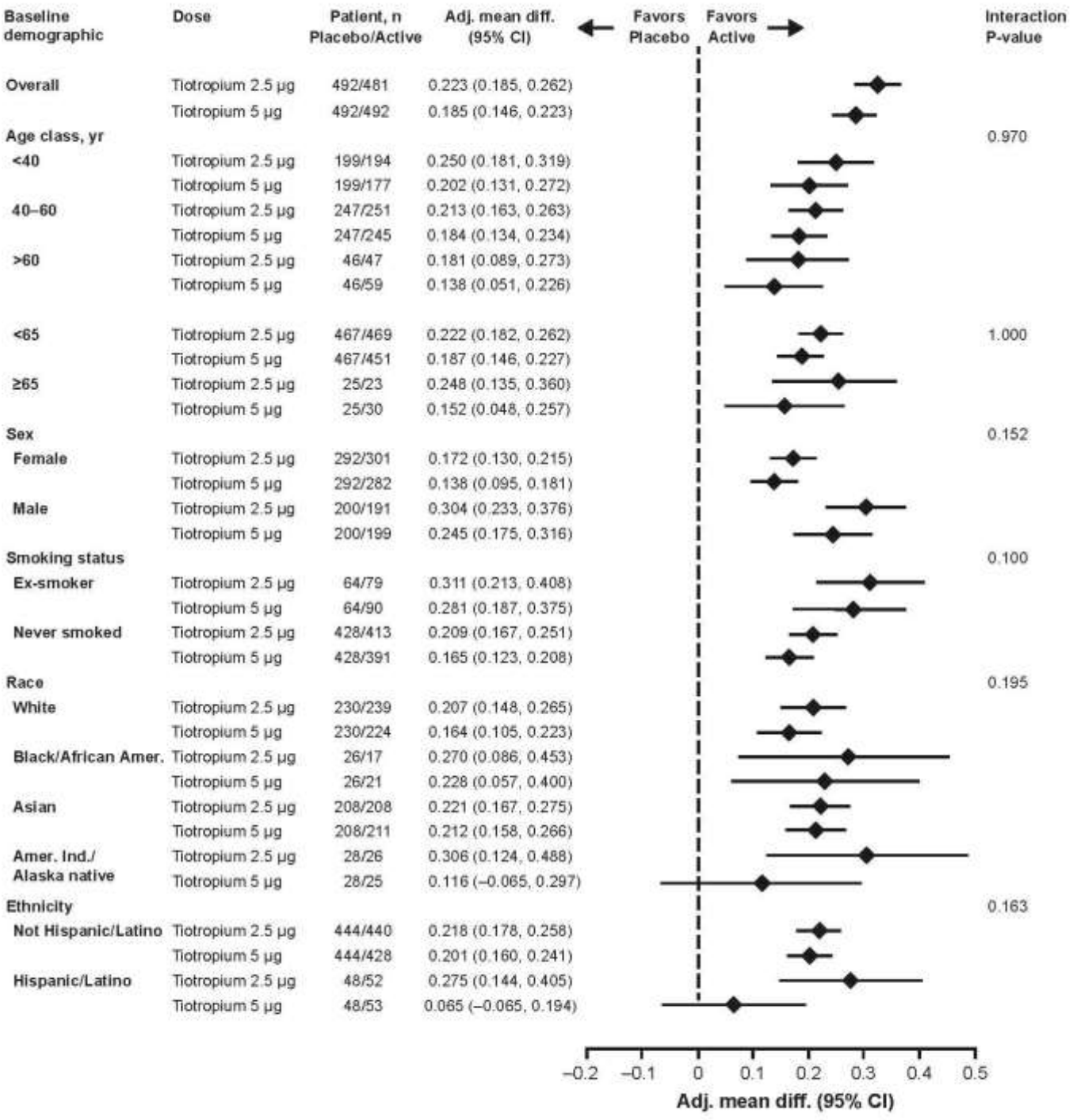
Figure 1. Study design



BID = twice daily; HFA-MDI = hydrofluoroalkane metered-dose inhaler; ICS = inhaled corticosteroids; QD = once daily.

Figure 2. Adjusted mean differences in peak $FEV_{1(0–3h)}$ after week 24 with 5 µg and 2.5 µg tiotropium Respimat versus placebo by (A) baseline demographics and (B) baseline characteristics

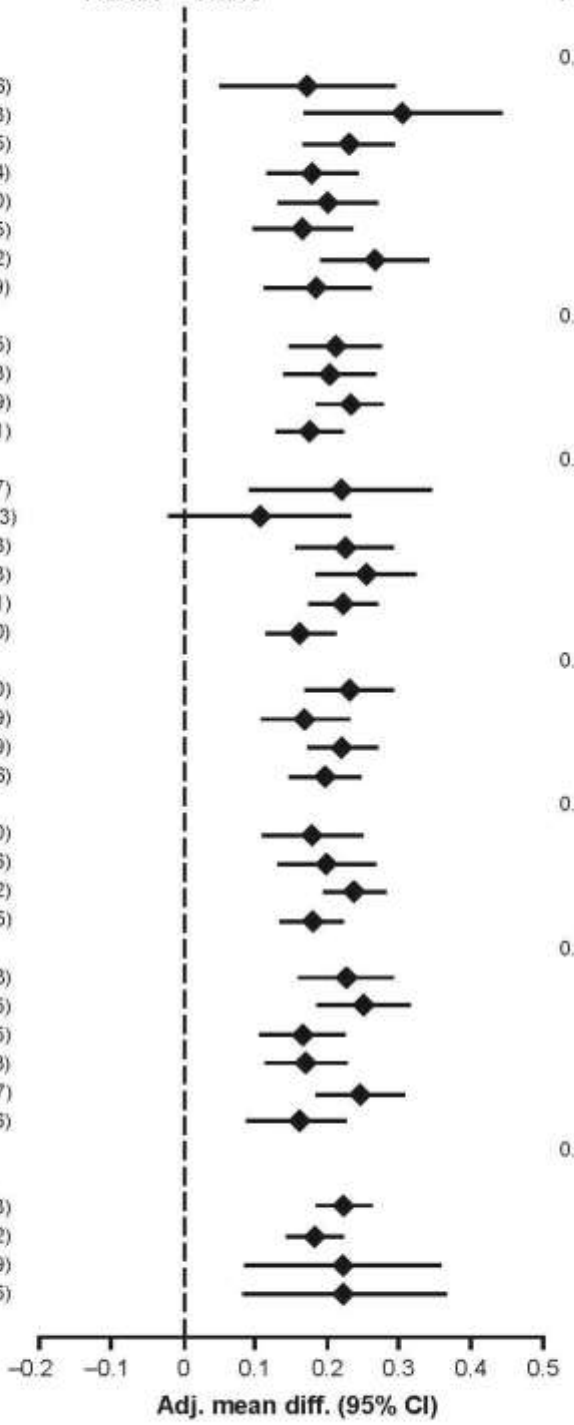
(2A)



Full analysis set. Amer. = American; Amer. Ind. = American Indian; CI = confidence interval; peak $FEV_{1(0-3h)}$ = peak forced expiratory volume in 1 s within 3 h after the administration of maintenance therapy and study drug; yr = year.

