

A review of the efficacy and safety of once-daily tiotropium Respimat 2.5 micrograms in adults and adolescents with asthma

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ABSTRACT

Background: Despite current guidelines, many patients with asthma remain symptomatic, particularly those intolerant of, unresponsive to, or uncontrolled by long-acting beta 2-agonists (LABAs). Tiotropium bromide, delivered through the Respimat soft-mist inhaler in 2 puffs of 1.25 micrograms each, is approved for the long-term, maintenance treatment of asthma in patients aged ≥ 6 years.

Objective: An overview of the use of once-daily tiotropium Respimat 2.5 micrograms in adults and adolescents with varying degrees of asthma severity. The role of the parasympathetic nervous system in the pathophysiology of asthma, the development of tiotropium for respiratory disease, and the value of the Respimat inhaler are also discussed.

Methods: A literature search of all phase II and phase III trials of once-daily tiotropium Respimat 2.5 micrograms.

Results: Once-daily tiotropium Respimat 2.5 micrograms was studied in five phase III studies: three studies in adults and two in adolescents aged 12–17 years. Tiotropium Respimat 2.5 micrograms demonstrated efficacy in adults and adolescents with mild, moderate, or severe asthma, showing significant improvements in lung function and asthma control in patients with uncontrolled asthma despite inhaled corticosteroids (ICS) or ICS plus LABA use. The adverse event profile of tiotropium was very acceptable, with safety similar to placebo.

Conclusion: Once-daily tiotropium Respimat 2.5 micrograms has positive attributes that include efficacy, a safety profile similar to placebo, once-daily dosing, administration by inhalation, and delivery in the easy-to-use and consistent-dosing Respimat device. However, more data are needed on the effects of tiotropium on clinical outcomes, patients' day-to-day lives, and real-world effectiveness.

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Asthma is a heterogeneous disease marked by chronic inflammation of the airways;¹ it has multiple phenotypes,² and distinct underlying pathophysiologic mechanisms (*i.e.*, endotypes),^{3,4} and can occur across a range of severities.⁵ Asthma is typically treated in a stepwise fashion, with low-dose inhaled corticosteroids (ICS) as first-line controller pharmacologic therapy.¹ The addition of long-acting β_2 -agonists (LABAs) as second-line controller therapy may help achieve asthma control,⁶ but not all patients respond,⁷ and it may result in tachyphylaxis⁸ or worse outcomes

when added to ICS.^{9–11} Fifty-eight percent of adults and 46% of children with asthma remain symptomatic despite treatment according to current guidelines.¹² New long-acting, cost-effective bronchodilator and/or anti-inflammatory options, therefore, are needed, particularly in patients intolerant of or unresponsive to LABAs, in patients with varying degrees of asthma severity, or as an add-on to ICS alone or to ICS plus LABA.

The once-daily, long-acting anticholinergic bronchodilator tiotropium bromide (commonly called tiotropium), delivered through the Respimat soft-mist inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) in 2 puffs of 1.25 μg each, was approved by the U.S. Food and Drug Administration (FDA) in September 2015, for the long-term, maintenance treatment of asthma in patients aged ≥ 6 years. The Global Initiative for Asthma guidelines¹³ indicate that tiotropium may be used in steps 4 and 5 in adults and adolescents with a history of exacerbations.

In the full phase II and phase III clinical development programs for asthma, tiotropium has been tested in 18 clinical trials in >6000 patients from 150 global sites in adults and children aged 1–5, 6–11, and 12–17 years. This included trials with a 5- μg every day (q.d.) dose,

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which is approved in the European Union as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently being treated with the maintenance combination of ICS (≥ 800 μg budesonide/day or equivalent) and LABAs and who experienced one or more severe exacerbations in the previous year.¹⁴ At the population-level there seemed to generally be no difference between the 5- and 2.5- μg q.d. doses, but at the individual level there may be, so the real-world question arises about whether there is any benefit to switching to 5 μg q.d. in a patient who is not getting benefit from 2.5 μg q.d. However, because 2.5 μg q.d. is the approved dose in the United States, data from the 5- μg dose are not discussed here. This article provides an overview of the use of tiotropium Respimat 2.5 μg q.d. in adults and adolescents with varying degrees of severity of asthma.

ROLE OF THE PARASYMPATHETIC NERVOUS SYSTEM IN THE PATHOPHYSIOLOGY OF ASTHMA

Acetylcholine released from parasympathetic neurons, or secreted non-neuronally, is responsible for inflammation, mucus production, and smooth-muscle contraction in the lungs.¹⁵ Bronchial smooth-muscle contraction is the main cause of reversible airway obstruction in asthma and is primarily a result of cholinergic activity.^{16–18} Even in patients with asthma on long-term ICS treatment, airway hyperresponsiveness is still present despite the histologic absence of inflammation in bronchial mucosal biopsy specimens,¹⁹ suggesting that increased cholinergic tone plays a role in asthma pathophysiology.²⁰ Patients with asthma have increased parasympathetic nerve activity.²¹ Acetylcholine may play a role in regulating airway inflammation and remodeling;^{22,23} its release and related muscarinic effector systems are dysregulated in asthma.^{24,25}

