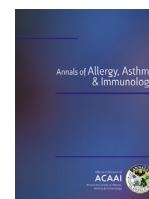




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Review

Emerging therapeutic options for the treatment of patients with symptomatic asthma

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ABSTRACT

Objective: Asthma is a chronic inflammatory disorder of the airways with increasing worldwide prevalence. Despite treatment according to guidelines, a considerable proportion of patients with asthma remain symptomatic. Different potential therapeutic options for the treatment of these patients are currently in development and undergoing clinical trials, and it is important to regularly review their status.

Data Sources: A search of ClinicalTrials.gov was performed and supported by a PubMed literature search and restricted to the previous 10 years to ensure currency of data. The results were manually filtered to identify relevant articles.

Study Selections: Emerging therapies that are currently in phase 2 and 3 development include anti-interleukin agents (benralizumab, reslizumab, dupilumab, brodalumab, lebrikizumab, and mepolizumab), a chemoattractant receptor-homologous molecule expressed on a T-helper type 2 lymphocyte antagonist (OC000459), a phosphodiesterase-4 inhibitor (roflumilast), and long-acting muscarinic antagonists (glycopyrronium bromide, umeclidinium bromide, and tiotropium bromide).

Results: The clinical trial program of the long-acting muscarinic antagonist tiotropium is currently the most advanced, with data available from different phase 2 and 3 studies. Results demonstrate that it is an efficacious add-on to at least inhaled corticosteroid maintenance therapy across severities of symptomatic asthma.

Conclusion: The results of ongoing and future studies will help to determine whether these emerging therapeutic options will help address the unmet need for improvement in asthma management.

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Introduction

Asthma is an inflammatory disease of the airways, with multifactorial pathophysiology. It is one of the most common chronic conditions, with a global prevalence of up to 18%, and is expected to affect approximately 400 million people worldwide by 2025.¹ Current Global Initiative for Asthma guidelines recommend stepwise treatment to achieve and maintain asthma control.² After initial treatment with inhaled corticosteroids (ICS), an increase in the ICS dose or the addition of another controller therapy, including long-acting β_2 -agonists (LABAs), leukotriene modifiers, or theophylline, is recommended to achieve control. In patients with more severe disease where control cannot be achieved add-on therapy with anti-immunoglobulin E or oral glucocorticosteroids is recommended.

Despite treatment according to current guidelines, such as the Global Initiative for Asthma guidelines, at least 40% of patients with

asthma remain symptomatic.^{3–6} In the United States, the Asthma Control Characteristics and Prevalence Survey Studies reported uncontrolled asthma in 58.8% and 49.7% of adult and pediatric patients, respectively,⁷ whereas the European REcognise Asthma and Link to Symptoms and Experience survey reported uncontrolled asthma in 45% of respondents.⁸ Poorly controlled asthma puts patients at risk of future exacerbations and thus has a significant impact on patients' lifestyles and on the use of health care resources and health care costs.^{9–13} It is important to recognize that although the degree to which a patient's asthma is controlled might be related to disease treatment or severity, it also might be affected by different variables, including comorbidities such as allergic rhinitis and gastroesophageal reflux, poor treatment adherence, incorrect inhaler technique, allergen exposure, or concurrent smoking.¹⁴

There is an ongoing need for improvements in the management and control of asthma. This review examines recently published clinical data on emerging therapeutic options for the treatment of patients with symptomatic asthma.

Emerging Therapeutic Options for the Treatment of Asthma

Different promising therapeutic options are currently in development and undergoing clinical trials for the

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treatment of symptomatic asthma, including anti-interleukin (IL) agents, chemoattractant receptor-homologous molecules expressed on T-helper type 2 lymphocyte (CRT_{H2}) antagonists, phosphodiesterase-4 inhibitors, and long-acting muscarinic antagonists (LAMAs). The emerging anti-IL agents benralizumab, reslizumab, dupilumab, brodalumab, lebrikizumab, and mepolizumab, the CRT_{H2} antagonist OC000459, the phosphodiesterase-4 inhibitor roflumilast, and the LAMAs glycopyrronium bromide, umeclidinium bromide, and tiotropium bromide were identified for inclusion based on recent literature.

Search Strategy

A search of ClinicalTrials.gov was performed using the drug names listed earlier AND *asthma* as search terms (Table 1). A PubMed literature search also was performed using the Boolean string *asthma** [title/abstract] AND *drug name* [title/abstract] AND *clinical trial* [ptyp] and was restricted to the previous 10 years to ensure currency of data (June 2015). The results were manually filtered to identify relevant articles or studies with data from well-designed clinical trials of the treatment of interest in human patients.

Anti-IL Agents in the Treatment of Asthma

Anti-IL agents are monoclonal anticytokine agents that decrease airway inflammation and prevent eosinophil activation.^{15,16} The literature search provided 16 publications relating to the anti-IL agents benralizumab, reslizumab, dupilumab, brodalumab, lebrikizumab, and mepolizumab (eTable 1A).

Benralizumab

An initial phase 1 study in 27 patients with asthma found that single-dose intravenous and multiple-dose subcutaneous benralizumab (anti-IL-5) decreased airway, bone marrow, and peripheral blood eosinophil counts, with comparable safety profiles.¹⁷ In a phase 2 study in 108 patients with acute asthma, a single dose of intravenous benralizumab was found to decrease the rate (1.82 vs 3.59 [total number of exacerbations per total duration of person-year follow-up], $P = .01$) and severity (0.65 vs 1.62 [total number of exacerbations per total duration of person-year follow-up], $P = .02$) of asthma exacerbations compared with placebo and had an acceptable safety profile.¹⁸ Patients with severe asthma are currently being recruited for additional phase 3 studies (Table 1).

Reslizumab

In a study of 106 patients with severe eosinophilic asthma, treatment with monthly reslizumab infusions (anti-IL-5) showed a

trend toward improved asthma control ($P = .0541$), significantly decreased sputum eosinophils ($P = .0068$), and significantly improved lung function, as measured by forced expiratory volume in 1 second (FEV₁; $P = .0023$), percentage of predicted FEV₁ ($P = .0010$), and forced vital capacity (FVC; $P = .0054$), compared with placebo.¹⁵ The results from the first phase 3 trials in 953 adult and adolescent patients (489 patients in study 1 and 464 patients in study 2) with moderate to severe eosinophilic asthma (NCT01287039 and NCT01285323) showed that monthly intravenous reslizumab significantly decreased the frequency of asthma exacerbations ($P < .0001$ in the 2 trials) and had a similar adverse-event profile compared with placebo.¹⁹ Additional phase 2 and 3 trials of reslizumab in adult and pediatric patients with eosinophilic asthma are currently ongoing (Table 1).

Dupilumab

Dupilumab (anti-IL-4) showed efficacy in a 12-week phase 2 trial of 104 patients with moderate to severe eosinophilic asthma (NCT01312961). Significant decreases in the incidence of asthma exacerbations ($P < .001$) and significant improvements in most measurements of lung function (FEV₁, $P < .001$) and asthma control (5-question Asthma Control Questionnaire [ACQ-5], $P = .001$) were observed after once-weekly subcutaneous administration of 300 mg of dupilumab compared with placebo; dupilumab also was found to decrease biomarkers associated with T-helper type 2 (T_{H2})-driven inflammation.¹⁶ A phase 2 trial and follow-on phase 3 trial are currently ongoing to evaluate the efficacy and safety of different doses and treatment regimens of dupilumab in patients with moderate to severe asthma (Table 1).

Brodalumab

In a phase 2 dose-ranging study in 302 adult patients with moderate to severe asthma (NCT01199289), no treatment differences were observed in 7-question ACQ (ACQ-7) scores, lung function, or asthma symptoms after subcutaneous brodalumab (anti-IL-17) at 140, 210, or 280 mg or placebo. Prespecified subgroup analyses showed an improvement in ACQ-7 score beyond the minimal clinically important difference after 210 mg of brodalumab only ($P = .02$; no adjustment for multiplicity) in patients with high bronchodilator reversibility (post-bronchodilator FEV₁ improvement $\geq 20\%$).²⁰ A second phase 2 study of brodalumab in patients with high bronchodilator reversibility is currently recruiting patients (Table 1).

Lebrikizumab

Lebrikizumab (anti-IL-13) at 250 mg, administered subcutaneously every 4 weeks, showed improved lung function in a phase 2

Table 1
Summary of emerging therapeutic options in the treatment of asthma, listed on ClinicalTrials.gov

Therapeutic class	Mode of administration	Mechanism of action	Drug name	Sponsor	Development phase
Anti-interleukin agents	injection	anti-inflammatory	benralizumab	AstraZeneca	3
				Kyowa Hakko Kirin Company	2
				MedImmune	1/2
			reslizumab	Teva	2/3
				GlaxoSmithKline	3
			dupilumab	Sanofi	2/3
CRT _{H2} antagonists	oral	anti-inflammatory	brodalumab	Amgen	2
			lebrikizumab	F. Hoffmann-La Roche	2/3
				Genentech	2
			mepolizumab	GlaxoSmithKline	2/3
			OC000459	Oxigen	2
				Atopix Therapeutics	1
Phosphodiesterase-4 inhibitors Long-acting muscarinic antagonists	oral	anti-inflammatory bronchodilator	roflumilast	Takeda	2/3
			glycopyrronium bromide	Chiesi	1/2
			umeclidinium bromide	GlaxoSmithKline	1/2
			tiotropium bromide	Boehringer Ingelheim	2/3

Abbreviation: CRT_{H2}, chemoattractant receptor-homologous molecules expressed on T-helper type 2 lymphocytes.

trial in 219 adult patients with inadequately controlled asthma despite medium- to high-dose ICS therapy (NCT00930163). Improvements in FEV₁ were significant compared with placebo ($P = .02$), with greater improvements observed in patients with high serum-periostin levels.²¹ In a second phase 2 trial in 212 patients with asthma not receiving ICS (NCT00971035), monthly subcutaneous administration of lebrikizumab at 125, 250, or 500 mg did not provide any meaningful improvements in lung function.²² In a third phase 2 trial in 29 adult patients with mild allergic asthma (NCT00781443), monthly lebrikizumab treatment decreased the late asthmatic response (FEV₁ decrease $\geq 15\%$ 2–12 hours after allergen challenge) by 48% compared with placebo, with exploratory analyses showing that patients with allergic asthma exhibited a greater decrease compared with those with nonallergic asthma.²³ Additional phase 2 studies of lebrikizumab in the treatment of asthma are ongoing, with phase 3 studies currently recruiting patients (Table 1).