(2B)

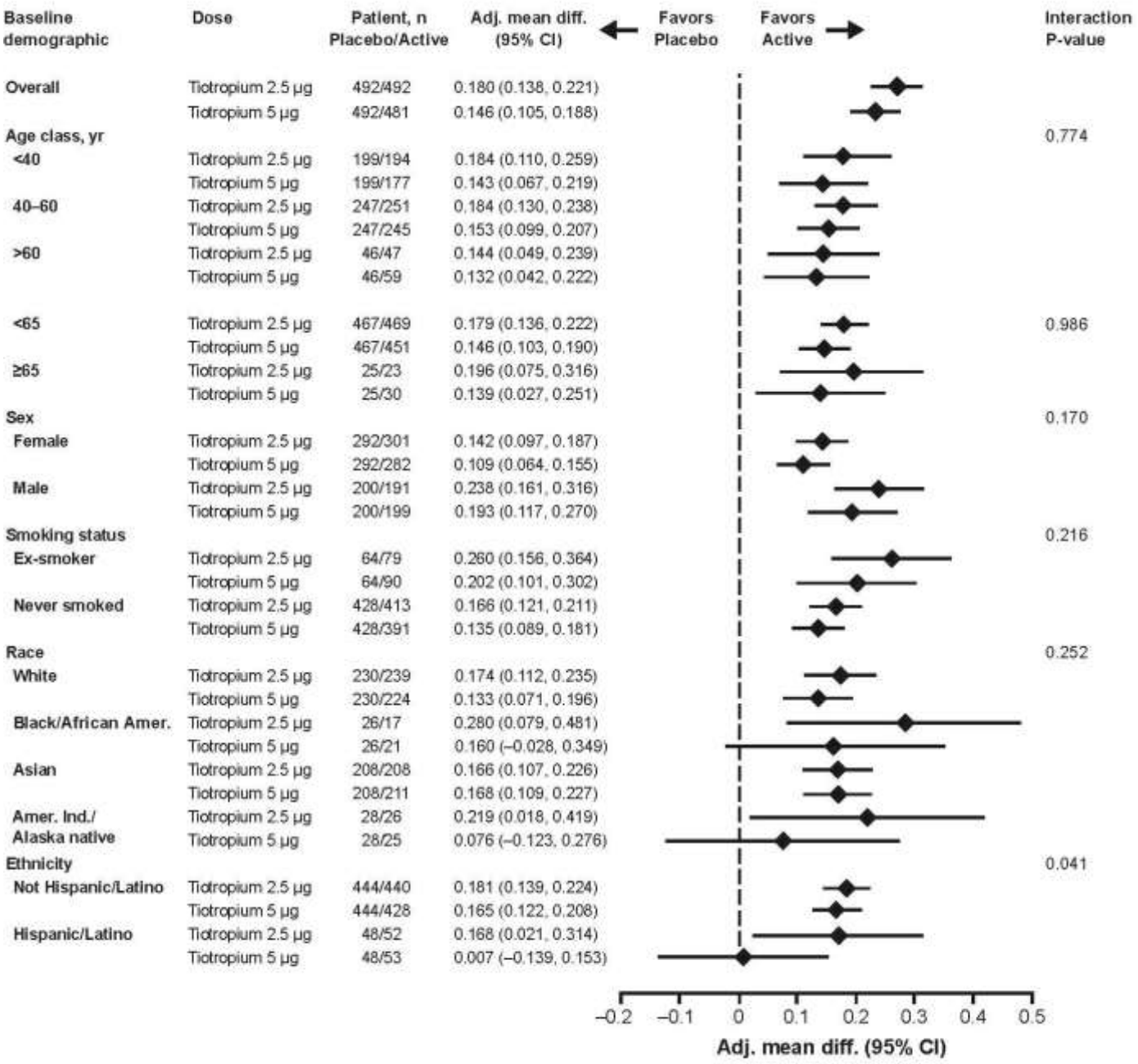
Baseline characteristic	Dose	Patient, n Placebo/Active	Adj. mean diff. (95% CI)	Interaction P-value
BMI class, kg/m²				0.750
<20	Tiotropium 2.5 µg	44/43	0.171 (0.047, 0.296)	
	Tiotropium 5 µg	44/30	0.304 (0.166, 0.443)	
20–<25	Tiotropium 2.5 µg	172/178	0.230 (0.165, 0.295)	
	Tiotropium 5 µg	172/177	0.178 (0.113, 0.244)	
25–<30	Tiotropium 2.5 µg	158/162	0.200 (0.130, 0.270)	
	Tiotropium 5 µg	158/157	0.164 (0.094, 0.235)	
≥30	Tiotropium 2.5 µg	118/109	0.266 (0.190, 0.342)	
	Tiotropium 5 µg	118/117	0.184 (0.110, 0.259)	
Age at onset				0.930
<18 years	Tiotropium 2.5 µg	181/194	0.210 (0.145, 0.275)	
	Tiotropium 5 µg	181/178	0.202 (0.137, 0.268)	
≥18 years	Tiotropium 2.5 µg	311/298	0.232 (0.184, 0.279)	
	Tiotropium 5 µg	311/303	0.174 (0.127, 0.221)	
Duration of asthma				0.032
<5 years	Tiotropium 2.5 µg	61/60	0.218 (0.090, 0.347)	
	Tiotropium 5 µg	61/62	0.105 (–0.023, 0.233)	
5–<20 years	Tiotropium 2.5 µg	174/157	0.224 (0.155, 0.293)	
	Tiotropium 5 µg	174/153	0.254 (0.184, 0.323)	
≥20 years	Tiotropium 2.5 µg	257/275	0.222 (0.174, 0.271)	
	Tiotropium 5 µg	257/266	0.161 (0.112, 0.210)	
LABA use prior to screening				0.892
No	Tiotropium 2.5 µg	192/184	0.229 (0.167, 0.290)	
	Tiotropium 5 µg	192/189	0.168 (0.107, 0.229)	
Yes	Tiotropium 2.5 µg	300/308	0.220 (0.171, 0.269)	
	Tiotropium 5 µg	300/292	0.196 (0.146, 0.246)	
FEV_1 at screening (% predicted)				0.144
≥60% to <80%	Tiotropium 2.5 µg	113/112	0.178 (0.107, 0.250)	
	Tiotropium 5 µg	113/137	0.198 (0.130, 0.266)	
≥80%	Tiotropium 2.5 µg	379/380	0.237 (0.192, 0.282)	
	Tiotropium 5 µg	379/344	0.179 (0.133, 0.225)	
FEV_1 reversibility at screening				0.084
<15%	Tiotropium 2.5 µg	120/108	0.226 (0.159, 0.293)	
	Tiotropium 5 µg	120/114	0.249 (0.184, 0.315)	
≥15% to ≤20%	Tiotropium 2.5 µg	149/139	0.164 (0.103, 0.225)	
	Tiotropium 5 µg	149/156	0.169 (0.110, 0.228)	
>20%	Tiotropium 2.5 µg	223/245	0.245 (0.182, 0.307)	
	Tiotropium 5 µg	223/211	0.161 (0.096, 0.226)	
Leukotriene modifiers at randomization				0.906
No	Tiotropium 2.5 µg	454/446	0.223 (0.183, 0.263)	
	Tiotropium 5 µg	454/441	0.182 (0.142, 0.222)	
Yes	Tiotropium 2.5 µg	38/46	0.221 (0.083, 0.359)	
	Tiotropium 5 µg	38/40	0.223 (0.081, 0.365)	