The M_1 , M_2 , and M_3 muscarinic receptor subtypes are found in human airways and mediate acetylcholine's effects on airway constriction.²⁶ Bronchoconstriction is induced by acetylcholine *via* M_3 receptors on smooth muscles in the lungs.²⁷ However, most airway smooth-muscle muscarinic receptors are M_2 receptors,²⁸ which lead to increased release of acetylcholine when blocked and limit β -adrenoreceptor-mediated relaxation of airway smooth muscles.²⁹ Bronchodilators with a high affinity for M_3 and low affinity for M_2 receptors are thus preferable.³⁰ Long-acting muscarinic antagonists (LAMAs) work differently than other classes of asthma drugs by modulating cholinergic activity in the airways. Tiotropium is the first LAMA approved for treating asthma and is functionally selective for,³¹ and dissociates less rapidly from,³² the M_1 and M_3 receptors compared with the M_2 receptor. Cholinergic blockade with single doses of tiotropium lasts >24 hours, which allows for once-daily administration.³²

DEVELOPMENT OF TIOTROPIUM FOR RESPIRATORY DISEASE

Tiotropium was initially approved by the FDA for chronic obstructive pulmonary disease (COPD) treatment in 2004.³³ Ipratropium bromide, a short-acting muscarinic antagonist, has also been used for treating COPD and asthma, particularly in the acute setting.³⁴ In patients with stable COPD, tiotropium was associated with better lung function and improved quality of life and with fewer hospital admissions and exacerbations of COPD when compared with ipratropium.³⁵ Tiotropium's longer half-life, higher functional selectivity and affinity for the M_3 receptor, and less M_2 receptor blockade may explain such improved outcomes.³⁶ Tiotropium binding studies show that tiotropium is ~ 10 times more potent than ipratropium.³² Evidence that treatment with tiotropium offered clinical benefit in patients with asthma was initially obtained from patients with COPD and with airway hyperresponsiveness and concomitant asthma.^{37–39}

DEVELOPMENT AND VALUE OF THE RESPIMAT INHALER

In addition to the pharmacologic properties of any pulmonary drug itself, effective delivery *via* the proper inhalation technique and device properties is crucial for achieving good outcomes.⁴⁰ A major problem of pressurized metered-dose inhalers (pMDIs), particularly among children and the elderly, is coordination of actuation and inhalation, which can result in a smaller and more variable amount of drug reaching the airways of the lungs.⁴¹ The pMDIs are poorly administered by 71% of patients with asthma, with 47% being due to poor coordination.⁴² A large proportion of patients with asthma also do not correctly use dry powdered inhalers (DPIs).⁴³ Common handling errors encountered with DPIs include failure to exhale before actuation or failure to hold one's breath after inhalation, incorrect positioning or rotation sequence, and failure to inhale forcefully and deeply.

The Respimat inhaler (Fig. 1), which is not breath actuated, overcomes some of the limitations encountered with pMDIs and DPIs. The Respimat inhaler uses a propellant-free mechanism to generate a fine mist that is released over ~ 1.5 seconds to deliver a metered dosage of medication. The dose delivered to the airways is independent of the variable inspiratory flow of a patient.⁴⁴ Patient preference studies with the Respimat inhaler have shown this inhaler to be easy to use regardless of a patient's age and that it is consistently well accepted and preferred to a pMDI or DPI.⁴⁵

PHASE II STUDIES WITH TIOTROPIUM RESPIMAT FOR THE TREATMENT OF ASTHMA

Several phase II studies showed better efficacy versus placebo of tiotropium Respimat at the 5- μg q.d.

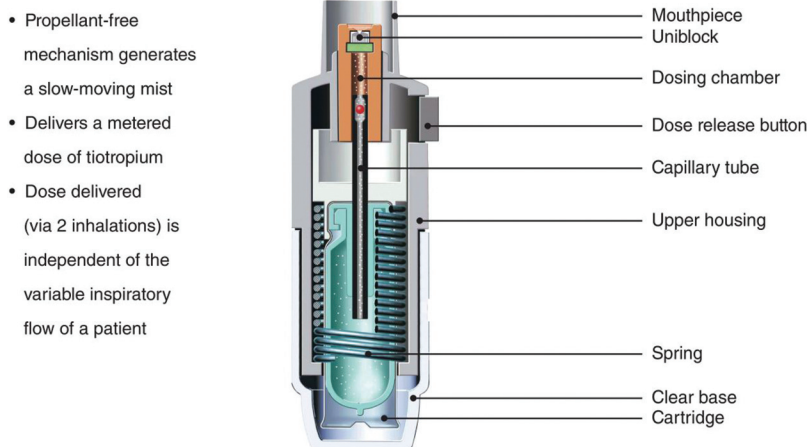


Figure 1. The Respimat inhaler.

dose when added to ICS in patients with symptomatic asthma.^{46–49} Tiotropium Respimat has also been tested at the 2.5- μ g q.d. dose in phase II studies. In a dose-ranging trial, tiotropium Respimat was tested as an add-on to medium-dose ICS (without LABA) in symptomatic adults with moderate persistent asthma.⁵⁰ This double-blind, four-way crossover study randomized 149 patients to once-daily evening administration of placebo Respimat or tiotropium Respimat 1.25, 2.5, or 5 μ g. Each treatment lasted 4 weeks. The primary end point of forced expiratory volume in 1 second (FEV₁) within 3 hours after dosing, FEV_{1(0–3hr)}, was met with significant improvements in all dose groups versus placebo ($p < 0.0001$), with a 128-mL difference in the 2.5- μ g group. Safety results were comparable among the groups.