Mepolizumab

Studies in patients with severe eosinophilic asthma showed that mepolizumab (anti-IL-5) decreased exacerbation risk, improved quality of life, lowered eosinophil counts, improved asthma control, and improved lung function. In a phase 2 trial of 621 patients (NCT01000506), treatment with intravenous mepolizumab significantly lowered the rate of clinically significant exacerbations (48% decrease in the 75-mg group, 39% decrease in the 250-mg group, 52% decrease in the 750-mg group, $P \leq .0005$ for all comparisons) compared with placebo.²⁴ In a parallel-group trial of 61 patients with refractory eosinophilic asthma, monthly treatment with 750 mg of intravenous mepolizumab was associated with fewer severe exacerbations ($P = .02$), lower blood ($P < .001$) and sputum ($P = .002$) eosinophil counts, and significant improvements in quality of life ($P = .02$) over 1 year compared with placebo, although no significant improvements in asthma symptoms, FEV₁, or airway hyperresponsiveness were observed between treatment groups.²⁵ After cessation of mepolizumab treatment, an increase in blood eosinophil count, severe exacerbation frequency, and asthma symptoms was observed.²⁶ In a phase 2 parallel-group study of 20 patients with corticosteroid-dependent eosinophilic asthma (NCT00292877), the proportion of patients who experienced an asthma exacerbation was significantly decreased ($P = .008$); there also were significant decreases in sputum ($P = .005$) and blood ($P = .004$) eosinophil levels and a significant improvement in asthma control ($P = .01$) after 750 mg of intravenous mepolizumab every 4 weeks.²⁷ In a phase 3 study of 576 patients with severe eosinophilic asthma (NCT01691521), exacerbation rate was decreased by 47% and 53% and FEV₁ was increased by 100 and 98 mL ($P < .05$ for all comparisons) in patients receiving 75 mg of intravenous mepolizumab and 100 mg of subcutaneous mepolizumab monthly, respectively, with significant improvements also observed in asthma control.²⁸ In a second phase 3 study in 135 patients with severe eosinophilic asthma, after treatment with 100 mg of subcutaneous mepolizumab every 4 weeks, there was a 32% decrease in exacerbation rate and a decrease of 0.52 in ACQ-5 score, with the decrease in background ICS use 2.39 times greater than in the placebo treatment group.²⁹ Conversely, in a study by Flood-Page et al³⁰ of 362 patients with moderate symptomatic asthma, no significant clinical benefit was observed in lung function, rescue medication use, asthma symptoms, exacerbation rate, or quality of life after 3 intravenous infusions of 250 or 750 mg of mepolizumab at monthly intervals. In a subset of 37 patients from this study, significant decreases in sputum and blood eosinophils were observed after treatment with 250 and 750 mg of intravenous mepolizumab every 4 weeks (sputum, $P = .006$ and $P = .004$, respectively; blood, $P < .001$ for the 2 doses). Several additional phase 2 and 3 studies of mepolizumab in the treatment of patients with severe eosinophilic asthma are ongoing but have yet to report data (Table 1).

CRT_{H2} Antagonists in the Treatment of Asthma

The CRT_{H2} is a G-protein–coupled receptor that mediates the activation of T_{H2} lymphocytes, eosinophils, and basophils in response to prostaglandin D₂.^{31–33} Airway prostaglandin D₂ levels are elevated in patients with asthma after an allergen challenge, suggesting a role in T_{H2}-mediated allergic inflammation, and therefore CRT_{H2} antagonists might inhibit the activation of lymphocytes, eosinophils, and basophils and decrease the asthma allergic response.^{32,33} Three publications related to OC000459 were identified (eTable 1B), which is currently in phase 2 development (Table 1).

OC000459

A phase 2 study of twice-daily OC000459 at 200 mg (NCT01057927) showed significantly improved quality of life ($P = .0113$) and nocturnal symptoms ($P = .008$) compared with placebo in 132 patients with moderate persistent asthma. Improvements in FEV₁ and sputum eosinophil count also were observed but were not statistically significant.³² In a 2-way phase 2 crossover study of 21 steroid-naïve patients with asthma (NCT01056692), treatment with twice-daily OC000459 at 200 mg was found to significantly inhibit the late asthmatic response to allergen challenge ($P = .018$) and significantly reduce the post-allergen increase in sputum eosinophils ($P = .002$); OC000459 treatment had no effect on the early asthmatic response to allergen challenge.³³ In a phase 2 dose-finding study of OC000459 once daily at 25 or 200 mg or twice daily at 100 mg in 519 patients with mild to moderate persistent asthma (NCT00890877), a significant improvement in FEV₁ was observed after treatment with the once-daily 25-mg dose ($P = .028$). Significant improvements also were observed in ACQ-7 ($P = .001$) and Asthma Quality of Life Questionnaire ($P = .002$) scores, and there was a nonsignificantly lower incidence of exacerbations and a significant decrease in respiratory infections ($P = .003$), in patients treated with OC000459 compared with placebo.³¹

Phosphodiesterase-4 Inhibitors in the Treatment of Asthma

Phosphodiesterases are involved in the degradation of cyclic adenosine monophosphate, a natural modulator of inflammation, which results in increased activity of inflammatory cells involved in the etiology of asthma, including T lymphocytes, eosinophils, macrophages, mast cells, monocytes, and neutrophils.^{34–37} Inhibition of phosphodiesterase activity results in maintenance of cyclic adenosine monophosphate levels and subsequent downregulation of inflammatory processes in cells involved in the pathophysiology of asthma.^{34–36} The PubMed literature search provided 6 publications related to roflumilast in the treatment of asthma (eTable 1C), with phase 2 and 3 trials ongoing (Table 1). Roflumilast is approved for use in the treatment of chronic obstructive pulmonary disease, and anti-inflammatory effects have been observed in patients with asthma.^{36–38}

Roflumilast

Treatment with roflumilast has been shown to significantly improve the late asthmatic response compared with placebo. In a 2-period crossover study in 13 patients with mild allergic asthma, treatment with a single dose of 1,000 μg of roflumilast significantly improved the late asthmatic response to a histamine challenge ($P = .005$).³⁷ A 3-period crossover study of 23 patients with mild asthma showed that once-daily treatment with 250 or 500 μg of roflumilast significantly decreased the early ($P = .0110$ and $P = .0009$, respectively) and late ($P = .0038$ and $P = .0046$, respectively) asthmatic reactions to allergens.³⁶ Further, in a phase 2 trial of 25 patients with mild allergic asthma (NCT01365533), 500 μg of roflumilast once daily inhibited the allergen-induced late-phase response (maximum percentage decrease in FEV₁, $P = .02$).³⁸

Improvements in lung function also have been reported after treatment with roflumilast. In a double-blinded, parallel-group trial of 693 adolescent and adult patients with mild to moderate asthma, treatment with once-daily roflumilast at 100, 250, or 500 μg significantly improved FEV₁ ($P < .001$ for all comparisons), with the 500- μg dose providing the greatest improvements. Morning and evening peak expiratory flow also were improved ($P \leq .006$ for all comparisons) compared with placebo.³⁴ In a noninferiority study of 499 adolescent and adult patients with persistent asthma, once-daily roflumilast at 500 μg was found to provide comparable improvements in FEV₁ and FVC compared with treatment with twice-daily beclomethasone dipropionate at 200 μg .³⁵

In addition to showing efficacy in adult and adolescent patients with asthma, roflumilast has shown efficacy in pediatric patients with asthma. A 2-period ascending-dose study in 13 children and 12 adolescents with mild to moderate asthma found that roflumilast was well tolerated and that pharmacokinetic parameters were similar to those observed in adults.³⁹

LAMAs in the Treatment of Asthma

The short-acting muscarinic antagonists ipratropium bromide and oxitropium bromide have been used in the treatment of asthma for several years; however, their widespread use has been limited because they are considered less effective than short-acting β_2 -agonists.⁴⁰ LAMAs block muscarinic acetylcholine receptors to impact on airway tone, smooth muscle contraction, mucus secretion, and vasodilation.^{40–43} LAMAs have not been thoroughly investigated in asthma because of the perception that they provide little bronchodilation above that induced by LABAs.^{44,45} This view has now changed, and some LAMAs are being investigated in clinical trials of asthma, including glycopyrrolate, umeclidinium, and tiotropium^{46,47} (Table 1).

A small phase 3 crossover study in 10 patients with asthma demonstrated that glycopyrrolate significantly prolonged bronchodilation and bronchoprotection compared with ipratropium (eTable 1D).⁴⁸ A double-blinded crossover study of umeclidinium monotherapy in 350 patients with asthma (eTable 1D) found no conclusive therapeutic benefit in patients not receiving ICS.⁴⁹ However, the results of a double-blinded crossover study of ICS and umeclidinium combination therapy in 421 patients with asthma (eTable 1D) showed improvements in trough FEV₁ (26–55 mL) and morning (15.9–22.9 L/min) and evening (16.2–28.8 L/min) peak expiratory flow compared with ICS alone.⁵⁰

The tiotropium clinical trial program is currently the most advanced, and tiotropium, delivered through a soft-mist inhaler, has recently been incorporated into the Global Initiative for Asthma 2015 treatment guidelines as a recommended alternative therapy at steps 4 and 5 in adult patients with a history of exacerbations.² Data from 14 studies of tiotropium in asthma (eTable 1D) are reviewed below in more detail.