Full analysis set. BMI = body mass index; CI = confidence interval; FEV_1 = forced expiratory volume in 1 s; LABA = long-acting β_2-agonist; peak $FEV_{1(0-3h)}$ = peak forced expiratory volume in 1 s within 3 h after the administration of maintenance therapy and study drug.

Figure 3. Adjusted mean differences in trough FEV_1 response after week 24 with 5 µg and 2.5 µg tiotropium Respimat versus placebo by (A) baseline demographics and (B) baseline characteristics

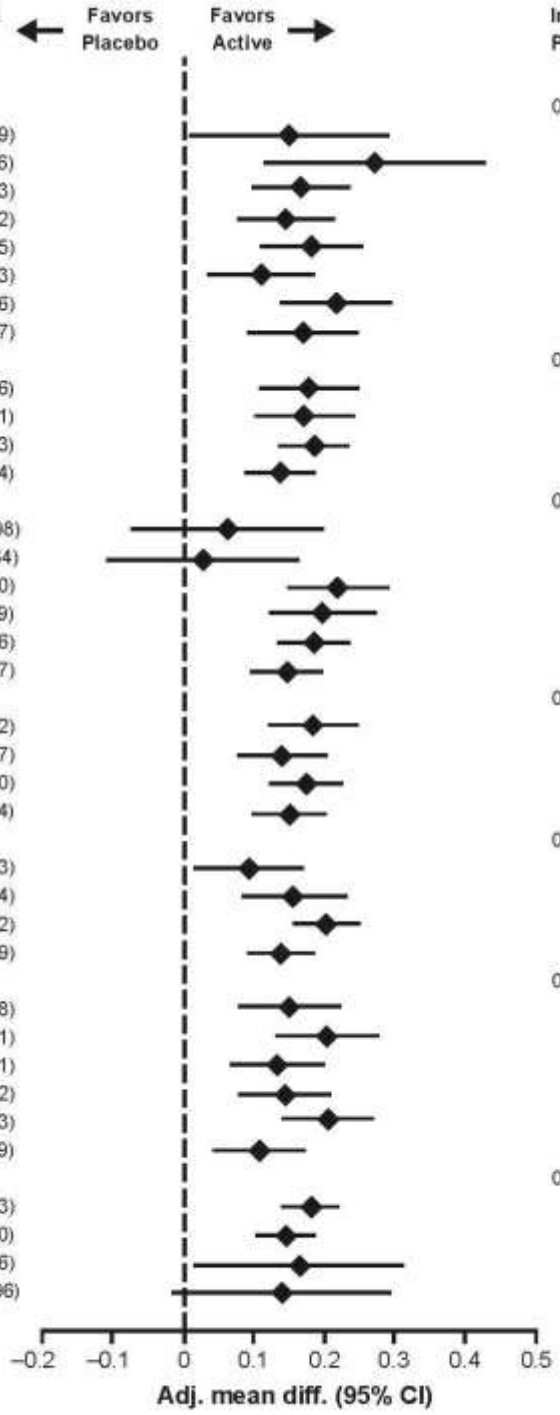
(3A)



Full analysis set. Amer. = American; Amer. Ind. = American Indian; CI = confidence interval; peak $FEV_{0\text{–}3\,h}$ = peak forced expiratory volume in 1 s within 3 h after the administration of maintenance therapy and study drug; yr = year.

(3B)

