

Tiotropium Respimat Is Effective for the Treatment of Asthma at a Dose Lower Than That for Chronic Obstructive Pulmonary Disease

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Abstract

Anticholinergic drug products are not part of the current treatment paradigm for asthma, despite their widespread availability for chronic obstructive pulmonary disease (COPD) and interest in their use for asthma. Published study results, mostly of short duration and primarily with ipratropium and tiotropium, have revealed inconsistent efficacy results. Consequently, the role of inhaled anticholinergic drugs in the treatment of asthma has been unclear. This commentary discusses and comments on data from five clinical trials in adults that were submitted by Boehringer Ingelheim to the U.S. Food and Drug Administration to support approval of tiotropium delivered by the Respimat device (Spiriva Respimat) for the treatment of asthma. These trials provided substantial evidence

that supported the approval of Spiriva Respimat at a recommended dose of 2.5 µg once daily for asthma. Notably, in trials that evaluated two doses of tiotropium, 2.5 µg and 5 µg (the dose approved for COPD), pulmonary function measures for Spiriva Respimat 2.5 µg once daily were better overall than those obtained for the 5-µg once-daily dose, thus justifying selection of the lower dose for asthma. Spiriva Respimat represents the first new class of drug approved by the U.S. Food and Drug Administration for the treatment of asthma in more than a decade. The availability of Spiriva Respimat for asthma along with other novel therapies currently under development has the potential to impact asthma treatment guidelines.

Keywords: cholinergic antagonists; Spiriva; United States Food and Drug Administration

(Received in original form October 26, 2015; accepted in final form November 25, 2015)

The opinions expressed in this article are those of the authors and do not reflect the official opinions of the U.S. Food and Drug Administration. Boehringer Ingelheim had no role in the preparation of the manuscript

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Ann Am Thorac Soc Vol 13, No 2, pp 173–179, Feb 2016

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DOI: 10.1513/AnnalsATS.201510-712PS

Internet address: www.atsjournals.org

The U.S. Food and Drug Administration (FDA) recently approved tiotropium bromide inhalation spray (Spiriva Respimat) for the treatment of asthma in patients 12 years of age and older at a dose of 2.5 µg once daily. An important observation was that in the trials that evaluated two doses of tiotropium, pulmonary function measures for the Spiriva Respimat 2.5-µg once-daily dose were generally better than those obtained for the 5-µg once-daily dose approved for COPD; the 2.5-µg dose was also supported by lower exacerbation rates (1). Although tiotropium and other inhaled anticholinergic drugs, such as ipratropium, aclidinium, and umeclidinium, are approved for use in patients with COPD in

the United States, until this recent approval, no anticholinergic drugs were approved for use in patients with asthma in the United States. Regardless, use of inhaled anticholinergics to treat asthma has long been a topic of interest, and some supportive data have been reported in published literature (2–8). For example, recent studies with tiotropium in adults with asthma have shown similar treatment effects of tiotropium and long-acting β-agonists (LABAs) on lung function and exacerbations, suggesting tiotropium may have a benefit (3, 8).

Several drug classes are available to treat patients with persistent asthma, but anticholinergic drugs are not part of the current treatment paradigm (9, 10). Inhaled

corticosteroid (ICS) drugs are considered to be the most effective therapy for persistent asthma. When an adequate dose of ICS has not provided asthma control, a second drug, such as an LABA, is often added, preferably for a limited time period, with the intent of discontinuing the LABA once sustained asthma control is achieved. However, for patients who fail to achieve adequate asthma control with first- and second-line therapies, few therapeutic options remain. For this reason, initial studies of tiotropium as add-on therapy for difficult-to-control asthma generated continued interest in the subject, but the exact role of anticholinergics, and tiotropium in particular, in asthma remained unanswered (11–14).

Although systematic reviews have suggested a beneficial role for anticholinergics in asthma, questions regarding long-term safety and efficacy improvements in measures such as symptom improvement, exacerbations, and disease control had not been consistently demonstrated. This commentary discusses the clinical trial data reviewed by the FDA to support approval of the 2.5- μ g once-daily dose of Spiriva Respimat for the treatment of asthma as well as the potential impact of the findings on future asthma treatment paradigms.