Tiotropium

Tiotropium, a long-acting anticholinergic bronchodilator, is currently approved by the US Food and Drug Administration for the treatment of patients with chronic obstructive pulmonary disease.^{51,52} It also has recently been approved for use in the treatment of asthma in the European Union and other countries worldwide. Further, it is currently under evaluation in the United States and other countries for the treatment of patients with asthma.

Early proof-of-concept studies in small numbers of patients indicated that tiotropium, delivered through the Spiriva HandiHaler device (Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Connecticut), provides sustained bronchodilation and protection against bronchoconstriction. A study by Fardon et al⁵³ in 26 patients with severe asthma demonstrated that once-daily tiotropium at 18 μg provided significant improvements in lung function. Tiotropium

at 18 μg also was shown to provide significant protection against methacholine challenge in a study of 10 patients with asthma and mild to moderate airway hyperresponsiveness.⁵⁴ Sposato et al⁵⁵ demonstrated that 18 μg of tiotropium provided greater protection against methacholine-induced bronchoconstriction than ipratropium bromide, with similar improvements in FEV₁ compared with oxitropium bromide, in a study of 44 patients with asthma.

In the large 3-way crossover Tiotropium Bromide as an Alternative to Increased Inhaled Corticosteroid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) study in 210 patients with uncontrolled asthma (NCT00565266), once-daily tiotropium at 18 μg (through the Spiriva HandiHaler) significantly improved asthma symptoms ($P < .001$) and lung function (morning and evening peak expiratory flow, $P < .001$; FEV₁, $P = .004$) compared with a doubling of the ICS dose and was noninferior to salmeterol in patients with symptomatic asthma.⁵⁶ A prespecified analysis of the TALC study data showed that a large number of patients who responded to treatment with albuterol and had increased airway obstruction demonstrated improved lung function after treatment with tiotropium.⁵⁷

Recent studies in patients with symptomatic asthma have evaluated the efficacy of once-daily tiotropium delivered by the Respimat Soft Mist inhaler (hereinafter referred to as tiotropium Respimat; Boehringer Ingelheim, Ingelheim am Rhein, Germany; Fig 1). The Respimat inhaler provides increased aerosol production time compared with pressurized metered-dose inhalers and dry-powder inhalers, which could benefit patients with low inspiratory capacity or poor timing of inhalation to actuation.⁵⁸

Phase 2 trials have examined the efficacy and safety of different doses and dosing regimens of tiotropium Respimat. Tiotropium at 10 and 5 μg as add-on to high-dose ICS plus LABA, taken each morning (NCT00365560), significantly improved peak FEV₁ ($P < .0001$ for all comparisons) and trough FEV₁ ($P < .0004$ for all comparisons) compared with placebo in 107 patients with severe symptomatic asthma. Adverse events were balanced across treatment groups, apart from dry mouth, which had a higher incidence in the 10- μg tiotropium treatment group (6.8%; 1.9% in the 5- μg group and 1.0% in the placebo group).⁵⁹ Once-daily evening dosing of tiotropium at 5, 2.5, and 1.25 μg as add-on to medium-dose ICS in 149 patients with moderate persistent asthma (NCT01233284) resulted in statistically significant improvements in lung function (peak FEV₁ within 3 hours after the dose [peak FEV_{1(0–3h)}], trough FEV₁, FEV₁ area under the curve [AUC]_[0–3h], peak FVC_[0–3h], trough FVC, and FVC AUC_[0–3h]), with the 5- μg dose associated with the greatest improvements in all measurements.⁶⁰ Improvements in lung function were found to be significant and equally well sustained for once-daily tiotropium at 5 μg (morning dosing) and twice daily at 2.5 μg (morning and evening dosing) as add-on to medium-dose ICS in a study of 94 patients with moderate symptomatic asthma (NCT01152450).⁶¹ In a study of 388 patients with moderate asthma with the B16-Arg/Arg genotype (NCT00350207), treatment with a once-daily evening dose of 5 μg of tiotropium was found to be superior to matching placebo ($P < .05$) and as efficacious as twice-daily salmeterol ($P = .002$) at maintaining improved lung function.⁶²

Phase 3 trials have examined the efficacy, safety, and tolerability of tiotropium Respimat in patients across severities of symptomatic asthma, as defined by ICS dose. In 2 randomized, double-blinded, 48-week, parallel-group trials with identical designs (NCT00772538 and NCT00776984), 912 patients with poorly controlled asthma received 5 μg of tiotropium once daily or placebo each morning as add-on to high-dose ICS plus LABA. Treatment with 5 μg of tiotropium significantly improved peak and trough FEV₁ ($P \leq .01$ for the 2 end points in the 2 trials) and increased the time to the first severe asthma exacerbation by 56 days, with a decrease of 21% in the risk of experiencing a severe exacerbation (pooled data, $P = .03$), compared with placebo.⁶³ In 2 randomized, double-blinded, double-dummy, parallel-group trials with identical design

