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*APPLICATION NUMBER:*

**207070Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	September 14, 2015
<b>From</b>	Anthony G. Durmowicz, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 207070
<b>Supplement#</b>	(b) (4) Original 1 (b) (4)
<b>Applicant</b>	Boehringer-Ingelheim
<b>Date of Submission</b>	August 15, 2014
<b>PDUFA Goal Date</b>	September 15, 2015 (after 3-month time clock extension)
<b>Proprietary Name / Established (USAN) names</b>	Spiriva Respimat/tiotropium
<b>Dosage forms / Strength</b>	Inhalation Spray/1.25 mcg (b) (4) tiotropium per spray
<b>Proposed Indication(s)</b>	Treatment of patients with asthma
<b>Recommended:</b>	Approval of the 2.5 mcg ( 2 sprays of the 1.25 mcg tiotropium strength) once daily dose (b) (4)

## 1. Introduction

Boehringer Ingelheim (BI) submitted this 505(b)(1) NDA for Spiriva Respimat (tiotropium inhalation spray) as an add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on least inhaled corticosteroids on August 15, 2014.

Tiotropium bromide is a long-acting anticholinergic that is currently marketed to treat patients with COPD as Spiriva HandiHaler (tiotropium inhalation powder) (approved in January 2004), and as Spiriva Respimat (tiotropium inhalation spray) (approved in September 2014). The dose of Spiriva Respimat for COPD is 5 mcg (2 inhalations of 2.5 mcg per spray), (b) (4)

(b) (4) the PDUFA time clock was extended by 3 months to accommodate the review of the new (b) (4) information.

This review will provide an overview of the application, with a focus on the clinical data used to support approval of the Spiriva Respimat 2.5 mcg once daily dose for the treatment of patients 12 years and older with asthma.

## 2. Background

There are several different drug classes, both anti-inflammatory and bronchodilators, approved in the US for treatment of asthma including inhaled corticosteroids (ICSs), inhaled long-acting beta-adrenergic agents (LABAs), leukotriene modifying drugs, methylxanthines, and omalizumab. ICSs are considered to be the most effective long-term therapy for persistent asthma, and are commonly used as the first drug when a maintenance therapy is necessary. When an adequate dose of ICS has not provided asthma control, a second drug, such as a LABA is added to the treatment regimen.

Tiotropium and other anticholinergic drugs in inhalation formulations are approved for use in patients with COPD, but none of the anticholinergic drugs are approved for asthma in the US. However, the use of anticholinergic drug products in asthma has been of interest for a number of years. Inhaled anticholinergics have been studied by academic investigators with some positive findings published in the literature and are commonly used clinically, specifically ipratropium bromide, to treat pediatric patients with severe asthma exacerbations.

Tiotropium in COPD patients has anticholinergic adverse effects, such as dry mouth, constipation, urinary retention, etc. In addition, safety concerns of stroke and cardiovascular death have been raised in the past with the use of inhaled anticholinergic drug products in patients with COPD. While these concerns in COPD have been alleviated based on data from large studies with Spiriva HandiHaler and Spiriva Respimat in patients with COPD, as many of the adverse reactions related to anticholinergic drug products are dose-related, it is important to select an appropriate dose and dose regimen to limit any potential safety concerns.

The Division and BI had several meetings on Spiriva Respimat for its asthma program dating back to an End-of-Phase 2 meeting in June 2008, a Type C general advice meeting in August 2009, and a Pre-NDA meeting in December 2013. At the End-of-Phase 2 meeting, general expectations of the development program for an anticholinergic in asthma were discussed such as establishment of dose and dosing frequency, the need to study the broad spectrum of patients with different asthma severities, and the need to assess asthma exacerbations. At the Type C meeting the revised clinical development program was discussed, including deferral of studies in patients less than 12 year of age. At the Pre-NDA meeting the content and format of the NDA and some clinical topics, such as effect size with regard to bronchodilation, and dose and dosing regimen were discussed.

### 3. Chemistry, Manufacture, and Controls

This application included CMC data for testing (b) (4) of Spiriva Respimat Inhalation Spray for the treatment of asthma. (b) (4)

All CMC data (b) (4) of Spiriva Respimat were referenced to the NDA 21-936. In addition, BI provided an update of the changes introduced to the manufacturing and control specifications for Spiriva Respimat since the approval of NDA 21-936. Upon the review of all supporting data, the CMC recommendation for this application is for approval.

The drug product (b) (4) are aqueous based, sterile and contained in a sealed cartridge. The 1.25 mcg strength contains (b) (4) tiotropium bromide monohydrate (b) (4) formulation contains (b) (4) of benzalkonium chloride (b) (4) of edetate sodium (b) (4) and hydrochloric acid (b) (4). There is no propellant.

The Spiriva Respimat drug-device combination product consists of a plastic/aluminum cartridge containing sterile aqueous formulation of tiotropium bromide and a Respimat delivery device, which was developed and is manufactured by BI in Germany. It is supplied as a co-packaged set of one cartridge and one Respimat inhaler, with color coded cartridge label and device cap. Light blue (sky blue) color is used for the 1.25 mcg of tiotropium per spray strength (b) (4)

Prior to use, the patient or care provider places the cartridge containing the formulation into the Respimat inhaler. To actuate the product, the patient turns the bottom of the inhaler 180°, which will cause a small volume of the formulation to be metered into a chamber (b) (4)

The patient then presses a trigger, which releases the (b) (4) the formulation through a nozzle (b) (4)

The product needs to be primed after the cartridge is placed in the Respimat device. The Respimat cartridge is designed to deliver 60 actuations after priming. The Respimat device is relatively new to the United States market, with one BI product, Combivent Respimat (ipratropium bromide and albuterol) Inhalation Spray, approved

for marketing in October 2011 and another, Striverdi Respimat (olodaterol hydrochloride), approved for marketing on August 2014.

The proposed expiry period of 36 months is supported by 36 months of real time stability data submitted for 3 batches of the drug product. Manufacturing and testing facilities associated with the drug substance and drug product have an acceptable GMP recommendation from Office of Compliance. All DMFs associated with this application were also found to be acceptable.

#### **4. Nonclinical Pharmacology/Toxicology**

The general nonclinical pharmacology and toxicology considerations for tiotropium bromide were addressed in the Spiriva HandiHaler application (NDA 21-395). Those studies are adequate for this application because the nominal dose of Spiriva Respimat for asthma is 2.5 mcg, which is lower than the nominal dose of Spiriva HandiHaler for COPD (18 mcg), resulting in lower systemic exposure.

#### **5. Clinical Pharmacology/Biopharmaceutics**

The general clinical pharmacology and biopharmaceutics considerations for tiotropium bromide were originally addressed in the Spiriva HandiHaler application (NDA 21-395); BI subsequently submitted PK data adequate to link the Spiriva HandiHaler application to the Spiriva Respimat 5 mcg dose approved for COPD. The data showed that systemic exposure to tiotropium following use of the Spiriva Respimat 5 mcg dose was slightly lower compared to the Spiriva HandiHaler 18 mcg dose. The Spiriva Respimat : Spiriva HandiHaler ratio and 90% CI for AUC<sub>0-6h</sub> was 76 % (70.4, 82.0) and for C<sub>max</sub> was 80.7 % (73.5, 88.5). This data would also support the lower 2.5 mcg Spiriva Respimat dose for asthma. The Spiriva HandiHaler program included a thorough QT study with Spiriva HandiHaler doses of 18 mcg and 54 mcg. The results did not show significant QT prolongation.