Spiriva Respimat Asthma Program

To support their asthma program, Boehringer Ingelheim conducted five 4- to 8-week-long crossover design dose-ranging or dose-regimen studies that explored inhaled doses ranging from 1.25 μ g to 10 μ g once daily. Although results demonstrated numerical improvements in FEV₁ at all doses compared with placebo, the dose-response relationship was inconsistent. The results were, however, supportive of studying a 2.5- μ g dose and a 5- μ g dose in the asthma pivotal trials. The pivotal trials included five studies in adults and two studies in adolescents. Because asthma drug efficacy for children and adolescents typically relies on partial extrapolation from adults, the clinical trials in adults are the focus of this commentary.

Spiriva Respimat Pivotal Asthma Study Design and Conduct

An overview of the five clinical trials in adults that served as the primary basis of support for the approval of Spiriva Respimat 2.5 μ g once daily in patients with asthma is shown in Table 1. Results from four of these trials have been reported in the literature (12, 15). All studies were randomized, double-blind, double-dummy, placebo-controlled, and parallel-arm in design, with notable differences in disease severity, background treatment, study treatment arms, and duration of treatment. All studies required patients to be on background maintenance asthma controller drugs, particularly ICSs,

at doses appropriate for asthma severity; background LABA use was required for two of the trials (416 and 417).

In trials 442, 418, and 419, patients were required to demonstrate reversibility (FEV₁ increase by ≥ 200 ml and $\geq 12\%$) to a β -agonist at screening. By contrast, to be enrolled in trials 416 and 417, patients were required to not be fully reversible post bronchodilator; in such cases, a diagnosis of asthma must have been previously confirmed by either an increased hyperresponsiveness to bronchoprovocation challenge (methacholine, histamine, mannitol, or exercise), a positive trial of glucocorticoids or a β_2 -adrenergic drug, or diurnal peak expiratory flow (PEF) variability. Trials 418 and 419 included an active comparator salmeterol treatment arm. Trials 442, 418, and 419 evaluated Spiriva Respimat 2.5 μ g and 5 μ g once daily, and trials 416 and 417 evaluated a single dose of Spiriva Respimat at the dose approved to treat patients with COPD, 5 μ g once daily. Patients were allowed to use open-label albuterol/salbutamol metered-dose inhaler (100 μ g/actuation) for rescue therapy.

Efficacy Measures in Pivotal Trials

Spirometry was performed at regular intervals, with measurements performed 10 minutes before study drug administration (trough FEV₁), and at 30 minutes, 1 hour, 2 hours, and 3 hours after drug administration. In trial 442, the primary efficacy endpoint assessed at Week 12 was the peak FEV₁ measurement obtained within 3 hours post dose (peak FEV_{1 (0-3 h)}), with trough FEV₁ a key secondary endpoint. In the other four trials, co-primary efficacy endpoints were peak FEV_{1 (0-3 h)} and trough FEV₁ at Week 24.

Important secondary endpoints included asthma exacerbations and symptom control. An asthma exacerbation was defined as an episode requiring treatment with systemic corticosteroids for at least 3 days due to two or more consecutive days of either a progressive increase in one or more asthma symptoms or a decrease in peak flow measurements. Asthma symptoms were captured as shortness of breath, cough, wheezing, and/or chest tightness. A decline in PEF measurements was defined as a

decrease in a patient's best morning PEF of greater than or equal to 30% from the patient's mean morning screening PEF. This definition of an exacerbation is consistent with consensus guidelines (16).

Improvements in asthma control and health status were assessed by the Asthma Control Questionnaire (ACQ) and Standardized Asthma Quality of Life Questionnaire (AQLQ[S]) (17). The ACQ measures adequacy of and change in asthma control using a seven-item questionnaire including asthma symptoms (breathlessness, nocturnal waking due to asthma, asthma symptoms on waking, activity limitation, and wheeze), rescue bronchodilator use, and lung function (FEV₁). The AQLQ(S) is an asthma-specific health-related instrument that measures physical and emotional impact of disease and consists of 32 items within four domains: symptoms, activity limitation, emotional function, and environmental stimuli. Both questionnaires are commonly used and referred to in asthma treatment guidelines (9, 10, 17).

Safety Measures in Pivotal Trials

Safety assessments included evaluation of deaths, serious adverse events (as defined in Code of Federal Regulations Title 21 312.32), common adverse events, vital signs, physical examination, clinical laboratory measures, and 12-lead ECGs. Analyses of major cardiovascular events and anticholinergic-related side effects (drying of mucosal surfaces, urinary retention, ocular effects) were of special interest.