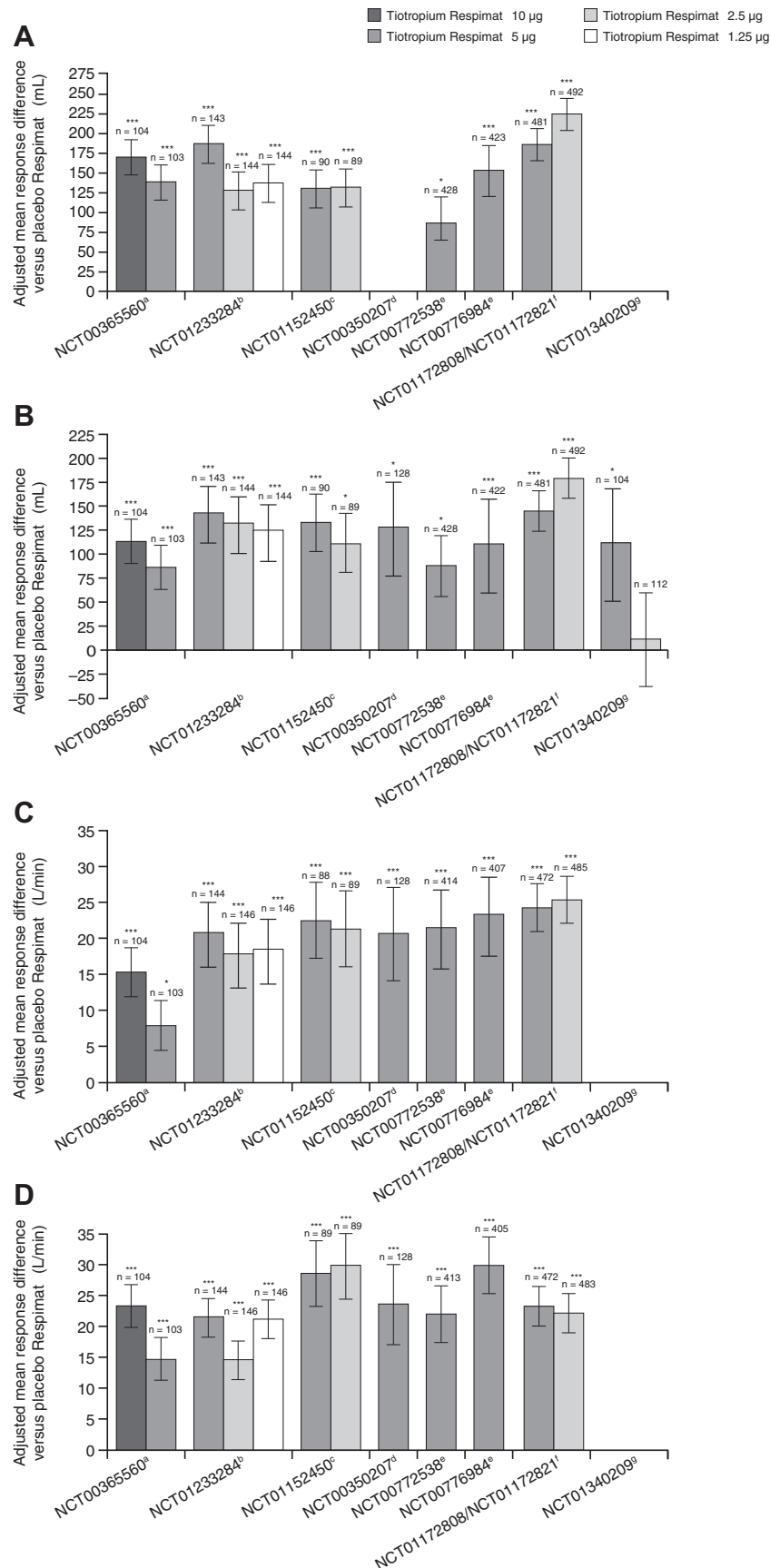


Figure 1. Overview of lung function results from clinical trials of tiotropium Respimat in adults with asthma: (A) peak forced expiratory volume in 1 second; (B) trough forced expiratory volume in 1 second; (C) morning peak expiratory flow; (D) evening peak expiratory flow. Error bars represent SE. ^aMeasured at week 8. ^bMeasured at week 4. ^cMeasured at the end of each 4-week treatment period. ^dMeasured at week 16. ^eMeasured at week 24. ^fPooled data; measured at week 24. ^gMeasured at week 52. ^hMeasured at week 52. ⁵⁵ ⁵⁶ ⁵⁷ ⁵⁸ ⁵⁹ ⁶⁰ ⁶¹ ⁶² ⁶³ ⁶⁴ ⁶⁵ ⁶⁶ ⁶⁷ ⁶⁸ ⁶⁹ ⁷⁰ ⁷¹ ⁷² ⁷³ ⁷⁴ ⁷⁵ ⁷⁶ ⁷⁷ ⁷⁸ ⁷⁹ ⁸⁰ ⁸¹ ⁸² ⁸³ ⁸⁴ ⁸⁵ ⁸⁶ ⁸⁷ ⁸⁸ ⁸⁹ ⁹⁰ ⁹¹ ⁹² ⁹³ ⁹⁴ ⁹⁵ ⁹⁶ ⁹⁷ ⁹⁸ ⁹⁹ ¹⁰⁰ ¹⁰¹ ¹⁰² ¹⁰³ ¹⁰⁴ ¹⁰⁵ ¹⁰⁶ ¹⁰⁷ ¹⁰⁸ ¹⁰⁹ ¹¹⁰ ¹¹¹ ¹¹² ¹¹³ ¹¹⁴ ¹¹⁵ ¹¹⁶ ¹¹⁷ ¹¹⁸ ¹¹⁹ ¹²⁰ ¹²¹ ¹²² ¹²³ ¹²⁴ ¹²⁵ ¹²⁶ ¹²⁷ ¹²⁸ ¹²⁹ ¹³⁰ ¹³¹ ¹³² ¹³³ ¹³⁴ ¹³⁵ ¹³⁶ ¹³⁷ ¹³⁸ ¹³⁹ ¹⁴⁰ ¹⁴¹ ¹⁴² ¹⁴³ ¹⁴⁴ ¹⁴⁵ ¹⁴⁶ ¹⁴⁷ ¹⁴⁸ ¹⁴⁹ ¹⁵⁰ ¹⁵¹ ¹⁵² ¹⁵³ ¹⁵⁴ ¹⁵⁵ ¹⁵⁶ ¹⁵⁷ ¹⁵⁸ ¹⁵⁹ ¹⁶⁰ ¹⁶¹ ¹⁶² ¹⁶³ ¹⁶⁴ ¹⁶⁵ ¹⁶⁶ ¹⁶⁷ ¹⁶⁸ ¹⁶⁹ ¹⁷⁰ ¹⁷¹ ¹⁷² ¹⁷³ ¹⁷⁴ ¹⁷⁵ ¹⁷⁶ ¹⁷⁷ ¹⁷⁸ ¹⁷⁹ ¹⁸⁰ ¹⁸¹ ¹⁸² ¹⁸³ ¹⁸⁴ ¹⁸⁵ ¹⁸⁶ ¹⁸⁷ ¹⁸⁸ ¹⁸⁹ ¹⁹⁰ ¹⁹¹ ¹⁹² ¹⁹³ ¹⁹⁴ ¹⁹⁵ ¹⁹⁶ ¹⁹⁷ ¹⁹⁸ ¹⁹⁹ ²⁰⁰ ²⁰¹ ²⁰² ²⁰³ ²⁰⁴ ²⁰⁵ ²⁰⁶ ²⁰⁷ ²⁰⁸ ²⁰⁹ ²¹⁰ ²¹¹ ²¹² ²¹³ ²¹⁴ ²¹⁵ ²¹⁶ ²¹⁷ ²¹⁸ ²¹⁹ ²²⁰ ²²¹ ²²² ²²³ ²²⁴ ²²⁵ ²²⁶ ²²⁷ ²²⁸ ²²⁹ ²³⁰ ²³¹ ²³² ²³³ ²³⁴ ²³⁵ ²³⁶ ²³⁷ ²³⁸ ²³⁹ ²⁴⁰ ²⁴¹ ²⁴² ²⁴³ ²⁴⁴ ²⁴⁵ ²⁴⁶ ²⁴⁷ ²⁴⁸ ²⁴⁹ ²⁵⁰ ²⁵¹ ²⁵² ²⁵³ ²⁵⁴ ²⁵⁵ ²⁵⁶ ²⁵⁷ ²⁵⁸ ²⁵⁹ ²⁶⁰ ²⁶¹ ²⁶² ²⁶³ ²⁶⁴ ²⁶⁵ ²⁶⁶ ²⁶⁷ ²⁶⁸ ²⁶⁹ ²⁷⁰ ²⁷¹ ²⁷² ²⁷³ ²⁷⁴ ²⁷⁵ ²⁷⁶ ²⁷⁷ ²⁷⁸ ²⁷⁹ ²⁸⁰ ²⁸¹ ²⁸² ²⁸³ ²⁸⁴ ²⁸⁵ ²⁸⁶ ²⁸⁷ ²⁸⁸ ²⁸⁹ ²⁹⁰ ²⁹¹ ²⁹² ²⁹³ ²⁹⁴ ²⁹⁵ ²⁹⁶ ²⁹⁷ ²⁹⁸ ²⁹⁹ ³⁰⁰ ³⁰¹ ³⁰² ³⁰³ ³⁰⁴ ³⁰⁵ ³⁰⁶ ³⁰⁷ ³⁰⁸ ³⁰⁹ ³¹⁰ ³¹¹ ³¹² ³¹³ ³¹⁴ ³¹⁵ ³¹⁶ ³¹⁷ ³¹⁸ ³¹⁹ ³²⁰ ³²¹ ³²² ³²³ ³²⁴ ³²⁵ ³²⁶ ³²⁷ ³²⁸ ³²⁹ ³³⁰ ³³¹ ³³² ³³³ ³³⁴ ³³⁵ ³³⁶ ³³⁷ ³³⁸ ³³⁹ ³⁴⁰ ³⁴¹ ³⁴² ³⁴³ ³⁴⁴ ³⁴⁵ ³⁴⁶ ³⁴⁷ ³⁴⁸ ³⁴⁹ ³⁵⁰ ³⁵¹ ³⁵² ³⁵³ ³⁵⁴ ³⁵⁵ ³⁵⁶ ³⁵⁷ ³⁵⁸ ³⁵⁹ ³⁶⁰ ³⁶¹ ³⁶² ³⁶³ ³⁶⁴ ³⁶⁵ ³⁶⁶ ³⁶⁷ ³⁶⁸ ³⁶⁹ ³⁷⁰ ³⁷¹ ³⁷² ³⁷³ ³⁷⁴ ³⁷⁵ ³⁷⁶ ³⁷⁷ ³⁷⁸ ³⁷⁹ ³⁸⁰ ³⁸¹ ³⁸² ³⁸³ ³⁸⁴ ³⁸⁵ ³⁸⁶ ³⁸⁷ ³⁸⁸ ³⁸⁹ ³⁹⁰ ³⁹¹ ³⁹² ³⁹³ ³⁹⁴ ³⁹⁵ ³⁹⁶ ³⁹⁷ ³⁹⁸ ³⁹⁹ ⁴⁰⁰ ⁴⁰¹ ⁴⁰² ⁴⁰³ ⁴⁰⁴ ⁴⁰⁵ ⁴⁰⁶ ⁴⁰⁷ ⁴⁰⁸ ⁴⁰⁹ ⁴¹⁰ ⁴¹¹ ⁴¹² ⁴¹³ ⁴¹⁴ ⁴¹⁵ ⁴¹⁶ ⁴¹⁷ ⁴¹⁸ ⁴¹⁹ ⁴²⁰ ⁴²¹ ⁴²² ⁴²³ ⁴²⁴ ⁴²⁵ ⁴²⁶ ⁴²⁷ ⁴²⁸ ⁴²⁹ ⁴³⁰ ⁴³¹ ⁴³² ⁴³³ ⁴³⁴ ⁴³⁵ ⁴³⁶ ⁴³⁷ ⁴³⁸ ⁴³⁹ ⁴⁴⁰ ⁴⁴¹ ⁴⁴² ⁴⁴³ ⁴⁴⁴ ⁴⁴⁵ ⁴⁴⁶ ⁴⁴⁷ ⁴⁴⁸ ⁴⁴⁹ ⁴⁵⁰ ⁴⁵¹ ⁴⁵² ⁴⁵³ ⁴⁵⁴ ⁴⁵⁵ ⁴⁵⁶ ⁴⁵⁷ ⁴⁵⁸ ⁴⁵⁹ ⁴⁶⁰ ⁴⁶¹ ⁴⁶² ⁴⁶³ ⁴⁶⁴ ⁴⁶⁵ ⁴⁶⁶ ⁴⁶⁷ ⁴⁶⁸ ⁴⁶⁹ ⁴⁷⁰ ⁴⁷¹ ⁴⁷² ⁴⁷³ ⁴⁷⁴ ⁴⁷⁵ ⁴⁷⁶ ⁴⁷⁷ ⁴⁷⁸ ⁴⁷⁹ ⁴⁸⁰ ⁴⁸¹ ⁴⁸² ⁴⁸³ ⁴⁸⁴ ⁴⁸⁵ ⁴⁸⁶ ⁴⁸⁷ ⁴⁸⁸ ⁴⁸⁹ ⁴⁹⁰ ⁴⁹¹ ⁴⁹² ⁴⁹³ ⁴⁹⁴ ⁴⁹⁵ ⁴⁹⁶ ⁴⁹⁷ ⁴⁹⁸ ⁴⁹⁹ ⁵⁰⁰ ⁵⁰¹ ⁵⁰² ⁵⁰³ ⁵⁰⁴ ⁵⁰⁵ ⁵⁰⁶ ⁵⁰⁷ ⁵⁰⁸ ⁵⁰⁹ ⁵¹⁰ ⁵¹¹ ⁵¹² ⁵¹³ ⁵¹⁴ ⁵¹⁵ ⁵¹⁶ ⁵¹⁷ ⁵¹⁸ ⁵¹⁹ ⁵²⁰ ⁵²¹ ⁵²² ⁵²³ ⁵²⁴ ⁵²⁵ ⁵²⁶ ⁵²⁷ ⁵²⁸ ⁵²⁹ ⁵³⁰ ⁵³¹ ⁵³² ⁵³³ ⁵³⁴ ⁵³⁵ ⁵³⁶ ⁵³⁷ ⁵³⁸ ⁵³⁹ ⁵⁴⁰ ⁵⁴¹ ⁵⁴² ⁵⁴³ ⁵⁴⁴ ⁵⁴⁵ ⁵⁴⁶ ⁵⁴⁷ ⁵⁴⁸ ⁵⁴⁹ ⁵⁵⁰ ⁵⁵¹ ⁵⁵² ⁵⁵³ ⁵⁵⁴ ⁵⁵⁵ ⁵⁵⁶ ⁵⁵⁷ ⁵⁵⁸ ⁵⁵⁹ ⁵⁶⁰ ⁵⁶¹ ⁵⁶² ⁵⁶³ ⁵⁶⁴ ⁵⁶⁵ ⁵⁶⁶ ⁵⁶⁷ ⁵⁶⁸ ⁵⁶⁹ ⁵⁷⁰ ⁵⁷¹ ⁵⁷² ⁵⁷³ ⁵⁷⁴ ⁵⁷⁵ ⁵⁷⁶ ⁵⁷⁷ ⁵⁷⁸ ⁵⁷⁹ ⁵⁸⁰ ⁵⁸¹ ⁵⁸² ⁵⁸³ ⁵⁸⁴ ⁵⁸⁵ ⁵⁸⁶ ⁵⁸⁷ ⁵⁸⁸ ⁵⁸⁹ ⁵⁹⁰ ⁵⁹¹ ⁵⁹² ⁵⁹³ ⁵⁹⁴ ⁵⁹⁵ ⁵⁹⁶ ⁵⁹⁷ ⁵⁹⁸ ⁵⁹⁹ ⁶⁰⁰ ⁶⁰¹ ⁶⁰² ⁶⁰³ ⁶⁰⁴ ⁶⁰⁵ ⁶⁰⁶ ⁶⁰⁷ ⁶⁰⁸ ⁶⁰⁹ ⁶¹⁰ ⁶¹¹ ⁶¹² ⁶¹³ ⁶¹⁴ ⁶¹⁵ ⁶¹⁶ ⁶¹⁷ ⁶¹⁸ ⁶¹⁹ ⁶²⁰ ⁶²¹ ⁶²² ⁶²³ ⁶²⁴ ⁶²⁵ ⁶²⁶ ⁶²⁷ ⁶²⁸ ⁶²⁹ ⁶³⁰ ⁶³¹ ⁶³² ⁶³³ ⁶³⁴ ⁶³⁵ ⁶³⁶ ⁶³⁷ ⁶³⁸ ⁶³⁹ ⁶⁴⁰ ⁶⁴¹ ⁶⁴² ⁶⁴³ ⁶⁴⁴ ⁶⁴⁵ ⁶⁴⁶ ⁶⁴⁷ ⁶⁴⁸ ⁶⁴⁹ ⁶⁵⁰ ⁶⁵¹ ⁶⁵² ⁶⁵³ ⁶⁵⁴ ⁶⁵⁵ ⁶⁵⁶ ⁶⁵⁷ ⁶⁵⁸ ⁶⁵⁹ ⁶⁶⁰ ⁶⁶¹ ⁶⁶² ⁶⁶³ ⁶⁶⁴ ⁶⁶⁵ ⁶⁶⁶ ⁶⁶⁷ ⁶⁶⁸ ⁶⁶⁹ ⁶⁷⁰ ⁶⁷¹ ⁶⁷² ⁶⁷³ ⁶⁷⁴ ⁶⁷⁵ ⁶⁷⁶ ⁶⁷⁷ ⁶⁷⁸ ⁶⁷⁹ ⁶⁸⁰ ⁶⁸¹ ⁶⁸² ⁶⁸³ ⁶⁸⁴ ⁶⁸⁵ ⁶⁸⁶ ⁶⁸⁷ ⁶⁸⁸ ⁶⁸⁹ ⁶⁹⁰ ⁶⁹¹ ⁶⁹² ⁶⁹³ ⁶⁹⁴ ⁶⁹⁵ ⁶⁹⁶ ⁶⁹⁷ ⁶⁹⁸ ⁶⁹⁹ ⁷⁰⁰ ⁷⁰¹ ⁷⁰² ⁷⁰³ ⁷⁰⁴ ⁷⁰⁵ ⁷⁰⁶ ⁷⁰⁷ ⁷⁰⁸ ⁷⁰⁹ ⁷¹⁰ ⁷¹¹ ⁷¹² ⁷¹³ ⁷¹⁴ ⁷¹⁵ ⁷¹⁶ ⁷¹⁷ ⁷¹⁸ ⁷¹⁹ ⁷²⁰ ⁷²¹ ⁷²² ⁷²³ ⁷²⁴ ⁷²⁵ ⁷²⁶ ⁷²⁷ ⁷²⁸ ⁷²⁹ ⁷³⁰ ⁷³¹ ⁷³² ⁷³³ ⁷³⁴ ⁷³⁵ ⁷³⁶ ⁷³⁷ ⁷³⁸ ⁷³⁹ ⁷⁴⁰ ⁷⁴¹ ⁷⁴² ⁷⁴³ ⁷⁴⁴ ⁷⁴⁵ ⁷⁴⁶ ⁷⁴⁷ ⁷⁴⁸ ⁷⁴⁹ ⁷⁵⁰ ⁷⁵¹ ⁷⁵² ⁷⁵³ ⁷⁵⁴ ⁷⁵⁵ ⁷⁵⁶ ⁷⁵⁷ ⁷⁵⁸ ⁷⁵⁹ ⁷⁶⁰ ⁷⁶¹ ⁷⁶² ⁷⁶³ ⁷⁶⁴ ⁷⁶⁵ ⁷⁶⁶ ⁷⁶⁷ ⁷⁶⁸ ⁷⁶⁹ ⁷⁷⁰ ⁷⁷¹ ⁷⁷² ⁷⁷³ ⁷⁷⁴ ⁷⁷⁵ ⁷⁷⁶ ⁷⁷⁷ ⁷⁷⁸ ⁷⁷⁹ ⁷⁸⁰ ⁷⁸¹ ⁷⁸² ⁷⁸³ ⁷⁸⁴ ⁷⁸⁵ ⁷⁸⁶ ⁷⁸⁷ ⁷⁸⁸ ⁷⁸⁹ ⁷⁹⁰ ⁷⁹¹ ⁷⁹² ⁷⁹³ ⁷⁹⁴ ⁷⁹⁵ ⁷⁹⁶ ⁷⁹⁷ ⁷⁹⁸ ⁷⁹⁹ ⁸⁰⁰ ⁸⁰¹ ⁸⁰² ⁸⁰³ ⁸⁰⁴ ⁸⁰⁵ ⁸⁰⁶ ⁸⁰⁷ ⁸⁰⁸ ⁸⁰⁹ ⁸¹⁰ ⁸¹¹ ⁸¹² ⁸¹³ ⁸¹⁴ ⁸¹⁵ ⁸¹⁶ ⁸¹⁷ ⁸¹⁸ ⁸¹⁹ ⁸²⁰ ⁸²¹ ⁸²² ⁸²³ ⁸²⁴ ⁸²⁵ ⁸²⁶ ⁸²⁷ ⁸²⁸ ⁸²⁹ ⁸³⁰ ⁸³¹ ⁸³² ⁸³³ ⁸³⁴ ⁸³⁵ ⁸³⁶ ⁸³⁷ ⁸³⁸ ⁸³⁹ ⁸⁴⁰ ⁸⁴¹ ⁸⁴² ⁸⁴³ ⁸⁴⁴ ⁸⁴⁵ ⁸⁴⁶ ⁸⁴⁷ ⁸⁴⁸ ⁸⁴⁹ ⁸⁵⁰ ⁸⁵¹ ⁸⁵² ⁸⁵³ ⁸⁵⁴ ⁸⁵⁵ ⁸⁵⁶ ⁸⁵⁷ ⁸⁵⁸ ⁸⁵⁹ ⁸⁶⁰ ⁸⁶¹ ⁸⁶² ⁸⁶³ ⁸⁶⁴ ⁸⁶⁵ ⁸⁶⁶ ⁸⁶⁷ ⁸⁶⁸ ⁸⁶⁹ ⁸⁷⁰ ⁸⁷¹ ⁸⁷² ⁸⁷³ ⁸⁷⁴ ⁸⁷⁵ ⁸⁷⁶ ⁸⁷⁷ ⁸⁷⁸ ⁸⁷⁹ ⁸⁸⁰ ⁸⁸¹ ⁸⁸² ⁸⁸³ ⁸⁸⁴ ⁸⁸⁵ ⁸⁸⁶ ⁸⁸⁷ ⁸⁸⁸ ⁸⁸⁹ ⁸⁹⁰ ⁸⁹¹ ⁸⁹² ⁸⁹³ ⁸⁹⁴ ⁸⁹⁵ ⁸⁹⁶ ⁸⁹⁷ ⁸⁹⁸ ⁸⁹⁹ ⁹⁰⁰ ⁹⁰¹ ⁹⁰² ⁹⁰³ ⁹⁰⁴ ⁹⁰⁵ ⁹⁰⁶ ⁹⁰⁷ ⁹⁰⁸ ⁹⁰⁹ ⁹¹⁰ ⁹¹¹ ⁹¹² ⁹¹³ ⁹¹⁴ ⁹¹⁵ ⁹¹⁶ ⁹¹⁷ ⁹¹⁸ ⁹¹⁹ ⁹²⁰ ⁹²¹ ⁹²² ⁹²³ ⁹²⁴ ⁹²⁵ ⁹²⁶ ⁹²⁷ ⁹²⁸ ⁹²⁹ ⁹³⁰ ⁹³¹ ⁹³² ⁹³³ ⁹³⁴ ⁹³⁵ ⁹³⁶ ⁹³⁷ ⁹³⁸ ⁹³⁹ ⁹⁴⁰ ⁹⁴¹ ⁹⁴² ⁹⁴³ ⁹⁴⁴ ⁹⁴⁵ ⁹⁴⁶ ⁹⁴⁷ ⁹⁴⁸ ⁹⁴⁹ ⁹⁵⁰ ⁹⁵¹ ⁹⁵² ⁹⁵³ ⁹⁵⁴ ⁹⁵⁵ ⁹⁵⁶ ⁹⁵⁷ ⁹⁵⁸ ⁹⁵⁹ ⁹⁶⁰ ⁹⁶¹ ⁹⁶² ⁹⁶³ ⁹⁶⁴ ⁹⁶⁵ ⁹⁶⁶ ⁹⁶⁷ ⁹⁶⁸ ⁹⁶⁹ ⁹⁷⁰ ⁹⁷¹ ⁹⁷² ⁹⁷³ ⁹⁷⁴ ⁹⁷⁵ ⁹⁷⁶ ⁹⁷⁷ ⁹⁷⁸ ⁹⁷⁹ ⁹⁸⁰ ⁹⁸¹ ⁹⁸² ⁹⁸³ ⁹⁸⁴ ⁹⁸⁵ ⁹⁸⁶ ⁹⁸⁷ ⁹⁸⁸ ⁹⁸⁹ ⁹⁹⁰ ⁹⁹¹ ⁹⁹² ⁹⁹³ ⁹⁹⁴ ⁹⁹⁵ ⁹⁹⁶ ⁹⁹⁷ ⁹⁹⁸ ⁹⁹⁹ ¹⁰⁰⁰