Baseline characteristic	Dose	Patient, n Placebo/Active	Adj. mean diff. (95% CI)	Interaction P-value
BMI class, kg/m²				0.789
<20	Tiotropium 2.5 µg	44/43	0.147 (0.005, 0.289)	
	Tiotropium 5 µg	44/30	0.268 (0.110, 0.426)	
20–<25	Tiotropium 2.5 µg	172/178	0.163 (0.093, 0.233)	
	Tiotropium 5 µg	172/177	0.142 (0.072, 0.212)	
25–<30	Tiotropium 2.5 µg	158/162	0.180 (0.105, 0.255)	
	Tiotropium 5 µg	158/157	0.108 (0.032, 0.183)	
≥30	Tiotropium 2.5 µg	118/109	0.215 (0.134, 0.296)	
	Tiotropium 5 µg	118/117	0.167 (0.088, 0.247)	
Age at onset				0.881
<18 years	Tiotropium 2.5 µg	181/194	0.176 (0.105, 0.246)	
	Tiotropium 5 µg	181/178	0.169 (0.098, 0.241)	
≥18 years	Tiotropium 2.5 µg	311/298	0.183 (0.132, 0.233)	
	Tiotropium 5 µg	311/303	0.133 (0.082, 0.184)	
Duration of asthma				0.089
<5 years	Tiotropium 2.5 µg	61/60	0.061 (–0.077, 0.198)	
	Tiotropium 5 µg	61/62	0.026 (–0.111, 0.164)	
5–<20 years	Tiotropium 2.5 µg	174/157	0.216 (0.142, 0.290)	
	Tiotropium 5 µg	174/153	0.194 (0.119, 0.269)	
≥20 years	Tiotropium 2.5 µg	257/275	0.184 (0.131, 0.236)	
	Tiotropium 5 µg	257/266	0.145 (0.092, 0.197)	
LABA use prior to screening				0.899
No	Tiotropium 2.5 µg	192/184	0.186 (0.120, 0.252)	
	Tiotropium 5 µg	192/189	0.141 (0.076, 0.207)	
Yes	Tiotropium 2.5 µg	300/308	0.177 (0.123, 0.230)	
	Tiotropium 5 µg	300/292	0.151 (0.097, 0.204)	
FEV_1 at screening (% predicted)				0.075
≥60% to <80%	Tiotropium 2.5 µg	113/112	0.093 (0.013, 0.173)	
	Tiotropium 5 µg	113/137	0.159 (0.083, 0.234)	
≥80%	Tiotropium 2.5 µg	379/380	0.204 (0.156, 0.252)	
	Tiotropium 5 µg	379/344	0.139 (0.090, 0.189)	
FEV_1 reversibility at screening				0.085
<15%	Tiotropium 2.5 µg	120/108	0.152 (0.077, 0.228)	
	Tiotropium 5 µg	120/114	0.206 (0.132, 0.281)	
≥15% to ≤20%	Tiotropium 2.5 µg	149/139	0.134 (0.067, 0.201)	
	Tiotropium 5 µg	149/156	0.147 (0.081, 0.212)	
>20%	Tiotropium 2.5 µg	223/245	0.207 (0.140, 0.273)	
	Tiotropium 5 µg	223/211	0.110 (0.041, 0.179)	
Leukotriene modifiers at randomization				0.908
No	Tiotropium 2.5 µg	454/446	0.180 (0.137, 0.223)	
	Tiotropium 5 µg	454/441	0.147 (0.104, 0.190)	
Yes	Tiotropium 2.5 µg	38/46	0.165 (0.014, 0.316)	
	Tiotropium 5 µg	38/40	0.142 (–0.013, 0.296)	

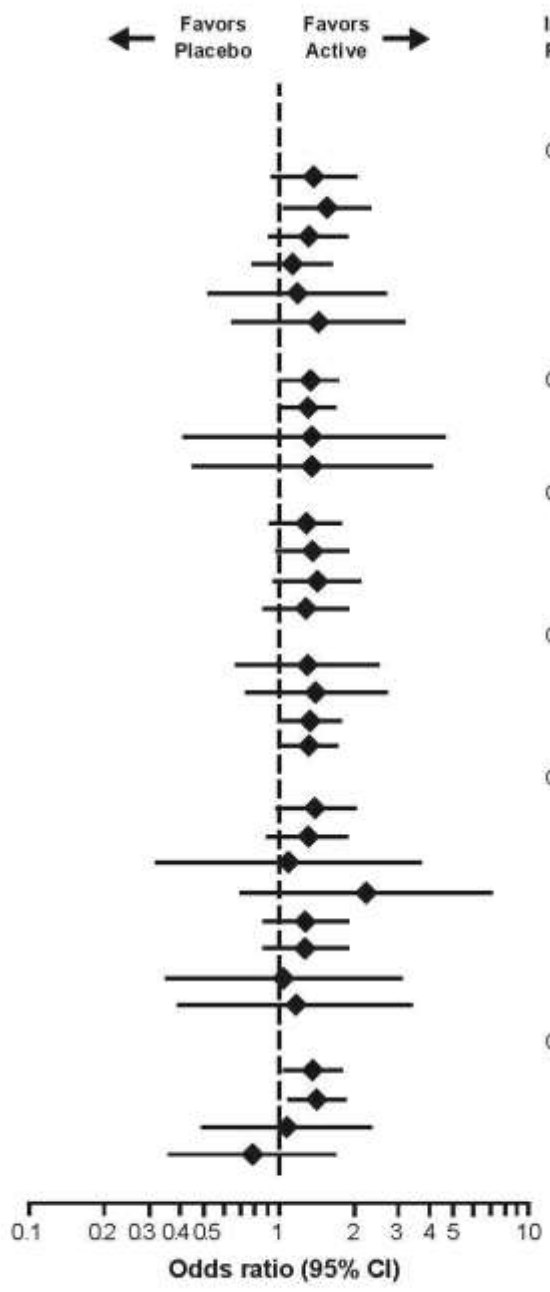


Full analysis set. BMI = body mass index; CI = confidence interval; FEV_1 = forced expiratory volume in 1 s; LABA = long-acting β_2-agonist; peak $FEV_{1(0-3h)}$ = peak forced expiratory volume in 1 s within 3 h after the administration of maintenance therapy and study drug.

Figure 4. Assessment of odds ratios in ACQ responders* after week 24 with 5 µg and 2.5 µg tiotropium Respimat versus placebo by (A) baseline demographics and (B) baseline characteristics

(4A)