Study Subject Characteristics

The five clinical trials randomized 3,477 adult patients with persistent asthma of varying severity. An overview of the baseline patient characteristics is provided in Table 2. A key distinction among the studies is that trials 416 and 417 enrolled patients with severe asthma who were required to have a post-bronchodilator FEV₁/FVC ratio less than or equal to 0.7, signifying a degree of fixed airway obstruction that fulfilled spirometric criterion for COPD. As a result, the mean

Table 1. Pivotal phase 3 clinical trials with Spiriva Respimat (tiotropium bromide) inhalation spray in adults with asthma

Trial ID (Year)	Patient Characteristics	Trial Duration (wk)	Treatment Groups	N*	Primary Efficacy Variable
442 (2012)	Mild asthma, symptomatic on low-dose ICS FEV ₁ ≥ 60 to ≤90%, bronchodilator reversibility by ≥12% and ≥200 ml	12	Spiriva Respimat 2.5 µg once daily Spiriva Respimat 5 µg once daily Placebo	154 155 155	ΔFEV ₁ (0–3 h) baseline to Week 12
418 (2012)	Moderate asthma, symptomatic on medium-dose ICS FEV ₁ ≥ 60 to ≤90%, bronchodilator reversibility by ≥12% and ≥200 ml	24	Spiriva Respimat 2.5 µg once daily Spiriva Respimat 5 µg once daily Salmeterol 50 µg twice daily Placebo	262 264 275 269	ΔFEV ₁ (0–3 h) baseline to Week 24, ΔFEV ₁ trough baseline to Week 24
419 (2012)	Moderate asthma, symptomatic on medium-dose ICS FEV ₁ ≥ 60 to ≤90%, bronchodilator reversibility by ≥12% and ≥200 ml	24	Spiriva Respimat 2.5 µg once daily Spiriva Respimat 5 µg once daily Salmeterol 50 µg twice daily Placebo	257 253 266 254	ΔFEV ₁ (0–3 h) baseline to Week 24, ΔFEV ₁ trough baseline to Week 24
416 (2011)	Severe asthma, symptomatic on high-dose ICS and LABA FEV ₁ ≤ 80%, FEV ₁ /FVC ≤ 0.7	48	Spiriva Respimat 5 µg once daily Placebo	237 222	ΔFEV ₁ (0–3 h) baseline to Week 24, ΔFEV ₁ trough baseline to Week 24
417 (2011)	Severe asthma, symptomatic on high-dose ICS and LABA FEV ₁ ≤ 80%, FEV ₁ /FVC ≤ 0.7	48	Spiriva Respimat 5 µg once daily Placebo	219 234	ΔFEV ₁ (0–3 h) baseline to Week 24, ΔFEV ₁ trough baseline to Week 24

Definition of abbreviations: FEV₁ (0–3 h) = peak FEV₁ measurement obtained within 3 hours post dose; ICS = inhaled corticosteroid; LABA = long-acting β-agonist.

*Treated set = all randomized patients who received at least one dose of randomized trial medication.

post-bronchodilator FEV₁/FVC ratio was 0.60 in both trials. By comparison, other studies enrolled patients with a greater degree of bronchodilator reversibility (~500 ml) typical of asthma. The patients in trials 416 and 417 were also on average 10 years older than patients in other trials and had a more extensive smoking history, factors along with the requirement for fixed obstruction that are relevant to placing the efficacy findings in context (18, 19).

Spirometric Efficacy Results

Each trial showed that both the 2.5-µg and 5-µg doses of Spiriva Respimat were statistically significantly better than placebo for the primary endpoint of peak FEV₁ (0–3 h) and for the primary or key secondary endpoint of FEV₁ trough at Week 12 (trial 442) or Week 24 (trials 418, 419, 416, and 417). In trials that evaluated both Spiriva Respimat doses, the FEV₁ treatment response was generally numerically higher by 16 to 24% for the

2.5-µg dose than the 5-µg dose for peak FEV₁ (0–3 h) and trough FEV₁ (Table 3); however, no statistical comparison of the two doses was prespecified or performed. Full bronchodilator effect was not attained until after several weeks of treatment.

Asthma Exacerbation Efficacy Results

The secondary endpoint of asthma exacerbation supported the FEV₁ benefit observed across studies and the effectiveness of the lower 2.5-µg dose. Results for asthma exacerbations in the 24-week trials (418 and 419) are shown in Table 4. There was a numerical exacerbation benefit for Spiriva Respimat 2.5 µg and 5 µg compared with placebo, with the 2.5-µg dose demonstrating a nominal statistical significance in trial 418. The rate of exacerbations with the 2.5-µg dose was less than half that observed for the 5-µg dose in trial 418, whereas the rates were approximately the same in trial 419;

as with the primary endpoint, statistical comparison between the two Spiriva Respimat doses was not prespecified or performed.