Another dose-ranging trial randomized 105 adolescents aged 12–17 years with symptomatic asthma to once-daily tiotropium Respimat 5 μ g ($n = 80$), 2.5 μ g ($n = 75$), or 1.25 μ g ($n = 75$), or placebo Respimat ($n = 75$) as an add-on to ICS with or without leukotriene receptor antagonists.⁵¹ To minimize the treatment burden, the study used an incomplete crossover design; each treatment lasted 4 weeks.⁵¹ All the patients were symptomatic as defined by a seven-question Asthma Control Questionnaire (ACQ-7) mean score of ≥ 1.5 at screening and before randomization, had a prebronchodilator FEV₁ of $>60\%$ and $\leq 90\%$ of the predicted normal, and had an FEV₁ increase of at least 12% and 200 mL from baseline 15–30 minutes after 400 μ g of salbutamol at screening; in patients aged 12–14 years, positive reversibility testing could be based solely on the relative ($\geq 12\%$) postbronchodilator response.⁵¹

The primary efficacy end point, FEV_{1(0–3hr)}, was only significant compared with placebo for the 5- μ g group (113 mL; $p = 0.004$). For secondary end points, the largest response over placebo Respimat in trough FEV₁ and FEV₁ area under the curve (within 3 hours after dosing [FEV₁ AUC_(0–3hr)]) was with the 5- μ g tiotropium dose (adjusted mean of difference, 151 mL; $p <$

0.0001 and 133 mL; $p = 0.001$, respectively). Morning and evening peak expiratory flow (PEF) were significantly better than placebo at the 5- and 2.5- μ g doses and greater at the 5- μ g dose than the 2.5- μ g dose. All dosing regimens were generally well tolerated. In children aged 6–11 years with symptomatic asthma, tiotropium Respimat 5, 2.5, or 1.25 μ g added to medium-dose ICS each showed a significantly better FEV₁ response compared with placebo, with safety and tolerability comparable with that of placebo.⁵²

PHASE III STUDIES WITH TIOTROPIUM RESPIMAT 2.5 μ g Q.D. FOR THE TREATMENT OF ASTHMA

Tiotropium Respimat 2.5 μ g has been tested in three phase III studies^{53–55} in adults aged 18–75 years and two phase III studies^{56,57} in adolescents aged 12–17 years. The general details and baseline characteristics of patients from these studies are shown in Table 1.

By contrast with patients with COPD, in whom air-flow limitation is typically not fully reversible,⁵⁸ the patients with asthma have an FEV₁ to forced vital capacity ratio of $\geq 70\%$ after use of a bronchodilator, which indicates reversibility. This was important in the context of the tiotropium Respimat studies for asthma to help define the population being studied.

Although most bronchodilators are dosed in the morning or dosed twice a day, in all phase III studies^{53–55} with tiotropium Respimat 2.5 μ g, dosing was in the evening or, for adolescents, in the afternoon⁵⁶ (except for PensieTinA-asthma,⁵⁷ which used morning dosing). For example, in the RubaTinA-asthma study,⁵⁶ patients delivered the study drug between 5 P.M. and 7 P.M. Evening or afternoon dosing could have been selected to administer dosing for maximum effect because asthma is known to generally be worse during nocturnal hours, and given tiotropium's long half-life, it would exert its effect during nocturnal hours. Parasympathetic activity is increased at night

Table 1 Phase III adult and adolescent studies of once-daily TioR 2.5 µg: Enrollment and baseline characteristics

	Study				
	GraziaTinA-asthma (N = 465)*	MezzoTinA-asthma (N = 2103)#	CadenTinA-asthma (N = 285)§	RubaTinA-asthma (N = 398)¶	PensieTinA-asthma (N = 392)
Asthma severity	Mild to moderate	Moderate	Moderate to severe	Moderate	Severe
Population age	Adults, 18–75	Adults, 18–75	Adults, in Japan, 18–75	Adolescents, 12–17	Adolescents, 12–17
TioR 2.5-µg group, ranges, y	53.2	61	63.2	35.2	37
% women					
Placebo group, % women	66.5	59	66.7	36.2	41.5
Maintenance treatment	Stable treatment with ICS (200–400 µg of budesonide or equivalent dose)**	Stable treatment with ICS with or without LABA (400–800 µg of budesonide or equivalent dose); LTRAs were permitted##	Stable treatment with ICS with or without LABA (400–800 µg of budesonide or equivalent dose)##	Stable treatment with ICS; ages 12–14 y: 200–800 µg of budesonide or equivalent dose; ages 15–17 y: 400–800 µg of budesonide or equivalent dose; LTRAs were permitted**	Stable treatment with high-dose ICS plus one or more controller therapies or medium-dose ICS plus two or more controller therapies; high-dose ICS included ages 12–14 y (>400 µg of budesonide or equivalent dose) and ages 15–17 y (800–1600 µg of budesonide or equivalent dose); medium-dose ICS included ages 12–14 y (200–400 µg of budesonide or equivalent dose) and ages 15–17 y (400–800 µg of budesonide or equivalent dose); LTRAs were permitted**
Treatment arms	TioR 2.5 µg q.d., TioR 5 µg q.d., placebo Respimat q.d.	TioR 2.5 µg q.d., TioR 5 µg q.d., placebo Respimat q.d., salmeterol 50 µg b.i.d.	TioR 2.5 µg q.d., TioR 5 µg q.d., placebo Respimat q.d.	TioR 2.5 µg q.d., TioR 5 µg q.d., placebo Respimat q.d.	TioR 2.5 µg q.d., TioR 5 µg q.d., placebo Respimat q.d.
Study duration, wk	12	24	52	48	12
Baseline pulmonary function	TioR 2.5 µg (n = 154), placebo (n = 155)	TioR 2.5 µg (n = 519), placebo (n = 523)	TioR 2.5 µg (n = 114), placebo (n = 57)	TioR 2.5 µg (n = 125), placebo (n = 138)	TioR 2.5 µg (n = 127), placebo (n = 135)