#### **6. Clinical Microbiology**

The inhalation solution is sterile and contained in a sealed cartridge containing (b) (4) of benzalkonium chloride (b) (4)

#### **7. Clinical/Statistical- Efficacy**

Although BI had conducted clinical studies for asthma using the Spiriva HandiHaler earlier, the main clinical program for the Spiriva Respimat for asthma was conducted over the course of approximately seven years (2006-2013). The key clinical studies submitted to support the current application are shown in Table 1.

**Table 1. Relevant dose determining and confirmatory clinical studies for Spiriva Respimat asthma program**

Study (dates)	Design	Population	Background Medication	Treatment	N	Duration	Primary Endpoint(s)	Sites (countries)
<b>Dose ranging studies</b>								
341 (8/06-11/07)	R, DB, PC, XO	Adults, severe asthma	High-dose ICS + LABA	SR 5 QD SR10 QD Placebo	107	8 weeks	FEV <sub>1</sub> peak <sub>0-3h</sub>	16 sites (Denmark, Germany, Netherlands)
380 (11/10-1/12)	R, DB, PC, XO	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD SR 1.25 QD Placebo	149	4 weeks	FEV <sub>1</sub> peak <sub>0-3h</sub>	19 sites (Germany, Austria, Ukraine)
424 (6/10-4/11)	R, DB, PC, IXO	Adolescents, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD SR 1.25 QD Placebo	105	4 weeks	FEV <sub>1</sub> peak <sub>0-3h</sub>	19 sites (Germany, Latvia, Lithuania, Slovenia, USA)
<b>Dose regimen studies</b>								
420 (7/10-8/11)	R, DB, PC, XO	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 BID Placebo	94	4 weeks	FEV <sub>1</sub> AUC <sub>0-24h</sub>	15 sites (Czech Republic, Estonia, Latvia, Austria, Germany)
441 (10/12-6/13)	R, DB, XO	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 BID	98	4 weeks	FEV <sub>1</sub> AUC <sub>0-24h</sub>	22 sites (Austria, Germany, Hungary, Slovenia)
<b>Efficacy and safety studies in adults</b>								
416 (10/08-7/11)	R, DB, PC, PG	Adults, severe asthma	High-dose ICS + LABA	SR 5 QD Placebo	237 222	48 weeks	FEV <sub>1</sub> peak <sub>0-3h</sub> Trough FEV <sub>1</sub>  *Time to 1 <sup>st</sup> severe exacerbation	73 sites (N. America, Australia, EU, Japan, Russia, Ukraine Serbia, South Africa)
417 (11/08-7/11)	R, DB, PC, PG	Adults, severe asthma	High-dose ICS + LABA	SR 5 QD Placebo	219 234	48 weeks	FEV <sub>1</sub> peak <sub>0-3h</sub> Trough FEV <sub>1</sub>  *Time to 1 <sup>st</sup> severe exacerbation	75 sites (N. America, Australia, New Zealand, EU, Japan, Russia, Ukraine Serbia, South Africa)
418 (9/10-11/12)	R, DB, PC, PG	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD Sal 50 BID Placebo	265 262 275 269	24 weeks	FEV <sub>1</sub> peak <sub>0-3h</sub> Trough FEV <sub>1</sub>  *ACQ responder rate	114 sites (N. America, EU, Russia, Brazil, China, Guatemala, India, Japan, Peru)
419 (8/10-11/12)	R, DB, PC, PG	Adults, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD Sal 50 BID Placebo	254 258 266 259	24 weeks	FEV <sub>1</sub> peak <sub>0-3h</sub> Trough FEV <sub>1</sub>  *ACQ responder rate	124 sites (N. America, EU, Brazil, China,

								Columbia, India, Japan, Peru)
442 (4/11-4/12)	R, DB, PC, PG	Adults, mild asthma	Low-dose ICS	SR 5 QD SR 2.5 QD Placebo	155 154 156	12 weeks	FEV <sub>1</sub> peak <sub>0-3h</sub> **Trough FEV <sub>1</sub>	65 sites (EU, Argentina, Croatia, Estonia, Guatemala, India, Korea, Latvia)
<b>Efficacy and safety studies in adolescents</b>								
444 (1/11-12/13)	R, DB, PC, PG	Adolescents, moderate asthma	Medium-dose ICS	SR 5 QD SR 2.5 QD Placebo	135 125 138	48 weeks	FEV <sub>1</sub> peak <sub>0-3h</sub> **Trough FEV <sub>1</sub>	65 sites (N. America, EU, Latvia, Ukraine, Russia, Korea, Chile)
456 (1/11-10/13)	R, DB, PC, PG	Adolescents, severe asthma	High-dose ICS + 1 controller OR medium-dose ICS + 2 controllers	SR 5 QD SR 2.5 QD Placebo	130 127 135	12 weeks	FEV <sub>1</sub> peak <sub>0-3h</sub> **Trough FEV <sub>1</sub>	68 sites (N. America, EU, Argentina, Australia, Guatemala, Israel, Latvia, Philippines, South Africa, Ukraine)
Abbreviations: R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel group, XO=crossover, IXO=incomplete crossover, ICS=inhaled corticosteroid, LABA=long-acting beta-agonist, SR=Spiriva Respimat, Sal 50=Salmeterol HFA 50 µg, QD=once daily, BID=twice daily, PEF=peak expiratory flow rate N=randomized subjects *Primary endpoint for pooled analysis **Key secondary endpoint Source: Module 2.7.6, Synopses of Individual Studies								

### ***Dose Ranging/Dose Regimen***

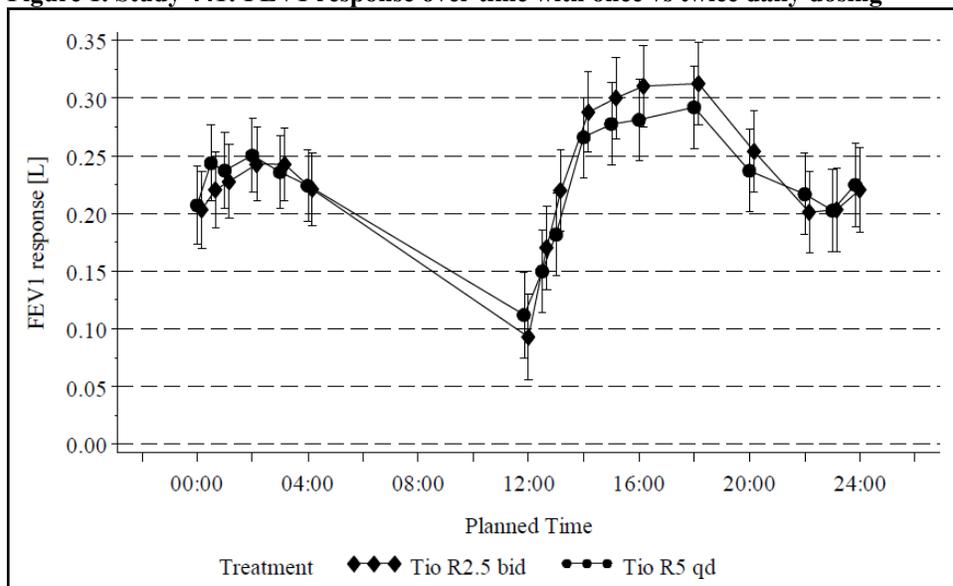
There were 3 dose ranging studies, 2 in adults and 1 in adolescents, and 2 dose-regimen studies in adults conducted for the asthma program that assessed doses ranging from 1.25 mcg to 10 mcg once daily (Table 1). The studies were randomized, double-blind, placebo-controlled, 4-week to 8-week, cross-over trials in 256 adult patients and 105 adolescent (age 12 to 17 years) patients. Patients enrolled in the dose-ranging studies had varying disease severity. For example, study 341 enrolled patients who had limited bronchodilator reversibility and relatively fixed airway obstruction with a post-bronchodilator FEV<sub>1</sub>/FVC of 0.58 suggesting the presence of persistent airflow limitation and, thus, of COPD. Other studies enrolled patients with moderate asthma and had bronchodilator reversibility typical of asthma.