ACQ and AQLQ Efficacy Results

The evaluation of ACQ and AQLQ by responder rate is of interest and clinical relevance because this captures the benefit at the individual patient level, which these instruments are designed to assess. For each questionnaire, a change of 0.5 units or greater has been identified as the minimally important difference and was used as the cutoff to define a “responder” (20, 21). In both of the 24-week trials (418 and 419), treatment with Spiriva Respimat resulted in more favorable AQLQ(S) and ACQ responder rates over placebo, with similar trends observed for the 2.5-µg and 5-µg doses, again supporting the effectiveness of the lower 2.5-µg dose in asthma (Table 5). Because the ACQ consists of two questions directly

Table 2. Selected baseline characteristics

	Trial ID				
	442	418	419	416	417
Demographics					
Mean age (range), yr	43 (18–74)	43 (18–75)	43 (18–75)	53 (18–75)	53 (18–75)
Mean asthma duration, yr	16	22	22	32	29
Smoking status, ex-smoker, %	18	14	19	22	26
Laboratory					
Absolute eosinophils, median, 10 ⁹ /L	0.33	0.36	0.35	0.35	0.38
Total IgE, median, µg/L	536	638	641	601	449
Pulmonary function tests, mean					
FEV ₁ , post-bronchodilator, L	2.851	2.670	2.687	1.763	1.812
Reversibility, pre-post Δ in FEV ₁ , L	0.556	0.488	0.477	0.215	0.218
Reversibility, %	25	23	22	15	15
FVC, post-bronchodilator, L	3.850	3.751	3.771	2.959	3.111
FEV ₁ /FVC ratio, post-bronchodilator	0.74	0.72	0.72	0.60	0.59

related to bronchodilator treatment effects (rescue medication use and FEV₁), the FDA also considered responder rates to the ACQ-5, which eliminated the two aforementioned components. The responder rates to the ACQ-5 were similar to the complete ACQ (ACQ-7), indicating that the results were not solely driven by the bronchodilatory activity of the Spiriva Respimat.

Safety Findings

Overall, systemic anticholinergic effects were infrequent. Although cardiovascular safety was less of a concern after the completion and review of the TIOSPIR (Tiotropium Safety and Performance in Respimat) trial in patients with COPD, the fact that very few major cardiovascular events (all nonfatal) occurred in the

asthma trials with no apparent imbalance between treatment groups was reassuring (22).

Discussion

The five clinical trials described herein demonstrated that Spiriva Respimat was statistically superior to placebo in terms of

Table 3. Lung function efficacy results from pivotal clinical trials in adults with varying asthma severity

Trial ID, Background Rx	Treatment	n	FEV ₁ (0–3 h) to Endpoint (L)			FEV ₁ Trough to Endpoint (L)		
			Δ from Baseline		Diff from Placebo	Δ from Baseline		Diff from Placebo
			Mean	95% CI		Mean	95% CI	
442, LD ICS	Spiriva Resp 5 µg once daily	152	0.262	0.128	0.06–0.20	0.137	0.122	0.05–0.19
	Spiriva Resp 2.5 µg once daily	151	0.293	0.159	0.09–0.23	0.125	0.110	0.04–0.18
	Placebo once daily	154	0.134			0.015		
418, MD ICS	Spiriva Resp 5 µg once daily	241	0.250	0.198	0.14–0.25	0.115	0.152	0.09–0.21
	Spiriva Resp 2.5 µg once daily	247	0.289	0.236	0.18–0.29	0.148	0.185	0.13–0.24
	Sal 50 µg twice daily	259	0.266	0.213	0.16–0.27	0.086	0.123	0.06–0.18
	Placebo once daily	250	0.053			–0.036		
419, MD ICS	Spiriva Resp 5 µg once daily	240	0.244	0.169	0.12–0.22	0.121	0.133	0.08–0.19
	Spiriva Resp 2.5 µg once daily	245	0.287	0.211	0.16–0.26	0.164	0.176	0.12–0.23
	Sal 50 µg twice daily	251	0.252	0.176	0.12–0.23	0.094	0.106	0.05–0.16
	Placebo once daily	242	0.075			–0.012		
416, HD ICS + LABA	Spiriva Resp 5 µg once daily	217	0.401	0.086	0.02–0.15	0.144	0.088	0.03–0.15
	Placebo once daily	211	0.315			0.056		
417, HD ICS + LABA	Spiriva Resp 5 µg once daily	205	0.401	0.154	0.09–0.22	0.155	0.111	0.05–0.17
	Placebo once daily	218	0.248			0.044		