Table 1 Continued

	Study				
	GraziaTinA-asthma (N = 465)*	MezzoTinA-asthma (N = 2103)#	CadenTinA-asthma (N = 285)§	RubaTinA-asthma (N = 398)¶	PensieTinA-asthma (N = 392)
FEV ₁ at baseline (randomization), mean ± SD, actual [L]/% of predicted	2.4 ± 0.8/75.8 ± 12.3 2.4 ± 0.7/77.5 ± 12.0	2.3 ± 0.7 2.3 ± 0.7	NR	2.680 ± 0.629/82.3 ± 10.3 2.736 ± 0.686/83.0 ± 10.2	2.546 ± 0.593/79.8 ± 9.9 2.451 ± 0.597/79.4 ± 12.2
Prebronchodilation	3.6 ± 1.0/95.6 ± 15.4	3.4 ± 0.9	NR	3.461 ± 0.835/92.6 ± 12.8	3.280 ± 0.821/89.8 ± 13.7
FVC, mean ± SD, actual [L]/% of predicted	3.5 ± 0.9/96.7 ± 14.3	3.5 ± 1.0		3.570 ± 0.845/95.0 ± 12.7	3.280 ± 0.771/93.4 ± 14.6
FEV ₁ :FVC at baseline (randomization), mean ± SD, %	67.4 ± 10.9 68.5 ± 10.5	66.5 ± 10.8 Placebo: Trial 205.418 (n = 269), 66 ± 10.3; trial 205.419 (n = 254), 65.3 ± 10.4	NR	78.4 ± 11.3 76.9 ± 9.7	NR
PEF _{A.M.} response, mean ± SD, L/min	350.5 ± 112.7 353.7 ± 114.8	NR	NR	343.6 ± 93.9 334.6 ± 93.4	332.8 ± 97.3 322.7 ± 90.1
PEF _{P.M.} response, mean ± SD, L/min	364.1 ± 110.0 363.7 ± 116.7	NR	NR	360.7 ± 91.3 356.7 ± 96.1	348.1 ± 97.8 342.5 ± 87.0
ACQ-7 total score, mean ± SD	2.1 ± 0.4 2.1 ± 0.4	2.17 ± 0.49 2.18 ± 0.50	1.94 ± 0.43 1.90 ± 0.32	2.1 ± 0.5 2.0 ± 0.4	2.2 ± 0.4 2.2 ± 0.5

N = Number of patients randomized; TioR = tiotropium Respimat; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; LTRA = leukotriene receptor antagonist; q.d. = once daily; b.i.d. = twice daily; FEV₁ = forced expiratory volume in 1 second; SD = standard deviation; NR = not reported; FVC = forced vital capacity; PEF_{A.M.} = morning peak expiratory flow; PEF_{P.M.} = evening peak expiratory flow; ACQ-7 = seven-question Asthma Control Questionnaire; NCT = national clinical trial.

*NCT01316380/Trial 205.442 (from Ref. 55).
 #NCT01172808/Trial 205.418 and NCT01172821/Trial 205.419 (from Ref. 53).
 §NCT01340209/Trial 205.464 (from Ref. 54).
 ¶NCT01257230/Trial 205.444 (from Ref. 56).
 ||NCT01277523/Trial 205.456 (from Ref. 57).

**ICS for ≥ 4 wk before enrollment.
 ##ICS with or without LABA for ≥ 4 wk before enrollment.

and decreased in the morning, with associated changes in bronchodilation.⁵⁹ A diurnal variation in lung function has also been observed with a study of tiotropium Respimat, with FEV₁ AUC from 12 to 24 hours (FEV₁ AUC_{12–24hr}) responses of 243 mL and 256 mL for the tiotropium Respimat 5- μ g and 2.5- μ g groups compared with 192 mL and 182 mL, respectively, for FEV₁ AUC_{0–12hr} responses.⁴⁷ A phase II pharmacokinetic–pharmacodynamic study that compared tiotropium Respimat 5 μ g q.d. taken in the evening with twice-daily tiotropium Respimat 2.5 μ g taken in the morning and evening found no difference in the FEV₁ AUC_{0–12hr}.⁴⁷ There was also not any difference in the median time to observed maximum plasma concentration between the morning and evening dosing of tiotropium 2.5 μ g.