Results demonstrated numerical improvements in FEV<sub>1</sub> at all doses compared to placebo; however, across the studies, the response was not dose-ordered. For adult patients in study 380, the difference in peak FEV<sub>1</sub> within 3 h post-dosing (peak FEV<sub>1</sub> 0-3h) from placebo for the Spiriva Respimat 1.25, 2.5, and 5 mcg doses was 0.138 L (95% CI 0.090, 0.186), 0.128 L (0.080, 0.176), and 0.188 L (0.140, 0.236), respectively. For adolescent patients in study 424, the difference in peak FEV<sub>1</sub>, 0-3h from placebo for the Spiriva Respimat 1.25, 2.5, and 5 mcg doses was 0.067 L (95% CI -0.005, 0.138), 0.057 L (-0.021, 0.135), and 0.113 L (0.036, 0.190), respectively. The 10 mcg dose offered no substantial benefit over lower doses and resulted in more systemic anticholinergic side effects (e.g., dry mouth).

It is notable, and somewhat atypical to note that some of the dose-ranging studies were conducted either at the same time or after the confirmatory studies which raises the question of their intent. Nevertheless, because of the inability to show dose separation between a 4-fold range of doses (2.5 mcg-10 mcg), most confirmatory studies included 2 doses of tiotropium 2.5 mcg and 5 mcg and, thus, served as dose ranging studies as well.

The two dose regimen studies in adults with asthma were randomized, double-blind, 4-week, cross-over trials comparing Spiriva Respimat 2.5 mcg twice-daily with 5 mcg once-daily. The results show that with the same nominal dose, the FEV1 response was comparable over a 24-hour period regardless of whether the dose was administered once-daily or twice-daily (Figure 1). Results for study 420 were similar.

**Figure 1. Study 441: FEV1 response over time with once vs twice daily dosing**



Source: CSR 205.441, Figure 11.4.1.2.1:1

In summary, results from the dose-ranging studies failed to demonstrate dose ordering between the range of 2.5 and 10 mcg doses, however, the 10 mcg dose had substantially more anticholinergic side effects and was eliminated. As a result, the 2.5 and 5 mcg doses were studied in confirmatory studies, both doses in adult studies 418, 419, and 442 and adolescent studies 444 and 456 but only the 5 mcg dose in adult studies 416 and 417. The dose regimen studies supported once daily dosing.

### ***Confirmatory studies in asthma***

BI conducted an extensive clinical program spanning approximately 7 years to support the safety and efficacy of orally inhaled tiotropium bromide via the Respimat device (Spiriva Respimat) once daily for the long-term maintenance treatment of asthma. Some characteristics of relevant confirmatory clinical studies that form the basis of this application are also shown in Table 1. The design and conduct of these studies are briefly described below, followed by review of the efficacy findings. Safety findings are discussed in Section 8.

### **Study 442**

Study 442 was a 12-week, double-blind, randomized, placebo-controlled, parallel-group study performed in patients 18 to 75 years of age with pre-bronchodilator FEV1 ranging from 60 to 90% of predicted values and at least 12% and 200 mL  $\beta$ -2 agonist reversibility. Patients were symptomatic, defined as a total score  $\geq 1.5$  on the Asthma Control Questionnaire (ACQ), while receiving stable therapy with low dose ICS (budesonide 200-400 mcg/day or equivalent). Stable regimens of low dose ICS, intranasal/topical corticosteroids, oral antihistamines, and mucolytics were allowed. Patients were randomized to receive in a blinded fashion one of the following inhaled medications: placebo; tiotropium Respimat 2.5 mcg qd, and tiotropium Respimat 5 mcg qd. All patients were allowed to use open-label albuterol/salbutamol HFA MDI (100 mcg/actuation) for rescue therapy. Spirometry was performed at weeks 0, 4, 8, and 12 with measurements performed 10 minutes prior to study drug administration (trough FEV1), and at 30 minutes, 1 hour, 2 hours, and 3 hours following drug administration (peak FEV1). The primary efficacy endpoint was the peak FEV1 measurement obtained within 3 hours post-dose with a key secondary endpoint of trough FEV1, both measured at week 12.

#### Studies 418 and 419

Studies 418 and 419 were replicate 24-week, double-blind, randomized, placebo-controlled, active comparator with double-dummy control, parallel-group studies performed in patients 18 to 75 years of age with pre-bronchodilator FEV1 ranging from 60 to 90% of predicted values and at least 12% and 200 mL  $\beta$ -2 agonist reversibility. Patients were symptomatic (ACQ total score  $\geq 1.5$ ) on therapy with medium dose ICS (budesonide 400-800 mcg/day or equivalent). Concomitant medications were similar to those allowed in trial 442 with the addition of medium dose ICS and leukotriene modifiers. Patients were randomized to receive in a blinded fashion one of the following inhaled medications: placebo; salmeterol 50 mcg bid; tiotropium Respimat 2.5 mcg qd; or tiotropium Respimat 5 mcg qd. All patients were allowed to use open-label albuterol/salbutamol HFA MDI (100 mcg/actuation) for rescue therapy. Spirometry was performed at weeks 0, 4, 8, 16, and 24 with measurements performed using the same procedures described for study 442 to obtain peak and trough FEV1. The co-primary efficacy endpoints were peak FEV1 within 3 hours post-dosing and trough FEV1 at week 24. Important secondary endpoints included asthma exacerbations and symptom control. For regulatory purposes, an asthma exacerbation was defined as an episode of progressive increase in one or more asthma symptoms (e.g., shortness of breath, cough, wheezing, and/or chest tightness) lasting for at least 2 consecutive days or a decrease of patient's best morning PEF of  $\geq 30\%$  from the patient's mean morning screening PEF for at least two consecutive days that required treatment with systemic (including oral) corticosteroids for at least 3 days. Asthma symptom improvement was assessed by the Standardized Asthma Quality of Life Questionnaire (AQLQ(S)) and Asthma Control Questionnaire (ACQ).