Definition of abbreviations: CI = confidence interval; FEV₁ (0–3 h) = peak FEV₁ measurement obtained within 3 hours post dose; HD ICS = high-dose inhaled corticosteroid; LABA = long-acting β-adrenergic agonist; LD ICS = low-dose inhaled corticosteroid; MD ICS = medium-dose inhaled corticosteroid; n = number of patients in the full analysis set with measurements available at the primary endpoint; Rx = Treatment; Sal = salmeterol administered via hydrofluoroalkane metered-dose inhaler; Spiriva Resp = tiotropium administered via Respimat.

Endpoint at Week 24 in all trials except for trial 442 (Week 12). Mean adjusted for treatment, pooled center, week/visit, baseline, treatment by week/visit, and baseline by week/visit.

Table 4. Asthma exacerbation results at 24 weeks from trials 418 and 419 in patients with moderate asthma severity

	Trial 418			Trial 419		
	Spiriva Resp 2.5 µg (N = 259)	Spiriva Resp 5 µg (N = 261)	Placebo (N = 265)	Spiriva Resp 2.5 µg (N = 256)	Spiriva Resp 5 µg (N = 252)	Placebo (N = 253)
Rate of asthma exacerbations per patient year						
Mean rate of events	0.08	0.19	0.24	0.13	0.14	0.18
Comparison to placebo, rate ratio (95% CI)	0.3 (0.20–0.51)	0.8 (0.6–1.1)	—	0.7 (0.46–1.08)	0.8 (0.5–1.2)	—
Time to first asthma exacerbation						
Comparison to placebo, hazard ratio (95% CI)	0.4 (0.2–0.8)	0.7 (0.4–1.4)	—	0.7 (0.3–1.3)	0.7 (0.4–1.4)	—

Definition of abbreviations: CI = confidence interval; N = full analysis set, defined as any patient who received at least one dose of trial medication and had at least one efficacy measurement while on treatment; Spiriva Resp = tiotropium administered via RespiMat.

improving FEV₁, an accepted efficacy measure for asthma. An important observation in the clinical program was that in the three 12- to 24-week trials that evaluated two doses of tiotropium, results for the Spiriva RespiMat 2.5-µg once-daily dose were better overall than those obtained for the 5-µg dose for FEV₁ measures. Except for the trough FEV₁ secondary endpoint in trial 442, the peak FEV₁ (0–3 h) and trough FEV₁ responses were numerically higher by 16 to 24% for the 2.5-µg dose compared with the 5-µg dose in the three trials that studied both doses (Table 3). A similar trend of numerically superior efficacy for the 2.5-µg dose compared with the 5-µg dose was also seen for reductions in exacerbations, whereas both the 2.5-µg and 5-µg doses had similar improvements in ACQ and AQLQ(S) (Tables 4 and 5).

Any dose-related differences in efficacy cannot be related to device or formulation, because both doses are administered using the same RespiMat device and have the same formulation, except for different tiotropium concentrations. Although the mechanism for the apparent reverse dose response is not clear, one could question if the higher dose leads to increased drying effects on the airways that may have a slightly detrimental impact on bronchodilator effect. In this light, although the incidence of anticholinergic adverse reactions was low for both doses, the 0.9% incidence for the adverse reaction “dry mouth” in patients who received the 5-µg dose was higher than the 0.4% incidence observed for those who received the 2.5-µg dose.

The reverse dose response noted in asthma raises the possibility of whether or not a lower dose would be effective in COPD as well. However, unlike the asthma program described in this commentary, data

from extensive dose-ranging over long dosing periods are not available for patients with COPD because awareness of potential dose-related safety issues such as cardiovascular safety in patients with COPD arose in the post-marketing setting. Nevertheless, a reverse dose response with decreasing efficacy with a twofold higher dose is unique and to our knowledge has not been described in patients with either asthma or COPD with any drugs. Typically, with higher doses in asthma trials, an efficacy plateau is attained with no incremental benefit, but with increasing pharmacological or toxic adverse effects. For Spiriva RespiMat, it is difficult to determine whether the small dose-related increase in anticholinergic side effects such as dry mouth (which are described in labeling with use of inhaled tiotropium) observed with the 5-µg dose may have a long-term effect on bronchial secretions resulting in less