Adult Studies

In adults with mild, moderate, or severe symptomatic asthma, tiotropium Respimat 2.5 μ g q.d. showed significant improvements in lung function and asthma control, with good tolerability, as an add-on to at least ICS maintenance therapy.^{53–55} A Cochrane Review of studies of tiotropium Respimat 2.5 μ g q.d. or 5 μ g q.d. in adult patients with uncontrolled asthma, which assessed the efficacy and safety of a LAMA added to ICS versus the same dose of ICS alone, concluded that in adults who took ICS without a LABA, LAMA add-on therapy improved lung function and reduced the likelihood of exacerbations that required oral corticosteroid treatment.⁶⁰ The review also concluded that the benefits of LAMA combined with ICS for quality of life, asthma control, and hospital admissions were unknown. Based on *post hoc* analyses from the MezzoTinA-asthma⁵³ and GraziaTinA-asthma⁵⁵ studies, tiotropium Respimat 2.5 μ g q.d. was associated with improvements in asthma symptom control (assessed by the ACQ-7 responder rate; a ≥ 0.5 reduction in score) across severities of symptomatic asthma, independent of allergic status as defined by serum immunoglobulin E (IgE) levels.⁶¹ Efficacy results for the three phase III studies performed with the 2.5- μ g q.d. dose in adults^{53–55} are shown in Table 2. Because achieving between-group mean score improvements that reach the established minimal important differences for the Asthma Quality of Life Questionnaire (AQLQ) or the ACQ has been shown to be unachievable,⁶² ACQ responder rates are shown in Table 2; AQLQ results are not shown in the table because not all studies measured this parameter. In the two replicate phase III PrimoTinA-asthma studies of tiotropium Respimat 5 μ g q.d., there also were no differences in AQLQ scores between the placebo and tiotropium groups.⁶³

Kerstjens *et al.*⁵⁵ was the only phase III study of tiotropium that contained a salmeterol arm. The odds

of achieving asthma control as assessed by an ACQ-7 score were significantly increased with 2.5- μ g tiotropium, although improvement in the AQLQ score was not significant compared with placebo. The large placebo effect (*e.g.*, 58% responder rate for the ACQ-7 analysis), possibly because of improved adherence to ICS in a clinical trial, could account for a lack of more distinguishing results. The 5- μ g dose was not superior to the 2.5- μ g dose, although the trial was not powered to detect such differences. Tiotropium may be a useful alternative to LABAs in patients with moderate asthma if LABA adverse events (AEs) are a concern.

Paggiaro *et al.*⁵⁵ were the first to investigate tiotropium Respimat in patients with milder asthma. After 12 weeks, tiotropium Respimat 2.5 μ g was superior to placebo for the peak FEV_{1(0–3hr)} (adjusted mean difference from placebo, 159 mL; $p < 0.001$) and adjusted mean trough FEV₁ and FEV₁ AUC_{0–3hr} responses as well as morning and evening PEF.⁵⁵ Based on the results, the investigators indicated that 5 μ g and 2.5 μ g may be equally efficacious in mild-to-moderate asthma.⁵⁵ Longer-duration studies of greater power would be needed to assess differences in clinical outcomes, as would the ability to detect a reduction in the magnitude of rescue medication use in patients with mild-to-moderate asthma.

Ohta *et al.*⁵⁴ was the only non-multicountry study, performed solely in Japan in patients with moderate-to-severe asthma. Significant improvements compared with placebo in lung function and symptoms were only found with the 5- μ g but not the 2.5- μ g tiotropium dose; however, the sample size was small based on regulatory requirements, and the study was not formally powered for efficacy.⁵⁴

Effects of asthma on daily life are more relatable to patients than pulmonary function outcomes. However, in none of the studies were there any significant differences with placebo on the number of night-time awakenings, with the exception of week 26 and week 27 in favor of tiotropium Respimat 2.5 μ g in the RubaTinA-asthma study.⁵⁶ There also were no significant differences in the weekly mean number of puffs of rescue medication used in any of the studies. Only the MezzoTinA-asthma⁵³ and CadenTinA-asthma⁵⁴ studies reported results for improvement in activity limitations, none of which were significant compared with placebo.

Adolescent Studies

The Global Initiative for Asthma 2017 guidelines¹³ currently recommend tiotropium as add-on therapy at steps 4 and 5 for adolescents with a history of exacerbations, and caution against ICS plus LABAs. Existing treatments for achieving good asthma control in children and adolescents may be inadequate, in part be-

Table 2 Phase III adult and adolescent studies of once-daily TioR 2.5 µg: Efficacy results*