#### Studies 416 and 417

Studies 416 and 417 were replicate 48-week, double-blind, randomized, placebo-controlled, parallel-group studies in patients 18 to 75 years of age with post-bronchodilator FEV1  $\leq 80\%$  of predicted and fixed obstruction defined as post-bronchodilator FEV1/FVC  $\leq 0.70$ ;  $\beta$ -2 agonist reversibility was not required. As such, the patients met the spirometric criteria for COPD. Patients were symptomatic on high dose inhaled corticosteroid (budesonide  $\geq 800$  mcg/day or equivalent) and long-acting beta agonist. Stable regimens of high dose ICS, oral

corticosteroids ( $\leq 5$  mg qd or 10 mg QOD), LABA, cromolyn/nedocromil, antihistamines, methylxanthines, mucolytics, leukotriene modifiers, and omalizumab were allowed. Patients were randomized to receive in a blinded fashion one of the following inhaled medications every morning: placebo or tiotropium Respimat 5 mcg qd. All patients were allowed to use open-label albuterol/salbutamol HFA MDI (100 mcg/actuation) for rescue therapy. Spirometry was performed at weeks 0, 4, 8, 16, 24, 32, 40, and 48 using the procedures described above for obtaining trough and peak FEV<sub>1</sub>. The co-primary and important secondary efficacy endpoints were the same as for the 24-week trials.

#### Studies 444 and 456 (adolescent patients)

The design of studies 444 and 456 in adolescent patients was similar to that of studies 416 and 417 (i.e., randomized, double-blind, placebo-controlled, parallel-group) except for the inclusion of a lower 2.5 mcg dose of tiotropium and an adolescent patient population with moderate (study 444) or severe (study 456) persistent asthma that was responsive to beta-2 agonist bronchodilators. Study 456 was also shorter (12 weeks treatment period) compared to study 444 (48 week treatment period with primary endpoint assessed at 24 weeks). For both studies and similar to study 442, there was a single primary endpoint, peak FEV<sub>1</sub> response within 3 hours post-dosing. The key secondary endpoint was trough FEV<sub>1</sub> at 12 weeks which was a co-primary endpoint in most of the adult studies (studies 416, 417, 418, and 419).

#### *Patient Characteristics/Demographics*

Selected characteristics of the patients enrolled in the studies are shown in Table 2. It is notable that in studies 416 and 417 (patients with severe asthma) enrolled patients who had limited bronchodilator reversibility and relatively fixed airway obstruction with a post-bronchodilator FEV<sub>1</sub>/FVC of 0.58. The presence of a post-bronchodilator FEV<sub>1</sub>/FVC  $< 0.70$  confirms the presence of persistent airflow limitation and, as such, meets the spirometric definition of COPD. Other studies enrolled patients with moderate or severe (adolescent study 456) who had the large bronchodilator reversibility typical of asthma. Therefore, result of studies 416 and 417 are less relevant for assessing efficacy in asthma.

**Table 2. Selected baseline patient characteristics for patients in asthma confirmatory studies**

	Adult $\geq 18$ yrs			Adolescent, 12-17 yrs	
	442	418/419	416/417	456	444
<b>Demographics</b>					
Mean age in years	43	43	53	14	14
Mean asthma duration (years)	16	22	30	8	8
Smoking status, ex-smoker (%)	18	16	24	0	0
<b>Laboratory</b>					
Absolute eosinophils, median ( $10^9/L$ )	0.33	0.36	0.35	0.43	0.37
Total IgE, median (microgram/L)	520	640	516	1002	1065
<b>Pulmonary function tests (mean)</b>					
Reversibility, pre-post $\Delta$ in FEV <sub>1</sub> (L)	0.556	0.483	0.217	0.682	0.670
FEV <sub>1</sub> , pre-bronchodilator (L)	2.296	2.219	1.571	2.408	2.572
FEV <sub>1</sub> , post-bronchodilator (L)	2.851	2.679	1.788	3.090	3.241
FVC, post-bronchodilator (L)	3.850	3.760	2.035	3.752	3.924
FEV <sub>1</sub> /FVC ratio, post-bronchodilator	0.74	0.72	0.59	0.83	0.83
Source: BI Clinical Overview, Table 4.1.2.1.3:2; Table 4.1.2.1.3:3; Table 4.1.2.1.3:5; BI Summary of Clinical Efficacy Table 3.1.9.1.1:1; BI Clinical Trial Report 205.456, Table 11.2.5:1; BI Clinical Trial Report 205.444, Table 11.2.5.1:1					

#### *Efficacy Results - Bronchodilator Effect*

The results of efficacy findings for pulmonary function across a spectrum of asthma severity are shown in Table 3. It should be noted that for patients in studies 416 and 417 that had fixed airway obstruction (which met the spirometric definition of COPD) only the 5 mcg dose, the dose approved for COPD, was assessed.

Results of the studies in adult patients showed statistically significant higher FEV<sub>1</sub> response, both peak FEV<sub>1</sub> 0-3 hr (primary efficacy variable) and trough FEV<sub>1</sub> (primary or secondary efficacy variable), with 5 mcg and 2.5 mcg doses of tiotropium compared to placebo. Studies 442 (mild asthma), 418 and 419 (moderate asthma) showed numerically higher FEV<sub>1</sub> responses for the 2.5 mcg dose compared to the 5 mcg dose, for both peak FEV<sub>1</sub> 0-3 hr and trough FEV<sub>1</sub>, which were consistent across studies, except for the secondary endpoint of trough FEV<sub>1</sub> in study 442. Effect sizes for tiotropium were comparable to that of salmeterol (studies 418 and 419). Results of studies in adolescent patients 12 to 17 years of age showed results generally consistent with results of the adult studies. In the studies in adolescent patients, some of the differences between tiotropium and placebo did not reach statistical significance, however, the studies in adolescent patients were generally smaller in size than studies in adult patients.

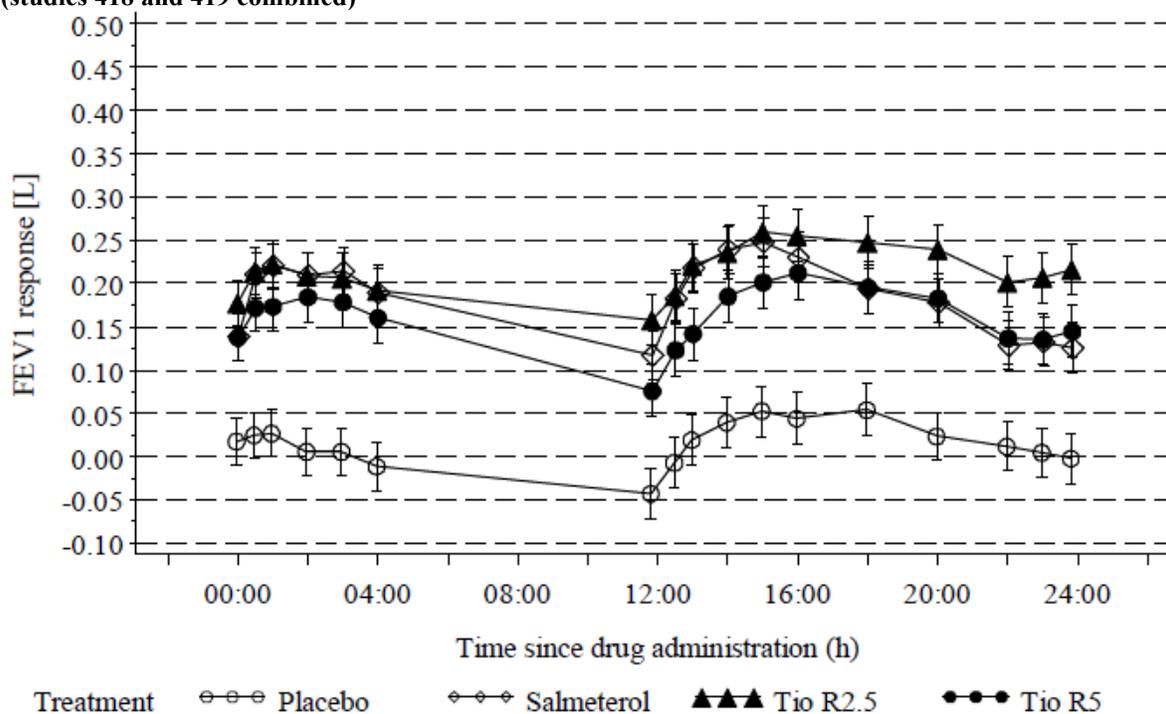
**Table 3. Summary of lung function efficacy results from confirmatory studies in patients with asthma of varying severity**