Table 5. Asthma Control Questionnaire and Standardized Asthma Quality of Life Questionnaire responder analysis at 24 weeks from trials 418 and 419 in patients with moderate asthma severity

	Trial 418			Trial 419		
	Spiriva Resp 2.5 µg (N = 259)	Spiriva Resp 5 µg (N = 261)	Placebo (N = 265)	Spiriva Resp 2.5 µg (N = 256)	Spiriva Resp 5 µg (N = 252)	Placebo (N = 253)
ACQ						
Responders, n (%)*	162 (63)	174 (67)	141 (53)	170 (66)	156 (62)	158 (63)
Comparison to placebo, odds ratio (95% CI)	1.5 (1.0–2.1)	1.8 (1.2–2.5)	—	1.2 (0.8–1.7)	1.0 (0.7–1.4)	—
AQLQ(S)						
Responders, n (%)*	149 (58)	149 (57)	133 (50)	147 (57)	145 (58)	140 (55)
Comparison to placebo, odds ratio (95% CI)	1.3 (0.9–1.9)	1.3 (0.9–1.9)	—	1.1 (0.8–1.6)	1.1 (0.8–1.6)	—

Definition of abbreviations: ACQ = Asthma Control Questionnaire; AQLQ(S) = Standardized Asthma Quality of Life Questionnaire; CI = confidence interval; N = full analysis set, defined as any patient who received at least one dose of trial medication and had at least one efficacy measurement while on treatment; Spiriva Resp = tiotropium administered via RespiMat.

*Individual responders defined as patients with ≥0.5-unit decrease in ACQ total score and/or ≥0.5-unit increase in AQLQ total score relative to baseline.

improvement in lung function and decreased benefit for other measures of asthma efficacy, such as exacerbations.

Although the publication of results from trials 416 and 417 generated interest because patients with severe, uncontrolled asthma remain the most difficult to treat and have few additional therapeutic options, these studies selectively enrolled patients with fixed obstruction to the same degree as nonsmokers with COPD and only evaluated a single 5- μ g dose of tiotropium, the dose approved to treat COPD. Given that these patients exhibited characteristics of asthma/COPD overlap syndrome (ACOS) more so than typical asthma, and that Spiriva Respimat 5 μ g is known to be effective in COPD, the results from these studies were not as relevant to the dose selection or approval of Spiriva Respimat for asthma. Nevertheless, the data from Spiriva Respimat 5 μ g are relevant to making treatment decisions for individual patients. Although asthma and COPD are distinct disease entities, there is increasing recognition of ACOS (23). Considering the available data with Spiriva Respimat for asthma and COPD, the appropriate dose for

asthma is 2.5 μ g once daily, and the appropriate dose for COPD is 5 μ g once daily. The appropriate dose for patients with ACOS could be either 2.5 μ g or 5 μ g once daily based on clinical judgment.

Although tiotropium is available for inhalation via both the HandiHaler and Respimat devices, it is important to note that data from this asthma development program is specific to Spiriva Respimat and should not be extrapolated to Spiriva HandiHaler. The two tiotropium products are unique, each possessing different drug delivery characteristics and different nominal daily doses, 18 μ g for Spiriva HandiHaler versus 5 μ g for Spiriva Respimat. Therefore, conclusions regarding the effectiveness of Spiriva HandiHaler in asthma cannot be made.

Conclusions

Although inhaled anticholinergics have been widely available for COPD for some time, Spiriva Respimat signifies the first anticholinergic to be approved for treatment of asthma and represents the first

new class of drug approved for asthma in more than a decade. In addition to the bronchodilator effects, Spiriva Respimat, when administered as add-on therapy to an inhaled corticosteroid, demonstrated beneficial trends on the clinically meaningful endpoint of asthma exacerbation and improvements in ACQ and AQLQ(S), which are important to providing context for the FEV₁ response. Absent some of the major safety concerns surrounding LABAs, such as asthma-related deaths and serious asthma exacerbations, clinicians may consider using Spiriva Respimat as an alternative long-acting bronchodilator. Given that the National Asthma Education and Prevention Program guidelines were last updated in 2007, the approval of Spiriva Respimat, along with the late-stage development of other novel asthma therapies such as IL-5 inhibitors, may trigger an update of the current guidelines to include these new classes of therapies. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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