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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	September 11, 2015
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	20-7070, Original 1 (b) (4)
Applicant Name:	Boehringer Ingelheim
Date of Submission:	August 15, 2014
PDUFA Goal Date:	September 15, 2015 after 3 month extension (original due date was June 15, 2015)
Proprietary Name:	Spiriva Respimat
Established Name:	Tiotropium bromide
Dosage form:	Inhalation Spray
Strength:	Tiotropium bromide 1.56 mcg (1.25 mcg of tiotropium) (b) (4) per spray
Proposed Indications:	Asthma
Action:	Approval for 2.5 mcg dose (2 sprays of 1.25 mcg tiotropium); (b) (4)

1. Introduction

Boehringer Ingelheim (BI) Pharmaceuticals submitted this 505(b)(1) new drug application for use of Spiriva Respimat as an add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on least inhaled corticosteroids. Tiotropium bromide is a long-acting anticholinergic that is currently approved as Spiriva HandiHaler (tiotropium bromide inhalation powder) (approved in January 2004), and as Spiriva Respimat (tiotropium bromide inhalation spray) (approved in September 2014), both for use in patients with COPD. (b) (4) During review of this application, the Division determined that for asthma the appropriate dose for Spiriva Respimat would be 2.5 mcg (b) (4). Later during the review cycle, BI amended the application with new labeling and CMC information with the 2.5 mcg dose (2 inhalations of 1.25 mcg per spray), which necessitates seeking marketing approval of a new 1.25 mcg strength Spiriva Respimat product. Because of the new labeling and CMC information the PDUFA time clock of the application was extended by 3 months. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for use in patients with persistent asthma. These include 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 often added, preferably for a limited time period with the intent of discontinuing the LABA once asthma control is achieved and maintained. Since some patients with persistent asthma use both an ICS and a LABA, these two drugs have been combined together in the same formulation and in the same device and marketed as inhaled combination products. There are four such combination products in the market in the United States for patients with asthma. These are Advair Diskus and Advair HFA Inhalation Aerosol (both are a combination of fluticasone propionate and salmeterol xinafoate), Symbicort (a combination of budesonide and formoterol fumarate), and Dulera (a combination of mometasone furoate and formoterol fumarate), and Breo Ellipta (combination of fluticasone furoate and vilanterol).

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 United States. 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. [1, 2] In the mid-1990s, BI conducted four studies with Spiriva HandiHaler in asthma with negative results. [3] The caveats in interpreting those studies were that they were small in size and limited duration (less than 100 patients per study and shorter than 1 month), and the design did not reflect the current asthma treatment guidelines, specifically all patients were not on ICS. Those studies have been now supplanted with studies submitted with this NDA with Spiriva Respimat that provides results from studies that are large in size, longer in duration, and all patients required to have persistent asthma and to be on ICS maintenance treatment and other maintenance treatment appropriate for the disease severity.

Tiotropium in COPD patients has anticholinergic adverse effects, such as dry mouth, constipation, urinary retention, etc. Safety concerns of stroke and cardiovascular death have been raised in the past with the use of these drug products in patients with COPD, and thus have been the subject of previous FDA advisory committee meetings. [4] These

[1] Qureshi F, Pestian J, Davis P, et al. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. N Eng J Med 1998; 339:1030-5.
[2] Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults for uncontrolled asthma. N Eng J Med 2010; 363:1715-26.
[3] FDA Advisory Committee Meeting of September 6, 2002: There is a statement in the FDA Briefing Book (Clinical Briefing Document, pages 11-12) that says: "This drug was developed under IND 46-687, which was originally submitted to the Agency on November 30, 1994. The indication listed at the time or the original submission was "bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis, emphysema, and moderate to severe (b) (4) asthma." In an Annual Report dated April 29, 1999, the Applicant notified the Agency that clinical development in patients with asthma had been discontinued. In a submission dated October 8, 2001, the Applicant stated that studies of the product in adults with asthma have failed to demonstrate effectiveness."
[4] FDA Early Communication about Ongoing Safety Review of Tiotropium. http://www.fda.gov/cder/drug/early_comm/tiotropium.htm

concerns in COPD have been alleviated based on data from large studies with Spiriva HandiHaler and Spiriva Respimat in patients with COPD. [5, 6] Nevertheless, it is important to select an appropriate dose and dose regimen of any anticholinergic in COPD and asthma to limit high systemic exposure and potential safety concerns.