Study ID * (Asth. Severity) Background Rx	Treatment in mg †	n	FEV <sub>1</sub> 0-3 hr to endpoint, in L			FEV <sub>1</sub> trough to endpoint, in L		
			Δ from baseline	Diff from placebo		Δ from baseline	Diff from placebo	
				Mean	95% CI		Mean	95% CI
<b>Adult patients, age 18 years and older</b>								
<b>442</b> (mild) <i>LD ICS</i>	TioR 5 QD	152	0.262	0.128	0.06, 0.20	0.137	0.122	0.05, 0.19
	TioR 2.5 QD PM	151	0.293	0.159	0.9, 0.23	0.125	0.110	0.04, 0.18
	Placebo QD	154	0.134			0.015		
<b>418</b> (moderate) <i>MD ICS</i>	TioR 5 QD	241	0.250	0.198	0.14, 0.25	0.115	0.152	0.09, 0.21
	TioR 2.5 QD PM	247	0.289	0.236	0.18, 0.29	0.148	0.185	0.13, 0.24
	Sal 50 BID	259	0.266	0.213	0.16, 0.27	0.086	0.123	0.06, 0.18
	Placebo QD	250	0.053			-0.036		
<b>419</b> (moderate) <i>MD ICS</i>	TioR 5 QD	240	0.244	0.169	0.12, 0.22	0.121	0.133	0.08, 0.19
	TioR 2.5 QD PM	245	0.287	0.211	0.16, 0.26	0.164	0.176	0.12, 0.23
	Sal 50 BID	251	0.252	0.176	0.12, 0.23	0.094	0.106	0.05, 0.16
	Placebo QD	242	0.075			-0.012		
<b>416</b> (severe) <i>HD ICS + LABA</i>	TioR 5 QD AM	217	0.401	0.086	0.02, 0.15	0.144	0.088	0.03, 0.15
	Placebo QD AM	211	0.315			0.056		
<b>417</b> (severe) <i>HD ICS + LABA</i>	TioR 5 QD AM	205	0.401	0.154	0.09, 0.22	0.115	0.111	0.05, 0.17
	Placebo QD AM	218	0.248			0.044		
<b>Adolescent patients, age 12 to 17 years</b>								
<b>456</b> (severe) <i>MD-HD ICS</i> + ≥1 controller	TioR 5 QD	130	0.528	0.090	-0.02, 0.20	0.284	0.054	-0.06, 0.23
	TioR 2.5 QD PM	126	0.550	0.111	0.002, 0.22	0.345	0.115	-0.00, 0.23
	Placebo QD	132	0.438			0.230		
<b>444</b> (moderate) <i>MD ICS</i>	TioR 5 QD	131	0.547	0.174	0.08, 0.27	0.400	0.117	0.01, 0.22
	TioR 2.5 QD PM	120	0.507	0.134	0.03, 0.23	0.367	0.084	-0.03, 0.19
	Placebo QD	137	0.373			0.283		
* Study ID shown (top to bottom) as BI study number. HD ICS = high dose inhaled corticosteroid; MD ICA = mid dose inhaled corticosteroid								
† TioR = tiotropium administered via Respimat; Sal = salmeterol administered via HFA MDI								
Source: BI Clinical Overview Table 4.2.2.1:1; BI Summary of Clinical Efficacy Table 3.2.1.1.1:1, Table 3.2.2.1.1:1, Table 3.2.3.1.1 1, Table 3.2.3.2:1, Table 3.2.5.1.1:1, Table 3.2.5.2:1, Table 3.2.6.1.1:1, Table 3.2.6.2:1,								

FEV<sub>1</sub> 24-hour measurements in subset of patients in studies in adults, where tiotropium was administered either AM or PM (AM dosing in studies 416 and 417, PM dosing in studies 418,

419, 442), showed sustained bronchodilator effect over 24-hour dosing interval (Figure 1 shows the pooled results from studies 418 and 419). An effect on FEV<sub>1</sub>, when used as maintenance treatment in these confirmatory studies, was noted after the first dose, but the effect sizes were numerically small. Increase in FEV<sub>1</sub> 0-3 hr response difference to placebo after the first dose of tiotropium 5 mcg were 0.064 L for studies 416 and 417 combined, 0.140 L for studies 418 and 419 combined, 0.092 L for study 442, 0.080 for study 456, and 0.139 L for study 444 (source of numbers are from page 65 of BI Clinical Overview). Increase in FEV<sub>1</sub> 0-3 hr response difference to placebo after the first dose of tiotropium 2.5 mcg were 0.158 L for study 418, 0.138 L for study 419, 0.062 L for study 442, 0.096 L for study 456, and 0.107 L for study 444 (source: CSR 418/419 Table 15.2.1.1.3:3, CSR 442 Table 15.2.2.1.3:1, and CSR 444/456 Table 15.2.1.1:1).

**Figure 1. FEV<sub>1</sub> response (in L) over time (in hours) from timed spirometric measurements at week 24 (studies 418 and 419 combined)**



(Source: BI Clinical Summary of Efficacy Figure 3.2.2.4.3:1)

### Exacerbations

Asthma exacerbation results were supportive of the FEV<sub>1</sub> results. Pooled analysis of asthma exacerbations for the COPD-like patients enrolled in studies 416 and 417 showed statistically a significant difference between Spiriva Respimat 5 mcg (only dose studied) and placebo (Table 4). The exacerbation benefit as defined by steroid use did not translate to a reduction in asthma hospitalizations. The percentage of patients with at least 1 hospitalization for asthma for the Spiriva HandiHaler 5 mcg and placebo treatment groups were similar (3.4% vs 4.5% for study 416, and 3.7% vs 4.3% for study 417). Pooled analysis of asthma exacerbation for studies 418 and 419 (pooled analysis was not pre-specified) showed numerical exacerbation benefit for Spiriva Respimat 5 mcg dose and 2.5 mcg dose (two doses studied) compared to placebo, and the difference between the 2.5 mcg and placebo were nominally statistically significant (Table 5).