(NCT01172808 and NCT01172821), 2,100 patients with moderate symptomatic asthma received 5 or 2.5 μg of tiotropium, or salmeterol or placebo, as add-on to medium-dose ICS. Because the results were highly comparable between studies, the investigators presented pooled data. Significant improvements in peak and trough FEV_1 were observed ($P < .001$ for all comparisons), with a larger proportion of ACQ-7 responders observed after 24 weeks of treatment with the tiotropium doses (5 μg , odds ratio 1.32, $P = .035$; 2.5 μg , odds ratio 1.33, $P = .031$), compared with placebo.⁶⁴

Tiotropium Respimat was found to have safety and tolerability that were comparable with those of placebo in all trials in which they were assessed.^{59–65} In a long-term study of 5 or 2.5 μg of tiotropium or placebo once daily as add-on to medium-dose ICS with or without a LABA each evening in 285 Japanese patients (NCT01340209), the safety and tolerability (primary end point of the study) of tiotropium were found to be comparable with those of placebo.⁶⁵

The first results from studies of tiotropium Respimat in adolescents and children are available. A phase 2, incomplete-crossover, dose-ranging study of 5, 2.5, and 1.25 μg of tiotropium as add-on to medium-dose ICS with or without a leukotriene receptor antagonist was conducted in 105 adolescent patients 12 to 17 years old with moderate symptomatic asthma (NCT01122680). Measurements of peak $\text{FEV}_{1(0-3\text{h})}$ ($P = .0004$), trough FEV_1 ($P < .0001$), and $\text{FEV}_1 \text{AUC}_{(0-3\text{h})}$ ($P = .001$) were significantly improved after treatment with 5 μg of tiotropium.⁶⁶ In a second phase 2 study of identical design in 101 children 6 to 11 years old with moderate symptomatic asthma (NCT01383499), significant improvements in measurements of peak $\text{FEV}_{1(0-3\text{h})}$ ($P < .001$ for all comparisons), trough FEV_1 ($P < .005$ for all comparisons), and $\text{FEV}_1 \text{AUC}_{(0-3\text{h})}$ ($P < .005$ for all comparisons) were observed after treatment with all doses of tiotropium.⁶⁷ As in the trials in adult patients, tiotropium was found to have comparable safety and tolerability as placebo.^{66,67} Further phase 2 and 3 studies of tiotropium as add-on to at least ICS in adolescents and children as young as 1 year are in progress.

Summary and Conclusions

There is currently an unmet need in the treatment of asthma, with a significant proportion of patients remaining symptomatic despite treatment according to guidelines. Different additional therapeutic options are undergoing development for use in the treatment of asthma, including anti-IL agents, $\text{CRT}_{\text{H}2}$ antagonists, phosphodiesterase-4 inhibitors, and LAMAs.

The tiotropium clinical trial program is currently the most advanced, with published data from different phase 2 and 3 randomized clinical trials in patients with asthma. Data from studies in adult and adolescent patients with asthma have shown that tiotropium is an efficacious add-on to at least ICS maintenance therapy, with comparable safety and tolerability as placebo. Tiotropium could offer an alternative treatment option, particularly for patients for whom current treatments are unsuitable or ineffective. In adult patients with severe asthma and a history of exacerbations, tiotropium has recently been recommended as an alternative therapeutic option at Global Initiative for Asthma steps 4 and 5.²

It should be considered that clinical trial efficacy is distinct from real-life effectiveness. A recent retrospective study in 2,042 patients with asthma highlighted that primary care physicians in the United Kingdom have been prescribing LAMAs for the treatment of asthma since 2002, predominantly as add-on therapy in older patients with poorly controlled asthma despite good treatment compliance, particularly in those who were current or former smokers.⁶⁸ In this real-life patient population, the addition of tiotropium, as 18 μg through the HandiHaler device (93%) or 5 μg through the Respimat Soft Mist inhaler (7%), provided a significant decrease in the incidence of exacerbations and antibiotic prescriptions for lower respiratory tract infections and a significant

increase in asthma control during the following year. Additional large studies of data from real-life asthma populations will help to improve individualized patient care and will be useful to help determine the position of tiotropium in relation to current asthma treatment guidelines. Once fully indicated by regulatory authorities and incorporated into asthma treatment guidelines across age groups and disease severities, the use of tiotropium in the treatment of asthma might become more widespread, given its availability in pharmacies and physicians' familiarity with using it to treat patients with chronic obstructive pulmonary disease.

Cost-effectiveness also is an important consideration in relation to real-life utility of treatments and deciding their relative place in therapeutic guidelines. This is particularly the case for biological therapies that target specific cytokines, which might require biomarker analyses to select the correct patients for treatment; such biomarker analyses are not required before treatment with tiotropium. In the first analysis of the cost-effectiveness of tiotropium, Willson et al⁶⁹ concluded that tiotropium provided a cost-effective treatment option in adult patients with severe asthma, as add-on to high-dose ICS plus LABA therapy. Further cost-effectiveness analyses, across age ranges and severities of asthma, could help to determine whether tiotropium add-on therapy provides an affordable treatment option that addresses the current unmet need in asthma treatment.

The clinical development of other emerging therapeutic options is less advanced compared with tiotropium; however, anti-IL agents, $\text{CRT}_{\text{H}2}$ antagonists, phosphodiesterase-4 inhibitors, and other LAMAs also might provide additional options for the treatment of asthma. The results of ongoing and future randomized clinical trials of these and other agents will help to address the current unmet need in patients with symptomatic asthma and to determine where these emerging therapeutic options will fit in future asthma treatment guidelines.

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Supplementary Data

Supplementary data related to this article can be found online at <http://dx.doi.org/10.1016/j.anai.2015.07.011>.

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eTable 1Summary of new therapeutic options in the treatment of asthma, with results published on PubMed: (A) anti-IL agents; (B) CRT_{H2} antagonists; (C) phosphodiesterase-4 inhibitors; (D) LAMAs