Regulatory interaction between the Agency and BI:

The Division and BI had typical milestone meetings on Spiriva Respimat for its asthma program. BI discussed the development of Spiriva Respimat with the Division at an End-of-Phase 2 meeting in June 2008, Type C general advice meeting in August 2009, and 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 – establishment of dose and dosing frequency, study of broad spectrum of persistent asthma severity, and evaluation of asthma exacerbation. 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, Manufacturing, and Controls

The drug substance tiotropium bromide is a well-known compound that is approved as the active component of an inhalation powder, Spiriva HandiHaler, as mentioned above. For Spiriva Respimat, tiotropium bromide is formulated as a sterile aqueous solution with standard excipients benzalkonium chloride (b) (4), edetate disodium (b) (4), water for injection, and hydrochloric acid (b) (4). The formulation is contained in a cartridge, which will be supplied separately from the Respimat Inhaler. Spiriva Respimat Inhalation Spray is supplied in a carton containing one Spiriva Respimat cartridge and one Spiriva Respimat Inhaler. Prior to first use, the cartridge containing the formulation is placed into the Respimat Inhaler. To actuate the product, the bottom of the inhaler is turned 180°, which causes a small volume of the formulation to be metered into a chamber (b) (4). Pressing a trigger on the Respimat inhaler releases (b) (4) the formulation through a nozzle (b) (4) The product needs to be primed after the cartridge is placed in the Respimat inhaler. The Respimat cartridge is designed to deliver 60 actuations after priming. Each actuation provides 1.25 mcg of tiotropium. The product has a dose indicator that is visible on the clear base. After the 60 actuations (30 doses) are delivered, a locking mechanism is engaged and no more drug can be dispensed. The Spiriva Inhalation Spray should be discarded after the locking mechanism is engaged or 3 months after first use, whichever comes first.

[5] Taskin DP, Celli B, Senn S. et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Eng J Med 2008; 359:1543-54.

[6] Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Eng J Med 2013: 369:1491-501.

BI submitted adequate stability data to support an expiry of 36 months for the drug product that consists of the Respimat device and the unassembled cartridge containing the formulation (stored separately), and an in-use period of 3 months after the cartridge is assembled with the Respimat Inhaler.

The steps needed to use the product and the internal mechanisms of the product are rather complex. During review of another Respimat product that contained tiotropium 2.5 mcg (Spiriva Respimat), a consultation with CDRH was obtained. The CDRH review did not raise any concerns with the manufacturing and quality of the product, but raised concerns on performance testing with regards to human factors. BI has previously performed adequate human factor and patient handling studies with a Respimat product. These assessments did not suggest any problems with patient handling, performance, and robustness of the Respimat product. The only issue identified was that some older patients or patients with hand joint problems may need assistance with initial assembly of the cartridge and the Respimat inhaler.

The drug substance and drug product including the Respimat device are manufactured at a BI facility in Ingelheim am Rhein, Germany. 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.

Two strengths for Spiriva Respimat (1.25 mcg or 2.5 mcg tiotropium per actuation) were used in the pivotal asthma clinical studies. The CMC data pertaining to the 1.25 mcg (b) (4) tiotropium (b) (4) adequate to support the comparability of the in vitro dose performance (b) (4). For COPD, Spiriva Respimat 2.5 mcg strength product is approved. BI (b) (4) propose marketing of Spiriva Respimat 1.25 strength product for asthma. BI subsequently provided CMC documentation for the Spiriva Respimat 1.25 mcg strength product to the NDA, which was reviewed and determined to be adequate for approval.

4. Nonclinical Pharmacology and 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 is (b) (4) which is lower than the nominal dose (18 mcg) of Spiriva HandiHaler, and the exposure to tiotropium in humans from these two products are similar. With the Spiriva Respimat NDA for COPD, BI submitted results from a cardiac safety study that showed that tiotropium did not affect the conductance of hERG-mediated potassium channels in HEK 923 cells or the action potential in isolated guinea pig papillary muscles. There are no outstanding nonclinical pharmacology and toxicity issues with this application, particularly given that the dose for Spiriva Respimat for asthma is half of that for COPD.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutics consideration for tiotropium bromide were addressed in the Spiriva HandiHaler application (NDA 21-395). Since Spiriva Respimat is an inhalation product intended for local action in the lung, the pharmacokinetic profile is primarily useful for determination of systemic safety. With the Spiriva Respimat COPD application, BI submitted adequate data to link the Spiriva HandiHaler and Spiriva Respimat for the approved COPD doses. Results from a large PK study (Study 458) 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 ratio (Spiriva Respimat : Spiriva HandiHaler and 90% CI for AUC 0-6 was 76 % (70.4, 82.0) and for Cmax was 80.7 % (73.5, 88.5). The shape of the plasma concentration time profile of Spiriva Respimat and Spiriva HandiHaler were similar. There are no outstanding clinical pharmacology and biopharmaceutics issues with this application.