**Table 4. Asthma exacerbations studies 416 and 417 (severe asthma in adults) pooled, all patients (ITT)**

	<b>Tio R5 mcg (N=452)</b>	<b>Placebo (N=265)</b>
<b>Rate of exacerbations per patient year</b>		
Mean rate of events Tio R5 vs Placebo, Ratio (95% CI)	0.53	0.66 0.80 (0.64, 1.00)
<b>Time to first asthma exacerbation</b>		
Number of patients with at least 1 event, n (%) Tio R5 vs Placebo, Hazard ratio (95% CI)	122 (27%)	149 (32%) 0.79 (0.62, 1.00)
TioR = tiotropium administered via Respimat		
Source: BI Clinical Overview Table 4.2.2.2.4:1; BI Summary of Clinical Efficacy Table 3.2.1.2:1, Table 3.2.1.2:2		

**Table 5. Asthma exacerbations, study 418, study 419, and studies 418 and 419 (moderate asthma in adults) pooled (pooling was not pre-specified), all patients (ITT)**

<b>Study 418:</b>	<b>Tio R 5 (n=261)</b>	<b>Tio R 2.5 (n=259)</b>	<b>Placebo (n=265)</b>
<b>Time to first asthma exacerbation</b>			
Number of patients with at least 1 event (n) % TioR5 vs Placebo, Hazard ratio (95% CI) TioR2.5 vs Placebo, Hazard ratio (95% CI)	17 (6.5)	9 (3.5)	24 (9.1) 0.7 (0.4, 1.4) 0.4 (0.2, 0.8)
<b>Rate of asthma exacerbation</b>			
Mean rate of events TioR5 vs Placebo, Ratio (95% CI), p-value TioR2.5 vs Placebo, Ratio (95% CI), p-value	0.19	0.08	0.24 0.8 (0.6, 1.1) 0.3 (0.2, 0.5)
<b>Study 419:</b>	<b>Tio R 5 (n=252)</b>	<b>Tio R 2.5 (n=256)</b>	<b>Placebo (n=253)</b>
<b>Time to first asthma exacerbation</b>			
Number of patients with at least 1 event (n) % TioR5 vs Placebo, Hazard ratio (95% CI) TioR2.5 vs Placebo, Hazard ratio (95% CI)	14 (5.6)	13 (5.1)	19 (7.5) 0.7 (0.4, 1.4) 0.7 (0.3, 1.3)
<b>Rate of asthma exacerbation</b>			
Mean rate of events TioR5 vs Placebo, Ratio (95% CI), p-value TioR2.5 vs Placebo, Ratio (95% CI), p-value	0.14	0.13	0.18 0.8 (0.5, 1.2) 0.7 (0.5, 1.1)
<b>Study 418 and Study 419 pooled:</b>	<b>Tio R 5 (n=513)</b>	<b>Tio R 2.5 (n=515)</b>	<b>Placebo (n=518)</b>
<b>Time to first asthma exacerbation</b>			
Number of patients with at least 1 event (n) % TioR5 vs Placebo, Hazard ratio (95% CI) TioR2.5 vs Placebo, Hazard ratio (95% CI)	31 (6%)	22 (4%)	43 (8%) 0.7 (0.5, 1.1) 0.5 (0.3, 0.8)
<b>Rate of asthma exacerbation</b>			
Mean rate of events TioR5 vs Placebo, Ratio (95% CI), p-value TioR2.5 vs Placebo, Ratio (95% CI), p-value	0.16	0.10	0.21 0.8 (0.6, 1.0) 0.5 (0.4, 0.7)
TioR = tiotropium administered via Respimat			
Source: BI Summary of Clinical Efficacy Table 3.2.2.3:1, Table 3.2.2.3:2, CSR 205.418 and 205.419, Tables 15.2.1.4:16, p400-401 and 15.2.1.4:19, p406			

*Asthma Control/Quality of Life Assessments*

Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ)  
ACQ and AQLQ are commonly used measurements tools for asthma.

The ACQ is an asthma-specific questionnaire designed to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. There are a total of 7 items: 5 items assessing symptoms, 1 item assessing rescue bronchodilator use, and 1 item assessing FEV1%. Items 1 through 6 are self-administered while item 7 is completed by clinic staff. Each item is scored on a 7-point scale with 0=no impairment and 6=maximum impairment for symptoms and rescue medication use. Likewise, there are 7 categories for FEV1%. Scores range between 0 and 6 with lower scores indicating better asthma control. A change in score of 0.5 on the 7-point scale is the smallest different that is considered clinically important, which is the minimal important difference for ACQ. An ACQ score  $\geq 1.0$  indicates that asthma is not well controlled. Shortened versions using symptoms alone (ACQ-5) or symptoms plus rescue bronchodilator use (ACQ-6) have been also used. Although the measurement properties of the shorter versions are not quite as good as those of the complete ACQ-7, they have utility in certain settings in which one is trying to separate the benefit of a bronchodilator such as tiotropium from the effects on asthma symptoms.

The AQLQ is an asthma-specific health-related quality of life instrument that assesses both the physical and emotional impacts of disease. There are a total of 32 items in 4 domains covering a 2-week recall period. The domains include: symptoms (11 items), activity limitation (12 items), emotional function (5 items), and environmental exposure (4 items). Scores range from 1 to 7 with higher scores indicating better quality of life. The standardized version, which BI used in the studies, incorporates five generic activities under the domain “activity limitation” rather than five individualized activities. The minimally important difference (MID) has also been determined to be a difference in score of 0.5.

ACQ was assessed in studies 416, 417, 418, 419, 442, 444, and 456. AQLQ was assessed in Studies 416, 417, 418, 419, and 444. ACQ was to be completed prior to other questionnaire and before the pre-dose spirometry was conducted. Results are shown in Table 6. There was a general favorable trend in response with tiotropium treatment for ACQ and AQLQ, with more consistent favorable response in studies 418 and 419 and with similar trends in response for the 2.5 mcg and 5 mcg doses. As such, the ACQ and AQLQ data are supportive of the 2.5 mcg dose as the appropriate dose for asthma.