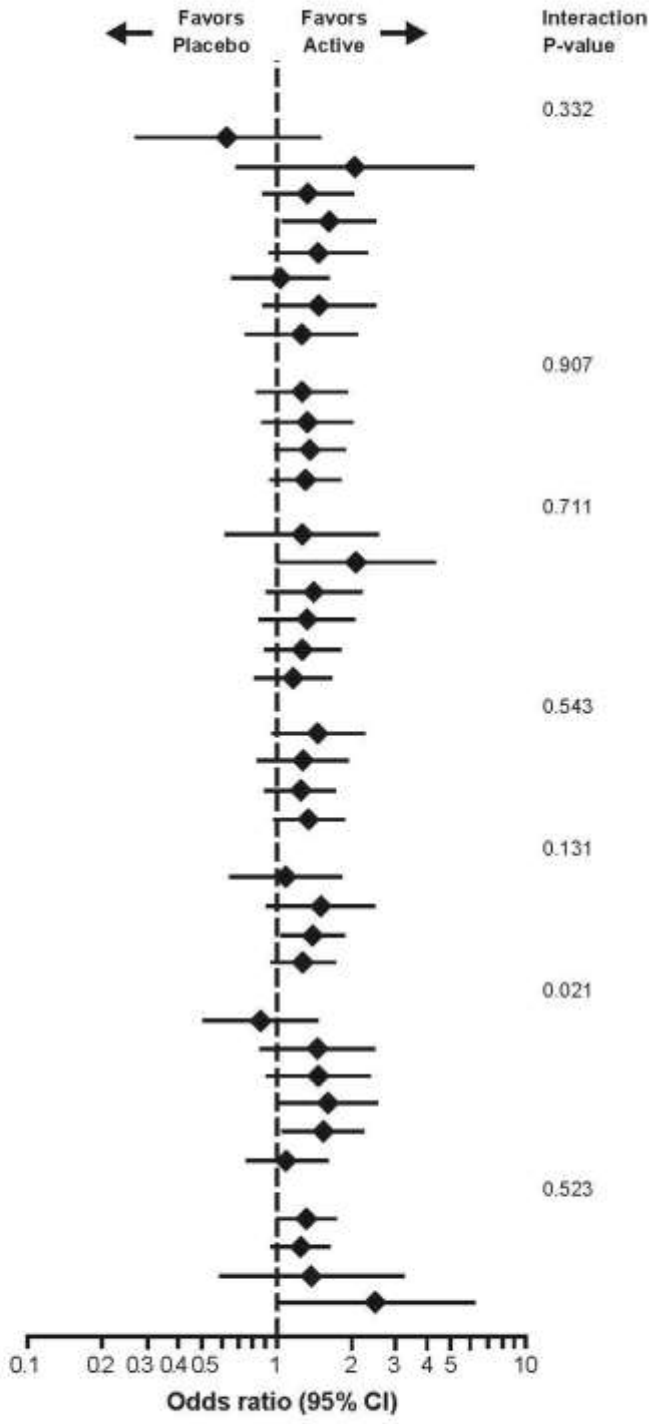
Baseline demographic	Dose	Patient, n Placebo/Active	Odds ratio (95% CI)	Interaction P-value
Overall	Tiotropium 2.5 µg	518/515	1.33 (1.03, 1.71)	
	Tiotropium 5 µg	518/513	1.32 (1.03, 1.70)	
Age class, yr				0.751
<40	Tiotropium 2.5 µg	216/208	1.38 (0.93, 2.04)	
	Tiotropium 5 µg	216/192	1.55 (1.04, 2.32)	
40–60	Tiotropium 2.5 µg	254/257	1.31 (0.91, 1.87)	
	Tiotropium 5 µg	254/258	1.13 (0.79, 1.61)	
>60	Tiotropium 2.5 µg	48/50	1.18 (0.52, 2.69)	
	Tiotropium 5 µg	48/63	1.44 (0.65, 3.17)	
<65	Tiotropium 2.5 µg	492/492	1.33 (1.03, 1.71)	0.920
	Tiotropium 5 µg	492/480	1.31 (1.01, 1.70)	
≥65	Tiotropium 2.5 µg	26/23	1.37 (0.41, 4.63)	
	Tiotropium 5 µg	26/33	1.35 (0.45, 4.10)	
Sex				0.872
Female	Tiotropium 2.5 µg	308/313	1.28 (0.92, 1.76)	
	Tiotropium 5 µg	308/297	1.36 (0.98, 1.89)	
Male	Tiotropium 2.5 µg	210/202	1.42 (0.95, 2.11)	
	Tiotropium 5 µg	210/216	1.28 (0.87, 1.88)	
Smoking status				0.980
Ex-smoker	Tiotropium 2.5 µg	70/82	1.29 (0.67, 2.50)	
	Tiotropium 5 µg	70/96	1.40 (0.74, 2.66)	
Never smoked	Tiotropium 2.5 µg	448/433	1.33 (1.02, 1.75)	
	Tiotropium 5 µg	448/417	1.30 (0.99, 1.70)	
Race				0.750
White	Tiotropium 2.5 µg	243/250	1.40 (0.97, 2.02)	
	Tiotropium 5 µg	243/238	1.30 (0.90, 1.87)	
Black/African Amer.	Tiotropium 2.5 µg	27/17	1.09 (0.32, 3.69)	
	Tiotropium 5 µg	27/22	2.22 (0.70, 7.08)	
Asian	Tiotropium 2.5 µg	218/219	1.27 (0.86, 1.87)	
	Tiotropium 5 µg	218/224	1.27 (0.86, 1.86)	
Amer. Ind./	Tiotropium 2.5 µg	29/27	1.04 (0.35, 3.08)	
Alaska native	Tiotropium 5 µg	29/29	1.16 (0.40, 3.38)	
Ethnicity				0.322
Not Hispanic/Latino	Tiotropium 2.5 µg	465/460	1.36 (1.05, 1.78)	
	Tiotropium 5 µg	465/456	1.41 (1.08, 1.84)	
Hispanic/Latino	Tiotropium 2.5 µg	53/55	1.07 (0.49, 2.33)	
	Tiotropium 5 µg	53/57	0.78 (0.36, 1.68)	



Full analysis set. ACQ = Asthma Control Questionnaire; Amer. = American; Amer Ind. = American Indian; CI = confidence interval; yr = year.
*An ACQ responder is defined as an improvement in ACQ-7 mean score of ≥0.5.

(4B)