BI submitted results from a thorough QT study in the Spiriva HandiHaler application (NDA 21-395), and the study results were cross-referenced to Spiriva Respimat application. The study used a positive control, placebo, and Spiriva HandiHaler at doses of 18 mcg and 54 mcg. The study subjects were treated with Spiriva HandiHaler for 12 days. The results showed no significant QT prolongation with Spiriva HandiHaler. Relative to placebo, the maximum mean change from baseline in the QTc interval was 3.2 msec and 0.8 msec for 18 mcg and 54 mcg doses, respectively.

6. Clinical Microbiology

The inhalation solution is manufactured using (b) (4) Once the cartridge is inserted into the Respimat Inhaler the formulation is open to contamination from the environment. The formulation contains benzalkonium chloride (b) (4).

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1 and Table 2. Table 1 shows the relevant dose-ranging and dose-regimen studies, and Table 2 shows the relevant confirmatory clinical studies.

In a typical clinical program, dose-ranging studies would be conducted first, and pivotal confirmatory studies would be conducted later taking into consideration information gained from the dose-ranging studies. The BI development program for Spiriva Respimat for asthma did not follow this typical and usual sequence. The timing of the conduct of the dose-ranging and dose-regimen studies (Table 1, first column) compared to the timing of the conduct of the confirmatory studies (Table 2, first column) suggest that some of the dose-ranging studies were conducted concurrent with or after the

conduct of the confirmatory studies. For example the confirmatory studies 416 and 417 were conducted before conduct of all dose-ranging and dose-regimen studies, except study 341. A strength of this development program was that the confirmatory studies were dose ranging as well and are perhaps more informative because of their larger sample size and longer duration compared to the dose-ranging studies (Table 1, Table 2). All confirmatory studies, except study 416 and 417 included two doses of tiotropium, 2.5 mcg and 5 mcg, which is reasonable for an asthma clinical program.

Table 1. Relevant dose-ranging and dose-regimen studies for Spiriva Respimat in patients with asthma

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variables ¶**	**Regions and Countries //**
Adult patients, age 18 years and older					
341 [08/06 to 11/07]	- 18 to 75 yr - Severe Asthma, symptomatic on high-dose ICS and LABA - XO - 3x8 weeks	TioR 10 mcg QD PM TioR 5 mcg QD PM Placebo QD PM	107	1^o: ΔFEV_1 0-3 hr response 2^o: ΔFEV_1 trough response	Denmark, Germany, Netherlands
380 [11/10 to 01/12]	- 18 to 75 yr - Moderate Asthma, symptomatic on mid-dose ICS - XO - 4x4 weeks	TioR 5 mcg QD PM TioR 2.5 mcg QD PM TioR 1.25 mcg QD PM Placebo QD PM	149	1^o: ΔFEV_1 0-3 hr response 2^o: ΔFEV_1 trough response	Austria, Germany, Ukraine
420 [07/10 to 08/11]	- ≥18 yr - Moderate Asthma, symptomatic on mid-dose ICS - XO - 3x4 weeks	TioR 5 mcg QD PM TioR 2.5 mcg BID Placebo QD PM	94	1^o: ΔFEV_1 0-24 hr response 2^o: ΔFEV_1 trough response	Austria, Czech Repblc, Estonia, Germany, Latvia
441 [10/12 to 06/13]	- ≥18 yr - Moderate Asthma, symptomatic on mid-dose ICS - XO - 2x4 weeks	TioR 5 mcg QD PM TioR 2.5 mcg BID	98	1^o: ΔFEV_1 0-24 hr response 2^o: ΔFEV_1 trough response	Austria, Germany, Hungary, Slovenia
Adolescent patients, age 12 to 17 years					
424 [06/10 to 04/11]	- 12 to 17 yr - Moderate Asthma, symptomatic on mid-dose ICS - IXO - 3x4 weeks	TioR 5 mcg QD PM TioR 2.5 mcg QD PM TioR 1.25 mcg QD PM Placebo	105	1^o: ΔFEV_1 0-3 hr response 2^o: ΔFEV_1 trough response	Germany, Latvia, Lithuania, Slovenia, USA

* Study ID shown (top to bottom) as BI study number, and [month/year study started to month/year study completed]
† XO=crossover, IXO=incomplete crossover
‡ TioR = tiotropium administered via Respimat
§ Intent to treat (treated set)
¶ Primary efficacy variables for all studies were analyzed using Analysis of Covariance (ANCOVA) model in the ITT population (patients who had baseline data and at least 1 on-treatment value after 4 weeks). A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM) was used for primary analysis.
// Europe and USA as listed under each study

Table 2. Relevant confirmatory clinical studies with Spiriva Respimat in patients with asthma