**Table 6. ACQ and AQLQ responder analyses at  $\geq 0.5$  threshold**

Trial	N	AQLQ(S)				ACQ-7				ACQ-5			
		Baseline	$\Delta$ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value	Baseline	$\Delta$ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value	Baseline	$\Delta$ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value
<b>Study 416</b>													
Spiriva Respimat 5 mcg	237	4.60	0.50	0.04 (-0.10, 0.19) 0.56	41% 0.89 (0.61, 1.31) 1.00	2.67	-0.69	-0.12 (-0.25, 0.01) 0.07	55% 1.07 (0.73, 1.57) 0.79	2.44	-0.75	-0.11 (-0.27, 0.04) 0.16	58% 1.08 (0.73, 1.59) 0.75
Placebo	222	4.58	0.44	--	44%	2.66	-0.56	--	54%	2.42	-0.61	--	56%
<b>Study 417</b>													
Spiriva Respimat 5 mcg	216	4.63	0.46	0.17 (0.02, 0.33) 0.03	44% 1.41 (0.95, 2.10) 0.09	2.60	-0.60	-0.20 (-0.33, -0.06) <0.01	52% 1.61 (1.09, 2.38) 0.02	2.36	-0.64	-0.19 (-0.34, -0.03) 0.02	56% 1.68 (1.14, 2.48) 0.01
Placebo	232	4.65	0.28	--	36%	2.58	-0.38	--	41%	2.33	-0.42	--	43%
<b>Study 418</b>													
Spiriva Respimat 5 mcg	242	4.78	0.71	0.07 (-0.06, 0.20) 0.30	57% 1.32 (0.92, 1.89) 0.13	2.23	-0.77	-0.13 (-0.25, -0.02) 0.03	67% 1.76 (1.22, 2.45) <0.01	2.22	-0.90	-0.09 (-0.22, 0.05) 0.22	68% 1.34 (0.92, 1.95) 0.13
Spiriva Respimat 2.5 mcg	246	4.87	0.67	0.07 (-0.06, 0.20) 0.27	58% 1.34 (0.94, 1.93) 0.11	2.18	-0.82	-0.2 (-0.32, -0.09) <0.01	63% 1.47 (1.02, 2.11) 0.04	2.19	-0.93	-0.13 (-0.27, 0.002) 0.05	65% 1.18 (0.81, 1.70) 0.42
Placebo	247	4.83	0.60	--	50%	2.15	-0.60	--	53%	2.16	-0.78	--	62%
<b>Study 419</b>													
Spiriva Respimat 5 mcg	240	4.76	0.74	-0.003 (-0.14, 0.13) 0.96	58% 1.09 (0.76, 1.58) 0.68	2.19	-0.80	-0.08 (-0.20, 0.03) 0.16	62% 0.98 (0.67, 1.42) 1.00	2.22	-0.93	-0.01 (-0.15, 0.12) 0.86	67% 1.01 (0.69, 1.49) 1.00
Spiriva Respimat 2.5 mcg	245	4.77	0.75	0.01 (-0.12, 0.14) 0.87	57% 1.09 (0.76, 1.57) 0.70	2.17	-0.83	-0.13 (-0.24, -0.01) 0.03	66% 1.19 (0.81, 1.74) 0.40	2.20	-0.94	-0.03 (-0.17, 0.11) 0.67	67% 1.02 (0.69, 1.50) 1.00
Placebo	240	4.88	0.70	--	55%	2.21	-0.72	--	63%	2.24	-0.93	--	67%
<b>Study 442</b>													
Spiriva Respimat 5 mcg	152	--	--	--	--	2.08	-0.70	0.01 (-0.12, 0.15) 0.83	58% 0.97 (0.60, 1.57) 1.00	2.18	-0.82	0.09 (-0.06, 0.24) 0.24	59% 0.85 (0.52, 1.38) 1.00
Spiriva	149	--	--	--	--	2.12	-0.68	0.06	59%	2.16	-0.79	0.13	62%

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Trial	N	AQLQ(S)				ACQ-7				ACQ-5			
		Baseline	Δ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value	Baseline	Δ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value	Baseline	Δ from baseline	Mean difference from placebo (95% CI) p-value	Responders* Odds ratio (95% CI) p-value
Respimat 2.5 mcg								(-0.07, 0.19) 0.36	1.02 (0.63, 1.64) 1.00			(-0.02, 0.29) 0.09	0.96 (0.59, 1.57) 1.00
Placebo	154	--	--	--	--	2.10	-0.70	--	59%	2.15	-0.88	--	63%
<b>Study 444</b>													
Spiriva Respimat 5 mcg	132	5.34	0.61	0.08 (-0.09, 0.25) 0.35	53% 1.60 (0.96, 2.66) 0.07	2.02	-0.94	-0.10 (-0.26, 0.07) 0.25	75% 1.47 (0.84, 2.58) 0.19	2.15	-1.00	-0.06 (-0.26, 0.14) 0.55	74% 1.20 (0.68, 2.11) 0.60
Spiriva Respimat 2.5 mcg	120	5.43	0.63	0.14 (-0.04, 0.31) 0.12	47% (1.27 (0.76, 2.13) 0.40	2.05	-1.03	-0.16 (-0.33, 0.01) 0.07	76% 1.58 (0.89, 2.83) 0.13	2.19	-1.11	-0.15 (-0.35, 0.05) 0.14	74% 1.23 (0.69, 2.20) 0.55
Placebo	136	5.35	0.54	--	41%	2.02	-0.86	--	67%	2.15	-0.95	--	70%
<b>Study 456</b>													
Spiriva Respimat 5 mcg	--	--	--	--	--	2.10	-0.97	0.04 (-0.12, 0.20) 0.66	73% 0.99 (0.55, 1.76) 1.00	2.18	-1.05	0.06 (-0.13, 0.25) 0.53	74% 1.03 (0.57, 1.84) 1.00
Spiriva Respimat 2.5 mcg	--	--	--	--	--	2.15	-0.96	0.06 (-0.10, 0.22) 0.48	75% 1.08 (0.60, 1.95) 0.90	2.24	-1.02	0.12 (-0.07, 0.31) 0.20	71% 0.88 (0.50, 1.57) 1.00
Placebo	--	--	--	--	--	2.15	-1.03	--	73%	2.24	-1.15	--	73%
<p>*Responders defined as patients with an improvement of 0.5 units.            Results are from the 24 week timepoint except for trials 442 and 456 which were at 12 weeks.            AQLQ not assessed in 12-week trials 442 and 456.            Source: BI response to IR submitted August 4, 2015</p>													

### ***Summary of Efficacy***

The efficacy data reviewed above shows consistent bronchodilator efficacy for Spiriva Respimat 5 mcg and 2.5 mcg across studies as a maintenance treatment in patients who were symptomatic on ICS. In general, the bronchodilator benefit numerically trended in favor of Spiriva Respimat across various subgroups, such as gender, age, and ethnicity but the confidence intervals were large because of small numbers, particularly for those of African ethnicity. Although both doses of Spiriva Respimat showed efficacy, there was a consistent numerical trend of a higher response of 2.5 mcg over 5 mcg for lung function parameters in asthma studies in adult patients (Table 3). The exacerbation data also showed numerical benefit for both 5 mcg and 2.5 mcg doses (Table 4 and Table 5). The pivotal efficacy data provides robust dose ranging information that suggests 2.5 mcg as the appropriate dose for patients with asthma. Dose ranging information from the pivotal studies is more informative than the dedicated dose-ranging studies because the pivotal studies were longer in duration and larger in size. The reason for apparent reduction of FEV1 with 5 mcg compared to 2.5 mcg is not clear. One hypothesis is that increased drying of airways with a higher dose of an anticholinergic may negatively impact the bronchodilator effect.

## **8. Safety**

The safety assessment of Spiriva Respimat for asthma, based on studies shown in Table 1, is adequate to support its use in that population. In addition, extensive supportive safety information on tiotropium is available from the COPD programs of Spiriva HandiHaler and Spiriva Respimat. Safety assessments generally included recording of deaths, serious adverse events (SAEs), common adverse events (AEs) vital signs, physical examinations, clinical laboratory measures, and ECGs, analysis of major cardiovascular events (MACE), and events related to anticholinergic, such drying effects of mucosal surface, urinary retention, and ocular effects.