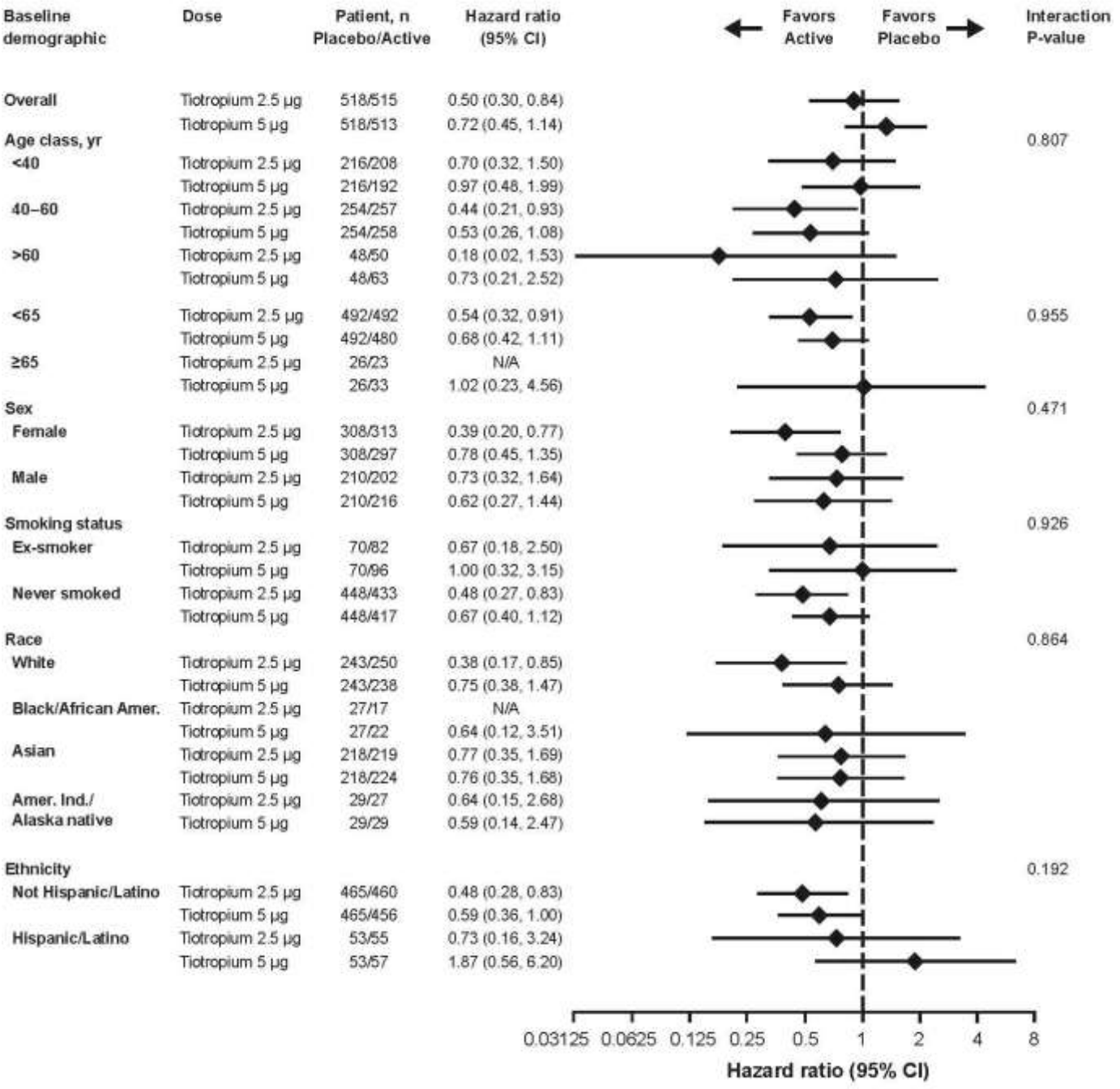
Baseline characteristic	Dose	Patient, n Placebo/Active	Odds ratio (95% CI)	Interaction P-value
BMI class, kg/m²				0.332
<20	Tiotropium 2.5 µg	45/44	0.63 (0.27, 1.50)	
	Tiotropium 5 µg	45/31	2.07 (0.69, 6.17)	
20–<25	Tiotropium 2.5 µg	186/188	1.33 (0.88, 2.02)	
	Tiotropium 5 µg	186/189	1.62 (1.06, 2.47)	
25–<30	Tiotropium 2.5 µg	163/168	1.47 (0.94, 2.30)	
	Tiotropium 5 µg	163/169	1.04 (0.67, 1.61)	
≥30	Tiotropium 2.5 µg	124/115	1.48 (0.88, 2.49)	
	Tiotropium 5 µg	124/124	1.26 (0.76, 2.09)	
Age at onset, yr				0.907
<18	Tiotropium 2.5 µg	194/202	1.27 (0.84, 1.90)	
	Tiotropium 5 µg	194/197	1.33 (0.88, 2.01)	
≥18	Tiotropium 2.5 µg	324/313	1.36 (0.99, 1.87)	
	Tiotropium 5 µg	324/316	1.31 (0.95, 1.80)	
Duration of asthma, yr				0.711
<5	Tiotropium 2.5 µg	66/65	1.27 (0.63, 2.55)	
	Tiotropium 5 µg	66/66	2.08 (1.01, 4.30)	
5–<20	Tiotropium 2.5 µg	183/164	1.41 (0.92, 2.18)	
	Tiotropium 5 µg	183/163	1.33 (0.86, 2.04)	
≥20	Tiotropium 2.5 µg	269/286	1.27 (0.90, 1.79)	
	Tiotropium 5 µg	269/284	1.16 (0.82, 1.64)	
LABA use prior to screening				0.543
No	Tiotropium 2.5 µg	198/196	1.47 (0.97, 2.23)	
	Tiotropium 5 µg	198/204	1.27 (0.85, 1.91)	
Yes	Tiotropium 2.5 µg	320/319	1.25 (0.91, 1.72)	
	Tiotropium 5 µg	320/309	1.35 (0.98, 1.86)	
FEV_1 at screening (% predicted)				0.131
≥60% to <80%	Tiotropium 2.5 µg	117/115	1.09 (0.65, 1.82)	
	Tiotropium 5 µg	117/148	1.51 (0.92, 2.46)	
≥80%	Tiotropium 2.5 µg	401/400	1.40 (1.05, 1.87)	
	Tiotropium 5 µg	401/365	1.28 (0.96, 1.72)	
FEV_1 reversibility at screening				0.021
<15%	Tiotropium 2.5 µg	124/111	0.86 (0.51, 1.45)	
	Tiotropium 5 µg	124/126	1.46 (0.86, 2.46)	
≥15% to ≤20%	Tiotropium 2.5 µg	155/144	1.47 (0.92, 2.34)	
	Tiotropium 5 µg	155/167	1.61 (1.02, 2.52)	
>20%	Tiotropium 2.5 µg	239/260	1.53 (1.06, 2.21)	
	Tiotropium 5 µg	239/220	1.10 (0.76, 1.59)	
Leukotriene modifiers at randomization				0.523
No	Tiotropium 2.5 µg	475/467	1.32 (1.01, 1.72)	
	Tiotropium 5 µg	475/468	1.25 (0.96, 1.63)	
Yes	Tiotropium 2.5 µg	43/48	1.38 (0.59, 3.22)	
	Tiotropium 5 µg	43/45	2.48 (1.00, 6.18)	



Full analysis set. ACQ = Asthma Control Questionnaire; BMI = body mass index; CI = confidence interval; FEV_1 = forced expiratory volume in 1 s; LABA = long-acting β_2-agonist; yr = year.
*An ACQ responder is defined as an improvement in ACQ-7 mean score of ≥0.5.