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
Adult patients, age 18 years and older					
Pivotal bronchodilator (or lung function) efficacy and safety studies					
442 [04/11 to 04/12]	- 18 to 74 yr - Mild Asthma, symptomatic on low-dose ICS, FEV_1 ≥60 to ≤90%, bronchodilator reversibility by ≥12% and ≥200 mL - Parallel arm, DB - 12 weeks	TioR 5 mcg QD PM TioR 2.5 mcg QD PM Placebo	155 154 155	1^o: ΔFEV_1 0-3 hr baseline to week 12 2^o: ΔFEV_1 trough baseline to week 24	12 countries: USA and Canada (00%) Europe (73%) Others (27%)
418 [09/10 to 11/12]	- 18 to 75 yr - Moderate Asthma, symptomatic on mid-dose ICS, FEV_1 ≥60 to ≤90%, bronchodilator reversibility by ≥12% and ≥200 mL - Parallel arm, DB - 24 weeks	TioR 5 mcg QD PM TioR 2.5 mcg QD PM Sal 50 mcg BID Placebo	264 262 275 269	1^o: ΔFEV_1 0-3 hr baseline to week 24 1^o: ΔFEV_1 trough baseline to week 24 2^o: Time to first severe asthma exacerbation	11 countries: USA and Canada (22%) Europe (24%) Others (54%)
419 [08/10 to 11/12]	- 18 to 75 yr - Moderate Asthma, symptomatic on mid-dose ICS, FEV_1 ≥60 to ≤90%, bronchodilator reversibility by ≥12% and ≥200 mL - Parallel arm, DB - 24 weeks	TioR 5 mcg QD PM TioR 2.5 mcg QD PM Sal 50 mcg BID Placebo	253 257 266 254	1^o: ΔFEV_1 0-3 hr baseline to week 24 1^o: ΔFEV_1 trough baseline to week 24 2^o: Time to first severe asthma exacerbation	11 countries: USA and Canada (23%) Europe (27%) Others (50%)
416 [10/08 to 07/11]	- 18 to 75 yr - Severe Asthma, symptomatic on high-dose ICS and LABA, FEV_1 ≤80%, $_{FEV1}$/FVC ≤0.7 - Parallel arm, DB - 48 weeks	TioR 5 mcg QD AM Placebo	237 222	1^o: ΔFEV_1 0-3 hr baseline to week 24 1^o: ΔFEV_1 trough baseline to week 24 Other 1^o: Time to first severe asthma exacerbation pooled with study 117	15 countries: USA and Canada (17%) Europe (62%) Others (21%)
417 [10/08 to 07/11]	- 18 to 75 yr - Severe Asthma, symptomatic on high-dose ICS and LABA, FEV_1 ≤80%, FEV_1/FVC ≤0.7 - Parallel arm, DB - 48 weeks	TioR 5 mcg QD AM Placebo	219 234	1^o: ΔFEV_1 0-3 hr baseline to week 24 1^o: ΔFEV_1 trough baseline to week 24 Other 1^o: Time to first severe asthma exacerbation pooled with study 116	15 countries: USA and Canada (21%) Europe (57%) Others (21%)
Adolescent patients, age 12 to 17 years					
Pivotal bronchodilator (or lung function) efficacy and safety study					
456 [01/11 to 10/13]	- 12 to 17 yr - Severe Asthma, symptomatic on mid-high dose ICS and ≥1 controller, FEV_1 ≥60 to ≤90%, bronchodilator reversibility by ≥12% and ≥200 mL - Parallel arm, DB - 12 weeks	TioR 5 mcg QD PM TioR 2.5 mcg QD PM Placebo	130 127 135	1^o: ΔFEV_1 0-3 hr baseline to week 12 2^o: ΔFEV_1 trough baseline to week 24	14 countries: USA and Canada (05%) Europe (70%) Others (25%)
444 [12/12	- 12 to 17 yr - Moderate Asthma,	TioR 5 mcg QD PM TioR 2.5 mcg QD PM	134 125	1^o: ΔFEV_1 0-3 hr baseline to week 24	12 countries: USA and

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
to 12/13]	symptomatic on mid-dose ICS, FEV_1 ≥60 to ≤90%, bronchodilator reversibility by ≥12% and ≥200 mL - Parallel arm, DB - 48 weeks	Placebo	136	2^o: ΔFEV_1 trough baseline to week 24	Canada (06%) Europe (80%) Others (14%)