### ***Deaths, SAEs, dropouts and discontinuations***

There were no deaths reported during the tiotropium asthma clinical development program.

Serious adverse events occurred with low frequencies in the clinical studies and were comparable between the tiotropium treatment arms and placebo treatment arms. Asthma was the only SAE reported for more than 1% of patients, which is not unusual in asthma clinical studies. Other SAEs (reported in 1 or 2 patients) were pneumonia, cholelithiasis, hypertension, and anaphylaxis. Anaphylaxis was reported in 2 patient on tiotropium compared to none in placebo treatment arms.

Dropouts and discontinuations were also low in the clinical studies. Events leading to dropouts and discontinuations were typical of events seen in asthma development programs and did not reveal any new safety signals. The most common cause of discontinuation was asthma, which was rare (less than 1%), and occurred with numerically lower frequency in tiotropium treatment arms compared to the placebo treatment arm.

### ***Common adverse events***

Common adverse events seen in the program were typical of asthma studies, and other studies using tiotropium. Events that were seen with higher frequency in tiotropium compared to

placebo treatment groups included dry mouth, cough, pharyngitis, dysphonia, sinusitis, skin rash, dry throat, and thirst. Tiotropium related AEs, such as dry mouth, dry throat, thirst, and dysphonia occurred more in tiotropium treatment arms but the overall frequency was low at about 0.3 to 0.7%. Of note is that the frequency of dry mouth was 0.9% with the 5 mcg dose compared to 0.4% with the 2.5 mcg dose, suggestive of dose-related drying effect with tiotropium. One could postulate that this drying effect could partly explain the dose-related decrease of FEV1 seen across clinical studies (Table 3).

### ***Laboratory findings and ECGs***

No clinically meaningful effects on hematologic or chemistry or ECG parameters were noted in the clinical program. There were some reports of abnormal laboratory parameters and ECG changes, but they were of no specific concern for patients with asthma who took tiotropium.

### ***MACE events***

There were no fatal MACE events in the clinical program. Non-fatal MACE events reported were stroke and myocardial infarction occurring both in tiotropium and placebo treatment arms. Frequency of these events were low (0.1% or 0.2%), and time adjusted rates were not different between tiotropium and placebo.

### ***Adolescent Patients Aged 12 to 17 years***

The safety data for the adolescent population are based on one 1-year and one 12-week double-blind, placebo-controlled trials in a total of 789 adolescent asthma patients on background treatment of at least ICS or ICS plus one or more controller. Overall, the adverse event profile for adolescent patients with asthma was similar to that observed in adult patients with asthma.

## **9. Advisory Committee Meeting**

An advisory committee meeting was not held for this NDA as after initial review there were no issues regarding review efficacy and/or safety that rose to the level that would require discussion at an advisory committee.

## **10. Pediatrics**

Unlike COPD, which does not exist in children, the asthma indication triggered PREA. For the required pediatric program BI agreed to complete three studies in adolescents 12 to 17 years of age (Studies 424, 444, and 456), which were submitted with this application. The other pediatric studies in patients ages 6-11 years have been deferred because the current application for adults and adolescents is ready for approval. The PREA required studies in pediatric patients 6-11 years of age will consist of the following 2 studies:

- A 12-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6-11 years of age with asthma evaluating at least two doses of tiotropium
- A 48-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6 to 11 years of age with asthma again evaluating at least two doses of tiotropium

As with other inhalation drug products, a partial waiver will be issued for children below 6 years of age because studies are impossible or highly impractical. The pediatric study plan was discussed and agreed to at the May 27, 2015, PeRC meeting.

## 11. Other Relevant Regulatory Issues

- Financial Disclosure: BI has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry: Financial Disclosure by Clinical Investigators. For the asthma program, 9 of the 721 principal investigators and three sub-investigators reported receipt of significant payments from BI; however, these payments did not raise questions about the integrity of the data as enrollment at any particular site was relatively small compared to the overall number of patients, and no single site or investigator appears to be driving the results.
- DSI audits information: DSI audited three sites that participated in 4 clinical studies (studies 416, 418, 419, and 444) either because of high enrollment or large treatment effect. Minor irregularities were identified but none that would impact data integrity. All studies were conducted in accordance with accepted ethical standards.

## 12. Labeling

- Proprietary Name: The name Spiriva Respimat has previously been judged as acceptable by DMEPA during review of the COPD NDA application.
- Physician Labeling: The label was reviewed by various disciplines within DPARP, the Office of Medical Policy Programs (OMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were made, most notably to include information regarding the new asthma indication. Labeling differences and discussion with BI have been focused on the need to present information in the label for both the 2.5 mcg and 5 mcg once daily doses of Spiriva Respimat that were studied in the Phase 3 trials. At this time the final labeling has been agreed upon.
- Carton and Immediate Container Label: These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is for approval of Spiriva Respimat (tiotropium inhalation spray) at a dose of 2.5 mcg once daily (2 sprays of the 1.25 mcg/spray drug product) for the long-term maintenance treatment of asthma in patients 12 years of age and older. (b) (4)

[Redacted]

[Redacted] (b) (4)

- Risk Benefit Assessment

The overall risk-benefit assessment supports approval of Spiriva Respimat at a dose of 2.5 mcg once daily for the long-term maintenance treatment of asthma in patients 12 years of age and older. The submitted safety data do not show any new or unique safety signals and drug-related anticholinergic side effects for the lower 2.5 mcg once daily dose appear no greater than observed for placebo. From an efficacy standpoint, the clinical program showed that tiotropium at a 2.5 mcg once-daily dose provided a statistically significant bronchodilator effect which, across most studies that included both the 2.5 and 5 mcg doses, was nominally greater than the treatment effect for the higher 5 mcg once daily dose. Efficacy was supported by reduced asthma exacerbations and improvement in quality of life measures [(ACQ and AQLQ(S)], again, equal to or greater than for the 5 mcg dose.

1. Recommendation for Post-marketing Risk Management Activities

No additional post-marketing risk management activities are recommended beyond standard pharmacovigilance methods.

2. Recommendation for other Post-marketing Study Commitments

There are two PREA-related post-marketing study commitments for the Spiriva Respimat asthma program in order to study Spiriva Respimat in pediatric patients 6-11 years of age. Studies in pediatric patients < 6 years of age have been waived because the necessary studies are impossible or highly impracticable as children < 6 years of age are usually incapable of consistently coordinating drug delivery with the device. This is because of the drug device delivery. The agreed to post-marketing studies are:

- Conduct a 12-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6-11 years of age with asthma. The study should evaluate at least two doses of tiotropium and include approximately 125 patients per treatment arm.

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- Conduct a 48-week, randomized, double-blind, parallel-group, placebo-controlled, efficacy and safety study of tiotropium delivered via the Respimat device in children 6 to 11 years of age with asthma. The study should evaluate at least two doses of tiotropium and include approximately 125 patients per treatment arm.

Study Completion: January 2016

Final Report Submission: October 2016

### 3. Recommended Comments to Applicant

No additional comments are recommended to be conveyed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANTHONY G DURMOWICZ  
09/14/2015