	Study				
	GraziaTinA-asthma#	MezzoTinA-asthma§	CadenTinA-asthma	RubaTinA-asthma	PensieTinA-asthma**
Groups, no. patients##					
TioR 2.5 µg	151	519	114	119	127
Placebo	154	523	57	137	135
Primary end point					
Peak FEV _{1(0-3hr)}} , mL	159 (36) (95% CI, 88-230)	223 (185-262) (TioR, <i>n</i> = 492)	NR	134 (95% CI, 34-234)	111 (95% CI, 2-220)
<i>p</i> Value	<0.001	<0.0001		<0.01	0.046
Non-primary end points					
Trough FEV ₁ , mL	110 (37) (95% CI, 38-182)	180 (138-221) (TioR, <i>n</i> = 492)	TioR (<i>n</i> = 107), PBO <i>n</i> = 49 12 (48), (95% CI, -82 to 106)	84 (56) (95% CI, -25 to 194)	TioR (<i>n</i> = 126), PBO (<i>n</i> = 132); 115 (0.059) (95% CI, 0-231)
<i>p</i> Value	0.003	<0.0001	0.797	0.131	0.051
FEV ₁ AUC _{(0-3hr)}} , mL	149 (34) (95% CI, 82-216)	NR	NR	130 (49) (95% CI, 34-225)	TioR (<i>n</i> = 126); PBO (<i>n</i> = 132); 113 (53) (95% CI, 9-217)
<i>p</i> Value	<0.001			0.008	0.034
Peak FEV _{1(0-3hr)}} , % predicted	4.2 (1.1) (95% CI, 2.0-6.4)	NR	NR	NR	NR
<i>p</i> Value	<0.001				
Trough FEV ₁ , % predicted	2.6 (1.2) (95% CI, 0.3-4.9)	NR	NR	NR	NR
<i>p</i> Value	0.02				
PEF _{A.M.} response, L/min	TioR (<i>n</i> = 150), PBO (<i>n</i> = 152); 26.3 (5.4) (95% CI, 15.7-36.9)	25.4 (19.0-31.7) (TioR, <i>n</i> = 485)	TioR (<i>n</i> = 103), PBO (<i>n</i> = 50) 8.646 (9.182) (95% CI, -9.388 to 26.680)	TioR (<i>n</i> = 105), PBO (<i>n</i> = 123); 14.038 (7.168) (95% CI, -0.025 to 28.102)	TioR (<i>n</i> = 124), PBO (<i>n</i> = 131); 10.49 (6.29) (95% CI, -1.86 to 22.83)
<i>p</i> Value	<0.001	<0.001	0.347	0.050	0.096
PEF _{P.M.} response, L/min	TioR (<i>n</i> = 149), PBO (<i>n</i> = 153); 22.4 (5.3) (95% CI, 12.0-32.8)	22.1 (15.8-28.4) (TioR, <i>n</i> = 483)	TioR (<i>n</i> = 105), PBO (<i>n</i> = 50) 11.458 (9.196) (95% CI, -6.601 to 29.517)	TioR (<i>n</i> = 104), PBO (<i>n</i> = 123); 15.274 (7.047) (95% CI, 1.448-29.101)	TioR (<i>n</i> = 124), PBO (<i>n</i> = 131); 11.06 (6.18) (95% CI, -1.07 to 23.19)
<i>p</i> Value	<0.001	<0.001	0.213	0.030	0.074
ACQ-7 total score	0.061 (0.067) (95% CI -0.071 to 0.194)	NR	NR	TioR (<i>n</i> = 120), PBO (<i>n</i> = 136); -0.160 (0.087) (95% CI, -0.330 to 0.010)	TioR (<i>n</i> = 126), PBO (<i>n</i> = 132) 0.058 (0.082) (95% CI -0.102 to 0.219)
<i>p</i> Value	0.36			0.065	0.476
ACQ responder rate	59.1% (<i>n</i> = 154)	64.5% (<i>n</i> = 515)	71.1%	79.2% (<i>n</i> = 125)	74.8% (<i>n</i> = 127)
	58.7% (<i>n</i> = 155)	57.7% (<i>n</i> = 518)	73.2%	68.1% (<i>n</i> = 138)	73.3% (<i>n</i> = 135)
OR (95% CI)	1.02 (0.63-1.64)	1.33 (1.03-1.72)		1.78 (0.98-3.27)	1.08 (0.60-1.95)
<i>p</i> Value	1.0000	0.0308		0.0577	0.8970
First severe exacerbation, HR (95% CI)§§	1.53 (0.43-5.44)	0.50 (0.30, -0.84)	NR	0.63 (0.21-1.87)	1.06 (0.07-16.95)
<i>p</i> Value	0.5071	0.0084		0.4023	0.9671

Table 2 Continued

	Study				
	GraziaTinA-asthma#	MezzoTinA-asthma§	CadenTinA-asthma	RubaTinA-asthma	PensieTinA-asthma**
First asthma worsening, HR (95% CI)§§	0.96 (0.53–1.75)	0.66 (0.52–0.84)	NR	1.04 (0.65–1.66)	0.75 (0.41–1.38)
p Value	0.8974	0.0007		0.8700	0.3567
TioR = Tiotropium Respimat; FEV₁ = forced expiratory volume in 1 second; FEV_{1(0–3hr)} = forced expiratory volume in 1 second within 3 hours of dosing; CI = confidence interval; NR = not reported; PBO = placebo; AUC = area under the curve, 0 to 3 hr; PEF_{AM} = morning peak expiratory flow; PEF_{PM} = evening peak expiratory flow; ACQ-7, seven-question Asthma Control Questionnaire; OR = odds ratio; NCT = national clinical trial. *Values are adjusted mean ± SE differences, unless otherwise specified, adjusted for treatment, center, visit, baseline, treatment-by-visit interaction, and baseline-by-visit interaction. #NCT01316380/Trial 205.442 (from Ref. 55). §NCT01172808/Trial 205.418 and NCT01172821/Trial 205.419 (from Ref. 53). NCT01340209/Trial 205.464 (from Ref. 54). NCT01257230/Trial 205.444 (from Ref. 56). **NCT01277523/Trial 205.456 (from Ref. 68). ###Numbers that differ from what is shown in these rows are shown in parentheses next to the end points. §§HR < 1 favors TioR.					

cause of a lack of response to treatment, improper inhaler technique, and poor adherence.⁶⁴ Moderate-to-high-dose ICS use is associated with hypothalamic-pituitary-adrenal axis suppression in children.⁶⁵ The ICS dose increases have been shown to be more common in children who are obese.⁶⁶ Obesity among black and Latino children and adolescents with asthma has also been linked with bronchodilator unresponsiveness.⁶⁷