Study; trial number	Treatment arm	Phase	Study design	Patient population	Background medication ^a	Key end points
A. Anti-IL agents						
Laviolette et al, 2013 ¹ ; NCT00659659	single dose of intravenous benralizumab 1 mg/kg or placebo (cohort 1) or 3 monthly subcutaneous doses of benralizumab 100 or 200 mg or placebo (cohort 2)	1	randomized, double-blinded, placebo-controlled study	27 patients 18–65 y old with eosinophilic asthma	ND; regular asthma medication maintained throughout study	adverse events ^b , airway eosinophils ^b , sputum, bone marrow, and blood eosinophils
Nowak et al, 2015 ² ; NCT00768079	single dose of intravenous benralizumab 0.3 or 1 mg/kg or placebo	2	randomized, double-blinded, placebo-controlled, parallel-group study	110 patients 18–60 y old with acute eosinophilic asthma	ND; added to current standard-of-care medication	proportion of patients with ≥1 exacerbation in placebo vs combined benralizumab group ^b , time-weighted rate of exacerbations, adverse events, blood eosinophil counts, asthma symptom changes, health care resource use
Castro et al, 2011 ³	infusions of reslizumab 3 mg/kg or placebo (0.9% saline) every 4 wk	ND	randomized, double-blinded, placebo-controlled, 15-wk study	106 patients 18–75 y old with severe eosinophilic asthma	high-dose ICS (fluticasone ≥440 mg BID) + ≥1 other agent (including SABA, LABA, leukotriene antagonist, and cromolyn sodium)	ACQ-7 ^b , FEV ₁ , % predicted FEV ₁ , FVC, blood and sputum eosinophils, incidence of asthma exacerbations
Castro et al, 2015 ⁴ ; NCT01287039 and NCT01285323	intravenous reslizumab 3 mg/kg or placebo every 4 wk	3	2 replicate randomized, double-blinded, placebo-controlled, parallel-group, 1-y studies	953 patients 12–75 y old with blood eosinophils ≥400 cells/μL and ≥1 exacerbation in previous year	medium- to high-dose ICS (fluticasone ≥440 μg QD) ± another controller (LABA, oral corticosteroids, leukotriene modifiers, and cromolyn sodium)	annual frequency of exacerbations ^b , FEV ₁ , ACQ-7, ASUI, rescue medication use, blood eosinophils, AQLQ, adverse events
Wenzel et al, 2013 ⁵ ; NCT01312961	subcutaneous dupilumab 300 mg or placebo once weekly	2	randomized, double-blinded, placebo-controlled, parallel-group, 12-wk study	104 patients 18–65 y old with moderate to severe asthma and elevated eosinophil levels	medium- to high-dose ICS + LABA (fluticasone 250 or 500 μg and salmeterol 50 μg BID or equivalent) for 4 wk (LABA discontinued and ICS tapered during weeks 6–9)	incidence of asthma exacerbations ^b , time to asthma exacerbation, FEV ₁ , PEF _{AM} , PEF _{PM} , ACQ-5, nocturnal waking, rescue medication use
Busse et al, 2013 ⁶ ; NCT01199289	subcutaneous brodalumab 140, 210, or 280 mg or placebo at day 1 and weeks 1, 2, 4, 6, 8, and 10	2a	randomized, double-blinded, placebo-controlled, dose-ranging, 12-wk study	302 patients 18–65 y old with moderate to severe asthma	stable-dose ICS (fluticasone 200–1,000 mg QD or equivalent for ≥3 mo before screening) for ≥30 d	ACQ-7 ^b , FEV ₁ , PEF _{AM} , rescue medication use, asthma symptom scores, symptom-free days, adverse events
Corren et al, 2011 ⁷ ; NCT00930163	subcutaneous lebrikizumab 250 mg or placebo every 4 wk	2	randomized, double-blinded, placebo-controlled, 24-wk study	219 adult patients with moderate to severe symptomatic asthma	medium- to high-dose ICS (fluticasone ≥200 and ≤1,000 μg) ± LABA or leukotriene modifiers	FEV ₁ ^b , incidence of asthma exacerbations and severe exacerbations, PEF _{AM} , ACQ-5, rescue medication use
Noonan et al, 2013 ⁸ ; NCT00971035	4 doses of subcutaneous lebrikizumab 125, 250, or 500 mg or placebo every 4 wk	2	randomized, double-blinded, placebo-controlled, dose-ranging, 12-wk study	212 patients 18–65 y old with asthma not receiving ICS treatment	none	FEV ₁ ^b , time to treatment failure, PEF _{AM} , PEF variability, reliever medication use
Scheerens et al, 2014 ⁹ ; NCT00781443	4 doses of subcutaneous lebrikizumab 5 mg/kg or placebo every 4 wk	2	randomized, double-blinded, parallel-group, placebo-controlled, 12-wk study	29 patients 18–55 y old with mild allergic asthma	intermittent short-acting inhaled β ₂ -adrenergic agonists only	allergen challenge ^b , adverse events, serum biomarkers, pharmacokinetics
Pavord et al, 2012 ¹⁰ ; NCT01000506	13 infusions of intravenous mepolizumab 75, 250, or 750 mg or placebo (100 mL 0.9% NaCl) every 4 wk	1	randomized, double-blinded, placebo-controlled, 52-wk study	621 patients 12–74 y old with refractory eosinophilic asthma	fluticasone ≥880 μg (or equivalent) daily ± maintenance oral corticosteroids	incidence of asthma exacerbations ^b , blood and sputum eosinophils, ACQ-6, quality of life
Halder et al, 2009 ¹¹ ; Halder et al, 2014 ¹²	12 infusions of intravenous mepolizumab 750 mg or placebo (150 mL 0.9% saline) every 4 wk	ND	randomized, double-blinded, placebo-controlled, parallel-group, 50-wk study	61 patients ≥18 y old with refractory eosinophilic asthma	high-dose corticosteroids	incidence of severe asthma exacerbations ^b , ACQ-5, AQLQ, FEV ₁ , bronchodilator use, airway hyperresponsiveness, blood and sputum eosinophil counts

Nair et al, 2009 ¹³ ; NCT00292877	5 infusions of intravenous mepolizumab 750 mg or placebo (normal saline diluent) every 4 wk	2	randomized, double-blinded, placebo-controlled, parallel-group, 26-wk study	20 adult patients with corticosteroid-dependent eosinophilic asthma	prednisone 5–25 mg and high-dose ICS (fluticasone 600–2,000 µg or equivalent)	incidence of asthma exacerbations ^b , decrease in prednisone dose ^b , ACQ, FEV ₁ , sputum and blood eosinophils
Ortega et al, 2014 ¹⁴ ; NCT01691521	intravenous mepolizumab 75 mg, subcutaneous mepolizumab 100 mg, or placebo every 4 wk	3	randomized, double-blinded, double-dummy, 32-wk study	576 patients 12–85 y old with severe eosinophilic asthma	fluticasone propionate ≥880 µg (or equivalent) plus ≥3 mo of treatment with an additional controller	exacerbation rate ^b , spirometry, hematology, ACQ-5, SGRQ, adverse events, vital signs
Bel et al, 2014 ¹⁵ ; NCT01691508	subcutaneous mepolizumab 100 mg or placebo every 4 wk	3	randomized, double-blinded, placebo-controlled, parallel-group, 20-wk study	135 patients with severe eosinophilic asthma	high-dose ICS (prednisone 5–35 mg or equivalent) plus additional controller	decrease in ICS use ^b , exacerbation rate, FEV ₁ , ACQ-5, SGRQ, safety, immunogenicity
Flood-Page et al, 2007 ¹⁶	intravenous mepolizumab 250 or 750 mg or placebo every 4 wk	ND	randomized, double-blinded, placebo-controlled, 12-wk study	362 patients 18–55 y old with moderate symptomatic asthma	ICS (beclomethasone 400–1,000 mg or equivalent)	PEF _{AM} ^b , FEV ₁ , asthma symptoms, rescue medication use, quality of life, incidence of asthma exacerbations, blood and sputum eosinophils
B. CRT_{H2} antagonists						
Barnes et al, 2012 ¹⁷ ; NCT01057927	oral OC000459 200 mg BID or placebo	2	randomized, double-blinded, parallel-group, 4-wk study	132 steroid-free patients 18–55 y old with moderate persistent asthma	none	FEV ₁ ^b , PEF, asthma symptoms, quality of life, rescue medication use, sputum eosinophils, serum IgE
Singh et al, 2013 ¹⁸ ; NCT01056692	oral OC000459 200 mg BID or placebo	2	randomized, double-blinded, placebo-controlled, 2-way crossover, 16-d study	21 steroid-naïve patients 18–45 y old with allergic asthma	none	allergen challenge ^b , sputum eosinophils, FEV ₁
Pettipher et al, 2014 ¹⁹ ; NCT00890877	oral OC000459 25 or 200 mg QD, 100 mg BID, or placebo	2	randomized, dose-finding, double-blinded parallel-group, 12-wk study	519 patients 18–55 y old with mild to moderate persistent asthma	none	FEV ₁ ^b , FVC, PEF, AQLQ, ACQ-7, incidence of exacerbations and respiratory tract infections, rescue medication use, asthma symptoms, adverse events
C. Phosphodiesterase-4 inhibitors						
Louw et al, 2007 ²⁰	single dose of oral roflumilast 1,000 µg or placebo with 2- to 5-wk washout between the 2 treatment periods	ND	randomized, double-blinded, 2-period, crossover study	13 patients 18–50 y old with mild allergic asthma	none	histamine challenge ^b , allergen challenge ^b
van Schalkwyk et al, 2005 ²¹	oral roflumilast 250 or 500 µg or placebo QD for 7–10 d with washout periods of 2–5 wk between each treatment period	ND	randomized, double-blinded, placebo-controlled, 3-period crossover study	23 patients 18–50 y old with mild asthma	none	allergen challenge ^b , FEV ₁
Gauvreau et al, 2011 ²² ; NCT01365533	oral roflumilast 500 µg or placebo QD	2	randomized, double-blinded, placebo-controlled, crossover, 14-d study	25 steroid-naïve patients 18–54 y old with mild allergic asthma	none	allergen challenge ^b , FEV ₁ , methacholine challenge, sputum eosinophils, pharmacokinetic assessments
Bateman et al, 2006 ²³	oral roflumilast 100, 250, or 500 µg QD	2/3	randomized, double-blinded, parallel-group, 12-wk study	693 patients 15–70 y old with mild to moderate asthma	none	FEV ₁ ^b , PEF _{AM} , PEF _{PM} , asthma symptom scores, rescue medication use, withdrawal owing to lack of efficacy
Bousquet et al, 2006 ²⁴	oral roflumilast 500 µg QD or beclomethasone 200 µg BID	ND	randomized, double-blinded, double-dummy, noninferiority, 12-wk study	499 patients 12–70 y old with persistent asthma	none	FEV ₁ ^b , FVC, PEF _{AM} , PEF _{PM} , asthma symptom scores, rescue medication use
Neville et al, 2008 ²⁵	single oral dose of roflumilast 100 µg in period 1 (3 d) and 250 µg in period 2 (4 d) with washout period of ≥14 d	ND	open-label, crossover, 2-period, ascending-dose study	25 children and adolescents with mild to moderate asthma	none	pharmacokinetic assessments ^b
D. LAMAs						
Hansel et al, 2005 ²⁶	single dose of inhaled glycopyrrolate 0.5, 1, or 2 mg, ipratropium 0.5 mg, and placebo with 7-d washout between treatments	3	randomized, double-blinded, placebo-controlled, 5-way crossover study	10 patients 18–60 y old with mild to moderate atopic asthma	none	methacholine challenge ^b , adverse events

(continued on next page)

eTable 1 (continued)