* Study ID shown (top to bottom) as BI study number, and [month/year study started to month/year study completed]
† DB = double blind, DD = double dummy
‡ TioR = tiotropium administered via Respimat; Sal = salmeterol administered via HFA MDI
§ Intent to treat (treated set)
¶ Primary and secondary efficacy variables for all studies were analyzed using Analysis of Covariance (ANCOVA) model in the ITT population (patients who had baseline data and at least 1 on-treatment value). A restricted maximum likelihood (REML)-based mixed effects model with repeated measures (MMRM) was used for primary analysis. For pooled exacerbation data from studies 416 and 417, Cox's proportional hazards regression model with treatment fitted as effect was used to calculate the hazard ratio and confidence intervals for time to first asthma exacerbation.
// Country Regions: USA and Canada; Japan; Europe (Austria, Belgium, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Israel, Italy, Latvia, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Spain, Turkey, Ukraine, and United Kingdom; and Others (Argentina, Australia, Brazil, Chile, China, Colombia, Guatemala, India, Mexico, New Zealand, Peru, Philippines, Republic of Korea, and South Africa).
** Asthma worsening or exacerbation defined as an episode of progressive increase in ≥1 asthma symptoms (like shortness of breath, cough, wheezing, chest tightness, or combination of these) for ≥2 consecutive days, OR, a decrease of a patient's mean morning PEF for ≥2 consecutive days. [Severe] asthma exacerbation defined as asthma exacerbation that required an initiation of treatment with systemic (including oral) corticosteroids for ≥3 days, OR, asthma exacerbation that required at least a doubling of the previous daily dose of systemic corticosteroids for ≥3 days.

Spiriva Respimat dose-ranging and dose-regimen studies in asthma:

Selection of appropriate dose and dosing regimen is an important consideration for the development of a product for asthma. Relevant dose-ranging studies and dose regimen studies conducted for the Spiriva Respimat program are shown in Table 1. There were 3 dose ranging studies, 2 in adults and 1 in adolescents, and 2 dose-regimen studies in adults.

Patients enrolled in the dose-ranging studies had varying disease severity. Selected characteristics of the patients enrolled in the studies are shown in Table 3. Study 341 enrolled patients who had limited bronchodilator reversibility and relatively fixed airway obstruction with a post-bronchodilator FEV_1/FVC of 0.58. The presence of a post-bronchodilator FEV_1/FVC <0.70 suggests the presence of persistent airflow limitation and thus of COPD. [7] Other studies enrolled patients with moderate asthma and had large bronchodilator reversibility typical of asthma.

[7] Global Initiative for Chronic Obstructive Lung Disease. 2015 update. At: www.goldcopd.org

Table 3. Selected baseline characteristics at screening for patients in the dose ranging and dose regimen studies

	Adults, 18 yrs and older				Adolescents, 12 to 17 yrs
	341	**380**	**420**	**441**	**424**
Demographics					
Age, mean in years	55	49	44	44	14
Asthma duration, mean in years	30	24	21	20	7
Smoking status, ex-smoker %	32	20	17	31	1
Pulmonary function test					
Reversibility, mean pre-post FEV1 Δ in L	0.218	0.500	0.551	0.578	0.653
FEV_1, mean in L (pre-bronchodilator)	1.733	2.306	2.513	2.634	2.742
FEV_1, mean in L (post-bronchodilator)	1.930	2.736	2.955	3.096	3.276
FVC, mean in L (pre-bronchodilator)	3.117	3.639	3.943	3.964	3.460
FVC, mean in L (post-bronchodilator)	3.335	3.945	4.218	4.278	3.846
FEV_1/FVC ratio (pre-bronchodilator)	0.56	0.64	0.64	0.66	0.79
FEV_1/FVC ratio (post-bronchodilator)	0.58	0.70	0.70	0.72	0.80

Sources: CSR 205.341, Tables 11.2:1, 11.2:3, 15.1.4:2; CSR 205.380, Tables 11.2.2:1, 11.2.5:1; CSR 205.420, Tables 11.2.1:1, 11.2.2:1, 11.2.5:1; CSR 205.424, Tables 11.2:1, 11.2:3, 15.1.4:1

Results of the efficacy findings of primary interest are shown in Table 4. The FEV_1 data across studies need to be considered with the caveat that patients in study 341 had limited bronchodilator reversibility and relatively fixed airway obstruction, and were on more background treatment than patients in other studies. The dose response study results show that there was a numerically higher FEV_1 response, both peak FEV_1 0-3 hr (primary efficacy variable) and trough FEV_1, with higher doses of tiotropium across all doses studied with no plateau effect between the 5 mcg and 10 mcg doses and reasonable response at the 1.25 mcg dose (Table 4, studies 341, 380, 424). The dose regimen study results show that with the same nominal dose, the FEV_1 response was comparable over 24-hour period regardless of the dose administered once-daily or twice-daily (Table 4, studies 420 and 441). FEV_1 time profile curves on the first day and last day of treatment showed response within three-hour of dosing and some increase in FEV_1 over the 4 week duration of treatment (Figure 1). Results of safety findings showed numerically higher frequency of dry mouth, a measure of systemic anticholinergic effect, with the 10 mcg dose compared to the 5 mcg dose. These results are supportive of studying the 5 mcg dose (the approved dose for COPD), along with lower dose or doses in confirmatory studies in asthma. As discussed below, BI studied the 5 mcg and the 2.5 mcg dose in most of the confirmatory studies in asthma.