Asthma affects both the small and large airways, with significant inflammation found in the small airways at all degrees of asthma severity.⁶⁸ Of note from the phase III adolescent studies of tiotropium Respimat 2.5 µg,^{56,57} the improvements are seen throughout the patients' lungs. Forced expiratory flow between 25% and 75% of the forced vital capacity (FEF_{25–75%}) may be more sensitive than FEV₁ to detect changes in small, peripheral airway function in pediatric patients with asthma.⁶⁹ In the RubaTinA-asthma⁵⁶ and PensieTinA-asthma⁵⁷ trials of adolescents aged 12–17 years, FEF_{25–75%} improvements were sustained over time and were more pronounced than improvements in peak and trough FEV₁ responses, which indicated that tiotropium Respimat 2.5 µg q.d. improves small-airway function in adolescents. Although FEF_{25–75%} was not a major focus in the studies with tiotropium Respimat, because small-airway dysfunction is associated with poorer asthma control,⁷⁰ the statistically significant FEF_{25–75%} improvements at most time points found in RubaTinA-asthma⁵⁶ and PensieTinA-asthma⁵⁷ underscore the value of tiotropium in asthma control. FEF_{25–75%} results at week 24 of the full analysis set of the RubaTinA-asthma study⁵⁶ are shown in Fig. 2.

Important from a patient standpoint were the statistically significant improvements seen in the weekly number of puffs of rescue medication used during the 24-hour period over the 48-week treatment period in the tiotropium Respimat 2.5-µg group versus placebo in the RubaTinA-asthma study.⁵⁶ No significant differences in the need for rescue medicine were seen in the PensieTinA-asthma study.⁵⁷ Two phase III studies in adolescents aged 12–17 years have been published;^{56,57} efficacy results for these studies are presented in Table 2. A limitation of both studies^{56,57} was the large placebo response observed, likely due to improved ICS adherence in a clinical trial environment. Tiotropium Respimat has also been tested in phase III studies in children aged 6–11 years⁷¹ and 1–5 years,⁷² but because this review focuses just on adult and adolescent studies, these pediatric studies are not presented. There is a lack of data that compare LAMAs with LABAs in adolescents with asthma.

SAFETY

Tiotropium Respimat 2.5 µg in all the phase III studies^{53–57} was safe and demonstrated a similar AE profile

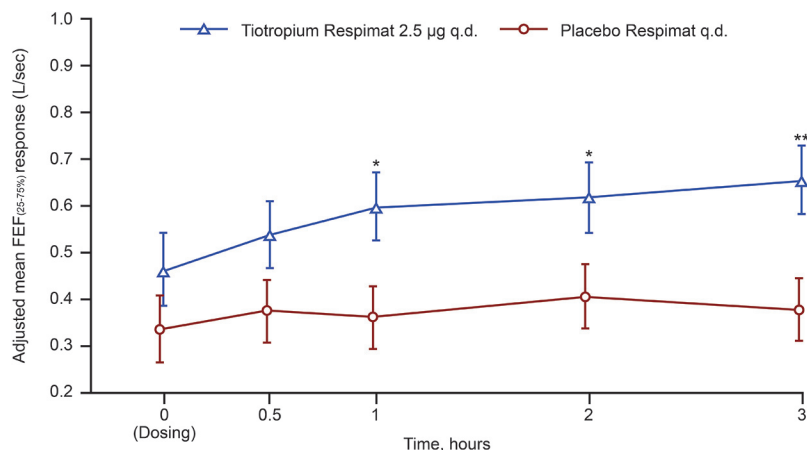


Figure 2. FEF_{25-75%} response at week 24 of the full analysis set of the RubaTinA-asthma study; common baseline mean $\pm$ standard deviation was 2.48 ± 0.97 L/s. * $p < 0.05$ versus placebo Respimat, ** $p < 0.01$ versus placebo Respimat (based on Ref. 56, Fig. 3). FEF_{25-75%} = Forced expiratory flow between 25% and 75% of the forced vital capacity; q.d. = once daily.

to placebo. Dry mouth is a common AE associated with anticholinergics.³⁶ A pooled safety analysis of 787 adult patients with a range of asthma severities on tiotropium Respimat 2.5 µg q.d. from the MezzoTinA-asthma, GraziaTinA-asthma, and CadenTinA-asthma trials showed that the most common treatment-related AEs were cough, dry mouth, headache, and thirst.⁷³ Treatment-related dry mouth occurred at similar rates with placebo: $n = 3$ (0.4%) for tiotropium Respimat 2.5 µg versus $n = 3$ (0.4%) for placebo; it was not classified as serious nor did it lead to treatment discontinuation. Constipation with placebo ($n = 4$ [0.5%]) occurred at similar rates with tiotropium Respimat 2.5 µg ($n = 1$ [0.1%]). No urinary retention was observed in either group. Cardiac disorder AEs were low and balanced equally between placebo and the 2.5-µg group; none of the serious cardiac disorder AEs were considered treatment related. Safety data from the phase III studies of tiotropium Respimat 2.5 µg q.d.⁵³⁻⁵⁷ are presented in Table 3.

PREDICTORS OF RESPONSE TO TIOTROPIUM

There is a need to identify phenotypic or endotypic subgroups that could maximally benefit from tiotropium treatment. Peters *et al.*⁷⁴ hypothesized that increased cholinergic tone, inferred from a lower resting heart rate, would predict a better response to tiotropium. In patients inadequately controlled on a low dose of ICS, morning treatment with 18 µg q.d. of tiotropium *via* the HandiHaler (Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) resulted in more asthma control days in patients with a ≤ 25 th percentile resting heart rate versus those with ≥ 75 th percentile resting heart rate.⁷⁴ However, because these results have not been replicated in patients with varying degrees of asthma severity who took tiotropium Respimat 2.5 µg q.d. and because accurate and sensitive measurement of cholinergic tone is difficult,⁷⁵ relevance to clinical practice remains to be determined.