Figure 5. Time to first severe exacerbation with 5 µg and 2.5 µg tiotropium Respimat versus placebo by (A) baseline demographics and (B) baseline characteristics

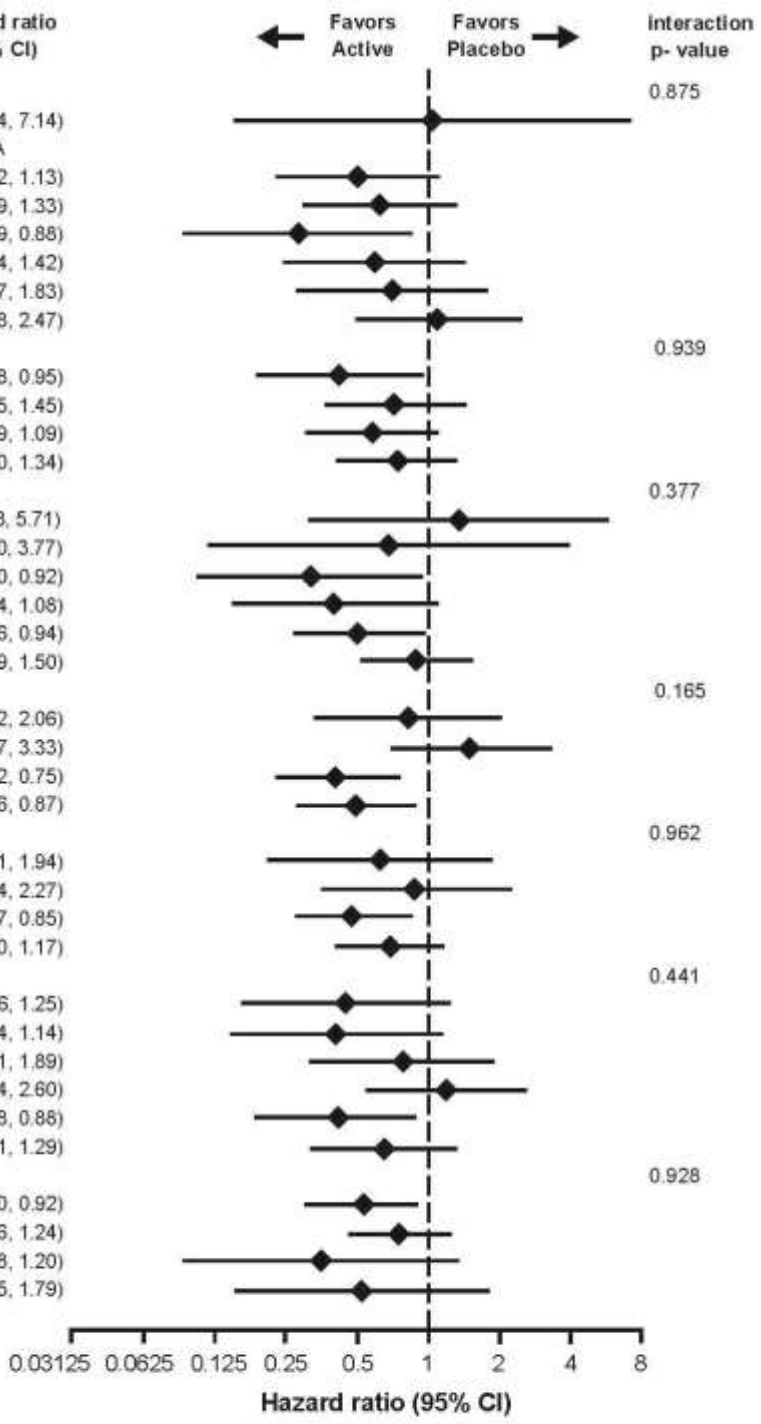
(5A)



Full analysis set. Amer. = American, Amer. Ind. = American Indian, CI = confidence interval, N/A = not applicable, yr = year.
N/A shows that no event occurred in the subgroup.

(5B)

Baseline characteristic	Dose	Patient, n Placebo/Active	Hazard ratio (95% CI)	interaction p- value
BMI class, kg/m^2				0.875
<20	Tiotropium 2.5 µg	45/44	1.00 (0.14, 7.14)	
	Tiotropium 5 µg	45/31	N/A	
20–<25	Tiotropium 2.5 µg	186/188	0.50 (0.22, 1.13)	
	Tiotropium 5 µg	186/189	0.62 (0.29, 1.33)	
25–<30	Tiotropium 2.5 µg	163/168	0.29 (0.09, 0.88)	
	Tiotropium 5 µg	163/169	0.59 (0.24, 1.42)	
≥30	Tiotropium 2.5 µg	124/115	0.71 (0.27, 1.83)	
	Tiotropium 5 µg	124/124	1.09 (0.48, 2.47)	
Age at onset, yr				0.939
<18	Tiotropium 2.5 µg	194/202	0.41 (0.18, 0.95)	
	Tiotropium 5 µg	194/197	0.71 (0.35, 1.45)	
≥18	Tiotropium 2.5 µg	324/313	0.57 (0.29, 1.09)	
	Tiotropium 5 µg	324/316	0.73 (0.40, 1.34)	
Duration of asthma, yr				0.377
<5	Tiotropium 2.5 µg	66/65	1.27 (0.28, 5.71)	
	Tiotropium 5 µg	66/66	0.62 (0.10, 3.77)	
5–<20	Tiotropium 2.5 µg	183/164	0.30 (0.10, 0.92)	
	Tiotropium 5 µg	183/163	0.39 (0.14, 1.08)	
≥20	Tiotropium 2.5 µg	269/286	0.49 (0.26, 0.94)	
	Tiotropium 5 µg	269/284	0.86 (0.49, 1.50)	
LABA use prior to screening				0.165
No	Tiotropium 2.5 µg	198/196	0.81 (0.32, 2.06)	
	Tiotropium 5 µg	198/204	1.49 (0.67, 3.33)	
Yes	Tiotropium 2.5 µg	320/319	0.40 (0.22, 0.75)	
	Tiotropium 5 µg	320/309	0.48 (0.26, 0.87)	
FEV_1 at screening (% predicted)				0.962
≥60% to < 80%	Tiotropium 2.5 µg	117/115	0.63 (0.21, 1.94)	
	Tiotropium 5 µg	117/148	0.88 (0.34, 2.27)	
≥80%	Tiotropium 2.5 µg	401/400	0.47 (0.27, 0.85)	
	Tiotropium 5 µg	401/365	0.69 (0.40, 1.17)	
FEV_1 reversibility at screening				0.441
<15%	Tiotropium 2.5 µg	124/111	0.44 (0.16, 1.25)	
	Tiotropium 5 µg	124/126	0.40 (0.14, 1.14)	
≥15% to ≤20%	Tiotropium 2.5 µg	155/144	0.76 (0.31, 1.89)	
	Tiotropium 5 µg	155/167	1.18 (0.54, 2.60)	
>20%	Tiotropium 2.5 µg	239/260	0.40 (0.18, 0.88)	
	Tiotropium 5 µg	239/220	0.63 (0.31, 1.29)	
Leukotriene modifiers at randomization				0.928
No	Tiotropium 2.5 µg	475/467	0.53 (0.30, 0.92)	
	Tiotropium 5 µg	475/468	0.76 (0.46, 1.24)	
Yes	Tiotropium 2.5 µg	43/48	0.31 (0.08, 1.20)	
	Tiotropium 5 µg	43/45	0.52 (0.15, 1.79)	