Table 4. Summary of lung function efficacy results from dose ranging and dose regimen studies in patients with moderate asthma

Study ID [*]	Treatments in mcg [†]	ΔFEV_1 0-3 hr to endpoint, in L		ΔFEV_1 trough to endpoint, in L	
Background Rx		Δ from baseline	Diff to placebo	Δ from baseline	Diff to placebo
341	TioR 10 QD PM	0.483	0.170	0.162	0.113
HD ICS and	Tio R 5 QD PM	0.451	0.139	0.136	0.086
LABA	Placebo QD PM	0.313	-	0.049	-

Study ID * ***Background Rx***	Treatments in mcg †	ΔFEV_1 0-3 hr to endpoint, in L		ΔFEV_1 trough to endpoint, in L	
		Δ from baseline	Diff to placebo	Δ from baseline	Diff to placebo
380 *MD ICS*	TioR 5 QD PM Tio R 2.5 QD PM TioR 1.25 QD PM Placebo QD PM	0.304 0.244 0.255 0.116	0.188 0.128 0.138 -	0.149 0.138 0.131 0.006	0.143 0.132 0.125 -
420 *MD ICS*	TioR 5 QD PM Tio R 2.5 BID Placebo QD PM	0.250 0.241 0.091	0.158 0.149	0.275 0.254 0.143	0.113 0.111
441 *MD ICS*	TioR 5 QD TioR 2.5 BID	0.217 0.219	- -	0.207 0.203	- -
424 *MD ICS*	TioR 5 QD Tio R 2.5 QD TioR 1.25 QD Placebo QD	0.602 0.546 0.556 0.489	0.113 0.056 0.067 -	0.442 0.353 0.384 0.292	0.151 0.062 0.092 -
* 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					
Source: BI Clinical Overview, Table 4.2.1:1					

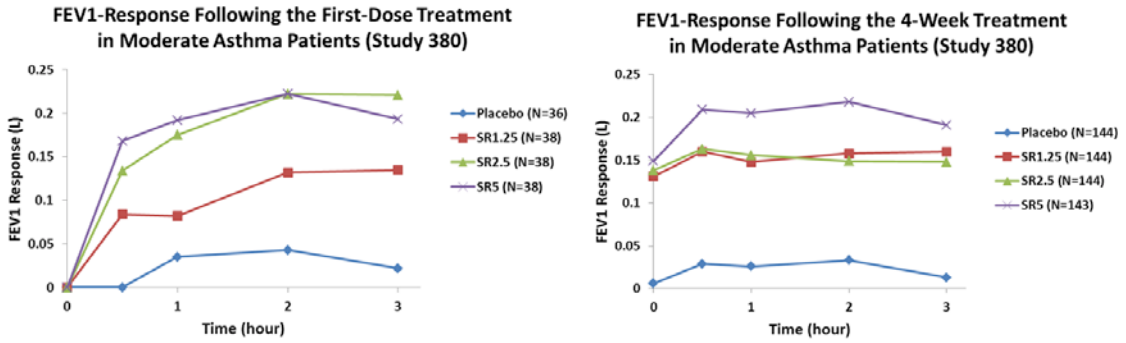

Figure 1. Adjusted mean post-evening dose FEV_1 (L) response over 3 hours in patients with asthma following the first dose (left panel) and after 4 weeks of treatment (right panel) in study 380. The mean values were adjusted by treatment, period, and FEV_1 baseline. The baseline was defined as the evening FEV_1 values measured 10 minutes before the first dose of Spiriva Respimat. (Source: FDA Clinical Pharmacology Team).