Kerstjens *et al.*⁷⁶ performed subgroup analyses of data from the two phase III PrimoTinA-asthma studies of tiotropium Respimat 5 µg q.d. performed in adults with severe symptomatic asthma despite treatment with ICS plus LABA therapy; they found that reduction in the risk of exacerbations and asthma worsening, as well as improved asthma symptom control, occurred independently of a broad range of baseline characteristics, including reversibility, allergic status, serum IgE, and smoking status. Based on data from MezzoTinA-asthma,⁵³ once-daily tiotropium Respimat may have potential as an add-on treatment to at least ICS maintenance therapy in patients with symptomatic asthma, independent of type 2 T-helper cell phenotype, and thus avoid the need for phenotyping.⁷⁷

Tiotropium Respimat 2.5 µg q.d. was beneficial versus placebo, independent of a baseline eosinophil count or IgE level, and, with increasing eosinophil counts, the effect versus placebo became smaller; however, the number of patients in the analysis decreased, which led to wide 95% confidence intervals. An exploratory analysis of the PrimoTinA-asthma⁶³ and MezzoTinA-asthma⁵³ trials of adults with symptomatic asthma indicated that tiotropium's improvements in lung function, exacerbation risk, and symptom control are independent of type 2 T-helper cell status.⁷⁸ Because of the costs of biologic treatments it therefore may be better to prescribe tiotropium add-on therapy before biologic treatments.

SUMMARY AND FUTURE DIRECTIONS

The longest study of tiotropium Respimat 2.5 µg q.d. was 1 year;⁵⁷ long-term studies in a range of asthma severities are thus needed to potentially detect clinical improvements that mirror the improvements in the objective and subjective measures of asthma control already noted with the shorter-term studies. Analysis of these data will help to concretize tiotropium's place in the armamentarium of asthma

Table 3 Phase III adult and adolescent studies of once-daily TioR 2.5 µg: Safety results

Adverse Events by Preferred Term in >5% of the Patients	Study				
	GraziaTinA-asthma*	MezzoTinA-asthma#	CadenTinA-asthma§	RubaTinA-asthma¶	PensieTinA-asthma
No. patients					
TioR	154	519	114	125	127
Placebo	155	523	57	138	135
Asthma worsening, %	15.6	16	29.8	21.6	11.0
	12.9	22	38.6	23.2	10.4
Decreased PEF rate, %	5.8	9	7.9	7.2	7.1
	3.9	15	21.1	5.8	9.6
Blurred vision	NR	0	NR	NR	NR
		0			
Dry mouth, %	0	<2	0.9	0.8	NR
	0.6	<2	0	0	
Dry eyes	NR	NR	NR	NR	NR
Urinary retention	NR	NR	NR	NR	NR
Nasopharyngitis, %	1.3	9	44.7	10.4	4.7
	3.2	9	42.1	12.3	3.0
Upper respiratory tract infection, %	1.3	5	7.0	1.6	0.8
	4.5	8	3.5	4.3	2.2
Headache, %	0.6	4	6.1	5.6	0.8
	0	3	1.8	1.4	1.5
Constipation, %	NR	<1	0	0	NR
		<1	5.3	0.7	

TioR = Tiotropium Respimat; PEF = peak expiratory flow; NR = not reported.

*NCT01316380/Trial 205.442 (from Ref. 55).

#NCT01172808/Trial 205.418 and NCT01172821/Trial 205.419 (from Ref. 53).

§NCT01340209/Trial 205.464 (from Ref. 54).

¶NCT01257230/Trial 205.444 (from Ref. 56).

||NCT01277523/Trial 205.456 (from Ref. 57).

therapy. For now, because the majority of patients with asthma have cholinergic hyperresponsiveness, it seems that tiotropium can be therapeutic as an add-on to ICS and as an add-on to ICS plus LABA medications.

Real-world evidence from observational studies of the effectiveness of tiotropium Respimat in a U.S. population is lacking. Because of the strict eligibility requirements of randomized controlled asthma trials, the external validity of these trials is uncertain.^{79,80} Consequently, the generalizability of the results of the trials that were discussed was not established, and the safety and clinical response of tiotropium Respimat in any given patient seen by a clinician may differ. Nonetheless, although this product was only approved by the FDA in 2015, tiotropium has actually been used off label for asthma treatment since 2002 in the United Kingdom and has been shown to be associated with significant decreases in the incidence of exacerbations under real-world conditions.⁸¹ Further investigation can

help determine if a similar situation exists in the United States. Safety issues can also be explored in the long term and in real-world studies of asthma. These include the potential for steroid sparing and the highly acceptable AE profile. Furthermore, tiotropium has positive attributes that include once-daily dosing, administration by inhalation, and delivery in the easy-to-use and consistent-dosing Respimat device.

CONCLUSION

Tiotropium Respimat 2.5 µg demonstrated efficacy, in terms of both pulmonary function and clinical outcomes, and excellent safety in adults and adolescents across a range of asthma severities—mild, moderate, and severe—who had uncontrolled asthma despite ICS or ICS plus LABA use. Whether the improvements found in objective measures of lung function will translate into sustained clinical improvements in the context of real-world settings remains to be evaluated.

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