Full analysis set. BMI = body mass index, CI = confidence interval; FEV_1 = forced expiratory volume in 1 s, LABA = long-acting β2-agonist; N/A = not applicable; yr = year.
N/A shows that no event occurred in the subgroup.

Table 1. Baseline demographics and characteristics (treated set)

	Total (n=2100)[a]	**Tiotropium Respimat 5 µg QD[b] (n=517)**	**Tiotropium Respimat 2.5 µg QD[b] (n=519)**	**Placebo[c] (n=523)**
Sex, n (%)				
Female	1239 (59.0)	300 (58.0)	316 (60.9)	311 (59.5)
Male	861 (41.0)	217 (42.0)	203 (39.1)	212 (40.5)
Age (years), mean ± SD	43.1 ± 12.9	44.3 ± 12.6	43.4 ± 12.9	42.8 ± 13.0
Smoking status, n (%)				
Never smoked	1756 (83.6)	420 (81.2)	437 (84.2)	453 (86.6)
Ex-smoker	344 (16.4)	97 (18.8)	82 (15.8)	70 (13.4)
Smoking history[d] (pack-years), mean ± SD	4.19 ± 2.81	4.5 ± 3.0	4.0 ± 2.9	4.1 ± 2.5
Race, n (%)				
White	1005 (47.9)	240 (46.4)	253 (48.7)	246 (47.0)
Black/African American	81 (3.9)	22 (4.3)	17 (3.3)	27 (5.2)
Asian	893 (42.5)	225 (43.5)	220 (42.4)	219 (41.9)
American Indian/ Alaska native	118 (5.6)	30 (5.8)	27 (5.2)	30 (5.7)
Ethnicity, n (%)				
Not Hispanic/Latino	1875 (89.3)	459 (88.8)	464 (89.4)	469 (89.7)
Hispanic/Latino	225 (10.7)	58 (11.2)	55 (10.6)	54 (10.3)
BMI (kg/m^2), mean ± SD	26.8 ± 6.2	27.1 ± 6.3	26.6 ± 6.1	27.0 ± 6.3
Median age at asthma onset, years (range)	24 (0–48)	24.0 (0–40)	24.0 (0–40)	24.0 (0–39)
Duration of asthma (years), mean ± SD	21.8 ± 14.3	23.0 ± 15.0	22.1 ± 14.3	21.1 ± 13.7
FEV_1 % predicted, mean ± SD[e]	75.1 ± 11.5	73.9 ± 11.3	75.4 ± 11.5	75.1 ± 11.5
FVC % predicted, mean ± SD[e]	96.7 ± 13.8	96.1 ± 14.0	96.6 ± 13.4	97.5 ± 14.0
FEV_1/FVC %, mean ± SD[e]	66.1 ± 10. 5	65.3 ± 10.2	66.5 ± 10.8	65.6 ± 10.4
ICS dose of stable maintenance	659.6 ± 212.9	663.9 ± 216.0	655.9 ± 213.2	668.3 ± 217.3

therapy, µg/day,[f] mean ± SD				
Concomitant therapies of interest, n (%)[g]				
Leukotriene modifiers	212 (10.1)	54 (10.4)	53 (10.2)	53 (10.1)
Systemic antihistamines	358 (17.0)	77 (14.9)	95 (18.3)	101 (19.3)
Anti-allergic agents (excluding corticosteroids)	108 (5.1)	24 (4.6)	31 (6.0)	27 (5.2)
Omalizumab	0	0	0	0
Immune modulatory agents and antibodies	18 (0.9)	4 (0.8)	5 (1.0)	6 (1.1)

[a]Includes patients receiving salmeterol.

[b]Plus placebo HFA-MDI BID.

[c]Placebo Respimat QD plus placebo HFA-MDI BID.

[d]Ex-smokers only.

[e]Measured at randomization visit.

[f]Budesonide equivalent dose.

[g]Within the 3 months before screening.

BID = twice daily; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HFA-MDI = hydrofluoroalkane metered-dose inhaler; ICS = inhaled corticosteroids; IgE = immunoglobulin E; QD = once daily; SD = standard deviation.

Supplementary information

Table S1. Overall summary of patients reporting adverse events

n (%)	Tiotropium Respimat 5 µg QD[a] (n=517)	Tiotropium Respimat 2.5 µg QD[a] (n=519)	Placebo[b] (n=523)
Patients with any AE	296 (57.3)	302 (58.2)	309 (59.1)
Patients with investigator-defined drug-related AEs	38 (7.4)	36 (6.9)	28 (5.4)
Patients with AEs leading to discontinuation	9 (1.7)	6 (1.2)	13 (2.5)
Patients with serious AEs	11 (2.1)	12 (2.3)	14 (2.7)
AEs reported in >5% of patients,[c] by preferred term			
Asthma	111 (21.5)	82 (15.8)	115 (22.0)
Decreased peak expiratory flow rate	59 (11.4)	49 (9.4)	79 (15.1)
Nasopharyngitis	41 (7.9)	49 (9.4)	48 (9.2)
Upper respiratory tract infection	19 (3.7)	27 (5.2)	41 (7.8)

Treated set; treatment period plus 30 days.

[a]Plus placebo HFA-MDI BID.

[b]Placebo Respimat QD plus placebo HFA-MDI BID.

[c]Reported in >5% of patients in any treatment arm of the MezzoTinA-asthma trials.

AE = adverse event, BID = twice daily, HFA-MDI = hydrofluoroalkane metered-dose inhaler, QD = once daily.