Spiriva Respimat confirmatory studies in asthma:

Some characteristics of relevant confirmatory clinical studies that form the basis of this application are shown in Table 2. 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.

b. Design and conduct of the studies

All studies were randomized, parallel-arm, and similar in design with differences in disease severity, background treatment, study treatment arms, and duration in treatment (Table 4). All studies required patients to be on background maintenance asthma controller drugs as follows: low-dose ICS for study 442, medium-dose ICS for studies 418 and 419, high-dose ICS plus LABA for studies 416 and 417, high-dose ICS plus at least 1 other controller drug or medium-dose ICS plus at least 2 other controller drug for study 456, and medium-dose ICS for study 444. All studies had placebo control to the Spiriva Respimat treatment arms. Studies 418 and 419 also included an active control salmeterol treatment arm. All patients were required to be symptomatic (i.e., inadequately controlled) as defined by ACQ score of 1.5 or higher at screening and randomization. The primary assessment of efficacy in all studies was based on pulmonary function; peak FEV1 0-3 hr was the primary efficacy assessment in all studies, and trough FEV_1 was either a co-primary or secondary efficacy assessment in all studies. The primary endpoint was change from baseline to week 24. Time to first asthma exacerbation was a primary efficacy variable using pooled data from studies 416 and 417 (co-primary, tested hierarchically), and as secondary endpoint in studies 418 and 419. There were other secondary and other endpoints based on spirometry measurements, peak expiratory endpoints, asthma questionnaires (e.g, ACQ, AQLQ, PASAPQ), and asthma symptoms including nighttime awakenings. Pulmonary function and asthma exacerbation are the two most important efficacy variables in the studies and forms the primary basis of efficacy assessment.

Asthma exacerbation is an important efficacy variable and places the FEV_1 data into context. Asthma exacerbation in the studies was assessed based on criteria developed by ATS/ERS (described in Table 2 footnote). [8] Although the ATS/ERS criteria uses the qualifier "severe" in defining asthma exacerbation (i.e., "severe asthma exacerbation"), in this document the qualifier "severe" is omitted because of the potential confusion with the term "serious" that has a regulatory context in defining adverse events,[9] and the common use of the term "serious asthma exacerbation" in the context of LABA related safety concerns of death, intubation, and hospitalization. Furthermore, the definition of exacerbation used in the studies is based on corticosteroid use (Table 4 footnote), which can be argued to be a lesser of a beneficial effect compared to asthma exacerbation resulting in hospitalization or emergency department visit.

[8] Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med 2009; 180:59-99.

[9] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Asthma worsening was another efficacy measure used in the clinical studies (described in Table 4 footnote), which is in the spectrum of asthma exacerbation that may or may not be symptomatic. This efficacy measure is not further covered in this document because of the availability of the harder and more accepted efficacy measure of asthma exacerbation described above.

Characteristics of patients enrolled in the Spiriva Respimat confirmatory studies in asthma:

Selected characteristics of the patients enrolled in the studies are shown in Table 5. These are relevant to place the efficacy findings in context. Studies 416 and 417, patients with severe asthma (Table 4) enrolled patients who had limited bronchodilator reversibility and relatively fixed airway obstruction with a post-bronchodilator FEV_1/FVC of 0.58. The presence of a post-bronchodilator FEV_1/FVC <0.70 confirms the presence of persistent airflow limitation and thus of COPD.[10, 11] Other studies enrolled patients with moderate asthma and had large bronchodilator reversibility typical of asthma. Therefore, result of studies 416 and 417 are less relevant for assessing efficacy in asthma.

Table 5. Selected baseline characteristics at screening for patients in the confirmatory studies

	Adults, 18 yrs and older			Adolescents, 12 to 17 yrs	
	442	**418 & 419**	**416 & 417**	**456**	**444**
Demographics					
Age, mean in years	43	43	53	14	14
Asthma duration, mean in years	16	22	30	8	8
Smoking status, ex-smoker %	18	16	24	0	0
Laboratory					
Absolute eosinophils, medial (10^9/L)	0.33	0.36	0.35	0.43	0.37
Total IgE, median (microgram/L)	520	640	516	1002	1065
Pulmonary function test					
Reversibility, mean pre-post FEV1 Δ in L	0.556	0.483	0.217	0.682	0.670
FEV1, mean in L (pre-bronchodilator)	2.296	2.196	1.571	2.408	2.572
FEV1, mean in L (post-bronchodilator)	2.851	2.679	1.788	3.090	3.241
FVC, mean in L (pre-bronchodilator)	3.412	3.381	2.743	3.213	3.394
FVC, mean in L (post-bronchodilator)	3.850	3.760	3.035	3.752	3.924
FEV1/FVC ratio (pre-bronchodilator)	0.68	0.66	0.58	0.76	0.77
FEV1/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

[10] Global Initiative for Chronic Obstructive Lung Disease. 2015 update. At: www.goldcopd.org