Study; trial number	Treatment arm	Phase	Study design	Patient population	Background medication ^a	Key end points
Lee et al, 2015 ²⁷ ; NCT01641692	3 of 8 treatments: inhaled umecclidinium 15.6, 31.25, 62.5, 125, or 250 μ g QD and umecclidinium 15.6 or 31.25 μ g BID, or placebo for 14 d with 12- to 14-d washout between treatments	2	double-blinded, 3-period, crossover, incomplete-block study	350 patients $\geq$ 18 y old with asthma	none	trough FEV ₁ ^b , PEF _{AM} , PEF _{PM} , rescue medication use, 0- to 24-h weighted mean FEV ₁ , adverse events, vital signs
Lee et al, 2015 ²⁸ ; NCT01573624	3 of 7 treatments: fluticasone furoate 100 μ g alone QD, fluticasone furoate 100 μ g QD + umecclidinium 15.6, 31.25, 62.5, 125, or 250 μ g QD or vilanterol 25 μ g QD for 14 d with 12- to 14-d washout between treatments	2	double-blinded, 3-period, crossover, incomplete-block study	421 patients $\geq$ 18 y old with asthma	ICS	trough FEV ₁ ^b , PEF _{AM} , PEF _{PM} , rescue medication use, symptom-free days, adverse events, vital signs
Fardon et al, 2007 ²⁹	inhaled fluticasone 500 μ g BID + salmeterol 100 μ g BID + tiotropium 18 μ g (HandiHaler) QD or inhaled fluticasone 500 μ g BID + salmeterol 100 μ g BID + placebo	ND	randomized, double-blinded, placebo-controlled, 4-wk crossover study	26 patients $\geq$ 18 y old with severe asthma	none	FEV ₁ , FVC, PEF _{AM} , PEF _{PM} , AQLQ, body plethysmography
Terzano et al, 2004 ³⁰	single dose of inhaled tiotropium 18 μ g (HandiHaler) or placebo	ND	comparative, 3-challenge study with 72-h washout between each challenge	10 patients with asthma and documented airway hyperresponsiveness	ND	methacholine challenge ^b
Sposato et al, 2008 ³¹	single dose of inhaled ipratropium 40 μ g, oxitropium 200 μ g, or tiotropium 18 μ g (HandiHaler)	ND	comparative study after 72-h washout	44 patients with intermittent bronchial asthma	none	methacholine challenge ^b , FEV ₁
Peters et al, 2010 ³² ; Peters et al, 2013 ³³ ; NCT00565266	inhaled tiotropium 18 μ g (HandiHaler) QD, beclomethasone 160 μ g BID (ie, double run-in dose), or salmeterol (Serevent Diskus; GlaxoSmithKline, Research Triangle Park, North Carolina) 50 μ g BID	ND	randomized, 3-way, double-blinded, triple-dummy, 14-wk crossover study	210 patients $\geq$ 18 y old with asthma	ICS (beclomethasone 80 μ g BID)	PEF _{AM} ^b , FEV ₁ , number of asthma-control days, asthma symptoms, rescue bronchodilator use, asthma exacerbations, use of health care services, biomarkers of airway inflammation, ACQ, asthma symptoms, AQLQ, adverse events
Kerstjens et al, 2011 ³⁴ ; NCT00365560	inhaled tiotropium Respimat 10 or 5 μ g or placebo Respimat QD (morning dosing)	2	randomized, double-blinded, 24-wk crossover study	107 patients 18–75 y old with severe persistent asthma	high-dose ICS (budesonide $\geq$ 800 μ g or equivalent) + LABA (theophylline, leukotriene modifiers, and oral glucocorticosteroids also permitted in stable doses)	peak FEV _{1(0–3h)} ^b , trough FEV ₁ , peak FVC, trough FVC, FEV ₁ AUC _(0–3h) , FVC AUC _(0–3h) , PEF _{AM} , PEF _{PM} , asthma symptoms, rescue medication use, asthma symptom-free days, mini-AQLQ, adverse events, vital signs
Beeh et al, 2014 ³⁵ ; NCT01233284	inhaled tiotropium Respimat 5, 2.5, or 1.25 μ g or placebo Respimat QD (evening dosing)	2	randomized, double-blinded, placebo-controlled, dose-ranging, 4-way, 16-wk crossover study	149 patients 18–75 y old with moderate asthma	medium-dose ICS (budesonide 400–800 μ g or equivalent)	peak FEV _{1(0–3h)} ^b , trough FEV ₁ , peak FVC, trough FVC, FEV ₁ AUC _(0–3h) , FVC AUC _(0–3h) , PEF _{AM} , PEF _{PM} , ACQ-7, adverse events, vital signs
Timmer et al, 2015 ³⁶ ; NCT01152450	inhaled tiotropium Respimat 5 μ g QD (evening, + placebo Respimat in morning), 2.5 μ g BID (morning and evening), or placebo Respimat (morning and evening)	2	randomized, double-blinded, placebo-controlled, 12-wk crossover study	94 patients 18–75 y old with moderate symptomatic asthma	medium-dose ICS (budesonide 400–800 μ g or equivalent)	FEV ₁ AUC _(0–24h) ^b , peak FEV _{1(0–24h)} , trough FEV ₁ , PEF _{AM} , PEF _{PM} , ACQ-7, pharmacokinetic assessments, adverse events
Bateman et al, 2011 ³⁷ ; NCT00350207	inhaled tiotropium Respimat 5 μ g QD (evening), salmeterol HFA-MDI 50 μ g BID (morning and evening), or matching placebo	2	randomized, double-blinded, double-dummy, placebo-controlled, parallel-group, 16-wk study	388 patients 18–67 y old with moderate asthma with B16-Arg/Arg genotype	medium- to high-dose ICS (budesonide 400–1,000 μ g or equivalent)	PEF _{AM} ^b , PEF _{PM} , FEV ₁ , asthma symptoms, rescue medication use, asthma symptom-free days, level of asthma control, adverse events, vital signs, mini-AQLQ

Kerstjens et al, 2012 ³⁸ ; NCT00772538 and NCT00776984	inhaled tiotropium Respimat 5 µg or placebo Respimat QD (morning dosing)	3	2 replicate randomized, double-blinded, placebo-controlled, parallel-group, 48-wk studies	912 patients 18–75 y old with poorly controlled asthma	high-dose ICS (budesonide >800 µg or equivalent) + LABA (continued use of stable-dose sustained-release theophylline, leukotriene modifiers, anti-IgE, and oral glucocorticoids [≤5 mg/d] was permitted)	peak FEV _{1(0–3h)} ^b , trough FEV ₁ ^b , time to first severe asthma exacerbation ^b , 24-h FEV ₁ measurements, individual peak and trough FEV ₁ and FVC measurements, FEV ₁ AUC _(0–3h) , FVC AUC _(0–3h) , time to the first episode of asthma worsening, PEF _{AM} , PEF _{PM} , ACQ-7, AQLQ, adverse events, vital signs
Kerstjens et al, 2015 ³⁹ ; NCT01172808 and NCT01172821	inhaled tiotropium Respimat 5 or 2.5 µg QD (evening dosing), salmeterol 50 µg HFA-MDI BID, or matching placebo	3	2 replicate randomized, double-blinded, double-dummy, placebo-controlled, parallel-group, 24-wk studies	2,100 patients 18–75 y old with moderate symptomatic asthma	medium-dose ICS (budesonide 400–800 µg or equivalent)	peak FEV _{1(0–3h)} ^b , trough FEV ₁ ^b , ACQ-7 responder rate ^b , peak FVC _(0–3h) , trough FVC, PEF _{AM} , PEF _{PM} , AQLQ, time to first severe exacerbation, time to first episode of asthma worsening, 24-h FEV ₁ and FVC, adverse events
Ohta et al, 2015 ⁴⁰ ; NCT01340209	inhaled tiotropium Respimat 5 or 2.5 µg or placebo Respimat QD (evening dosing)	3	randomized, double-blinded, placebo-controlled, parallel-group, 52-wk study	285 Japanese patients 18–75 y old with moderate symptomatic asthma	medium-dose ICS (budesonide 400–800 µg or equivalent) ± LABA	adverse events ^b , vital signs ^b , trough FEV ₁ , trough FVC, trough PEF, ACQ-7 responder rate, adverse events
Vogelberg et al, 2014 ⁴¹ ; NCT01122680	inhaled tiotropium Respimat 5, 2.5, or 1.25 µg or placebo Respimat QD (evening dosing)	2	randomized, double-blinded, placebo-controlled, dose-ranging, incomplete-crossover, 12-wk study	105 adolescents 12–17 y old with moderate symptomatic asthma	medium-dose ICS ± leukotriene receptor antagonists	peak FEV _{1(0–3h)} ^b , trough FEV ₁ , FEV ₁ AUC _(0–3h) , PEF _{AM} , PEF _{PM} , ACQ-7, adverse events, vital signs
Vogelberg et al, 2015 ⁴² ; NCT01383499	inhaled tiotropium Respimat 5, 2.5, or 1.25 µg or placebo Respimat QD (evening dosing)	2	randomized, double-blinded, placebo-controlled, dose-ranging, incomplete-crossover, 12-wk study	101 patients 6–11 y old with moderate symptomatic asthma	medium-dose ICS (budesonide 200–400 µg or equivalent) ± leukotriene receptor antagonists	peak FEV _{1(0–3h)} ^b , trough FEV ₁ , FEV ₁ AUC _(0–3h) , peak FVC _(0–3h) , trough FVC, FVC AUC _(0–3h) , PEF _{AM} , PEF _{PM} , individual FEV ₁ measurements, FEF _{25–75%} , ACQ-7, PAQLQ(S), adverse events

Abbreviations: ACQ, Asthma Control Questionnaire; ACQ-5, 5-question Asthma Control Questionnaire; ACQ-6, 6-question Asthma Control Questionnaire; ACQ-7, 7-question Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; ASUI, Asthma Symptom Utility Index; AUC_(0–3h), area under the curve within 3 hours after dose; BID, twice daily; CRT₄₂, chemoattractant receptor-homologous molecule expressed on T-helper type 2 lymphocytes; FEF_{25–75%}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; FVC_(0–3h), forced vital capacity within 3 hours after dose; FVC, forced vital capacity; HFA-MDI, hydrofluoroalkane metered-dose inhaler; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; ND, not defined; PAQLQ(S), Standardised Paediatric Asthma Quality of Life Questionnaire; peak FEV_{1(0–3h)}, peak forced expiratory volume in 1 second within 3 hours after dose; PEF, peak expiratory flow; PEF_{AM}, morning peak expiratory flow; PEF_{PM}, evening peak expiratory flow; QD, once daily; SABA, short-acting β_2 -agonist; SGRQ, St George's Respiratory Questionnaire.

^aExcluding rescue medication.

^bPrimary end point.

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