[11] Bel EH. Tiotropium for asthma – Promise and Caution. N Eng J Med 2012; 367: 1257-9. (Editorial to the published Studies 416, 417: Kerstjens HAM, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Eng E Med 2013: 367:1198-207). The Editorial by Bel EH questions the diagnosis of patients enrolled in these studies, and states: *"… … this study selectively enrolled patients who had persistent airflow limitation. The inclusion criterion of a postbronchodilator ratio of FEV_1 to forced vital capacity (FVC) of less than 0.7 puts these asthma patients in the same category as nonsmokers with COPD. It is not inconceivable that the beneficial effects of tiotropium are restricted to such nonsmoking COPD-look-alike patients with asthma, given the overwhelming evidence of the beneficial effects of tiotropium in COPD."*

c. Efficacy findings and conclusions

The clinical program is adequate to support efficacy of Spiriva Respimat at a dose of 2.5 mcg once-daily as an add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on least inhaled corticosteroids. (b) (4)

Spiriva Respimat, bronchodilator effects:

Results of the efficacy findings of pulmonary function are shown in Table 6. The FEV_1 data across studies need to be considered with the caveat that patients in different studies had different disease severity and were on different background treatment that limits comparability of efficacy magnitude across studies. Patients in studies 416 and 417 (essentially COPD patients) had limited bronchodilator reversibility and relatively fixed airway obstruction and were on more background treatment than patients in other studies.

Results of the studies in adult patients showed statistically significant higher FEV_1 response, both peak FEV_1 0-3 hr (primary efficacy variable) and trough FEV_1 (primary or secondary efficacy variable), with 5 mcg and 2.5 mcg doses of tiotropium compared to placebo (Table 6). Studies 442 (mild asthma), 418 and 419 (moderate asthma) showed numerically higher FEV_1 responses for the 2.5 mcg dose compared to the 5 mcg dose, for both peak FEV_1 0-3 hr and trough FEV_1, which were consistent across studies, except for the secondary endpoint of trough FEV_1 in study 442. Effect sizes for tiotropium were comparable to that of salmeterol (Table 6, 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 (Table 6). In the studies in adolescent patients, some of the differences between tiotropium and placebo did not reach statistical significance. The studies in adolescent patients were smaller in size than studies in adult patients.

Table 6. Summary of lung function efficacy results from confirmatory studies in patients with asthma of varying severity

Study ID * (Asth. Severity) *Background Rx*	**Treatment in mcg †**	**n**	**FEV_1 0-3 hr to endpoint, in L**			**FEV_1 trough to endpoint, in L**		
			Δ from baseline	**Diff from placebo**		**Δ from baseline**	**Diff from placebo**	
				Mean	**95% CI**		**Mean**	**95% CI**
Adult patients, age 18 years and older								
442 (mild)	TioR 5 QD	152	0.262	0.128	0.06, 0.20	0.137	0.122	0.05, 0.19
LD ICS	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		
418 (moderate)	TioR 5 QD	241	0.250	0.198	0.14, 0.25	0.115	0.152	0.09, 0.21
MD ICS	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		
419 (moderate)	TioR 5 QD	240	0.244	0.169	0.12, 0.22	0.121	0.133	0.08, 0.19
MD ICS	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		
416 (severe)	TioR 5 QD AM	217	0.401	0.086	0.02, 0.15	0.144	0.088	0.03, 0.15

Study ID * (Asth. Severity) *Background Rx*	**Treatment in mcg** †	**n**	**FEV_1 0-3 hr to endpoint, in L**			**FEV_1 trough to endpoint, in L**		
			Δ from baseline	**Diff from placebo**		**Δ from baseline**	**Diff from placebo**	
				Mean	**95% CI**		**Mean**	**95% CI**
Adult patients, age 18 years and older								
HD ICS + LABA	Placebo QD AM	211	0.315			0.056		
417 (severe)	TioR 5 QD AM	205	0.401	0.154	0.09, 0.22	0.115	0.111	0.05, 0.17
HD ICS + LABA	Placebo QD AM	218	0.248			0.044		
Adolescent patients, age 12 to 17 years								
456 (severe)	TioR 5 QD	130	0.528	0.090	-0.02, 0.20	0.284	0.054	-0.06, 0.23
MD-HD ICS	TioR 2.5 QD PM	126	0.550	0.111	0.002, 0.22	0.345	0.115	-0.00, 0.23
+ ≥1 controller	Placebo QD	132	0.438			0.230		
444 (moderate)	TioR 5 QD	131	0.547	0.174	0.08, 0.27	0.400	0.117	0.01, 0.22
MD ICS	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_1 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 2 shows results from studies 418 and 419). An effect on FEV_1, 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_1 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_1 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). The full benefit of treatment on FEV_1 were apparent after several weeks of treatment with tiotropium, and sustained improvement in peak FEV_1 0-3 hours and trough FEV_1 responses were observed throughout the entire treatment period in all studies with no reduction over time (Figure 3 and Figure 4).

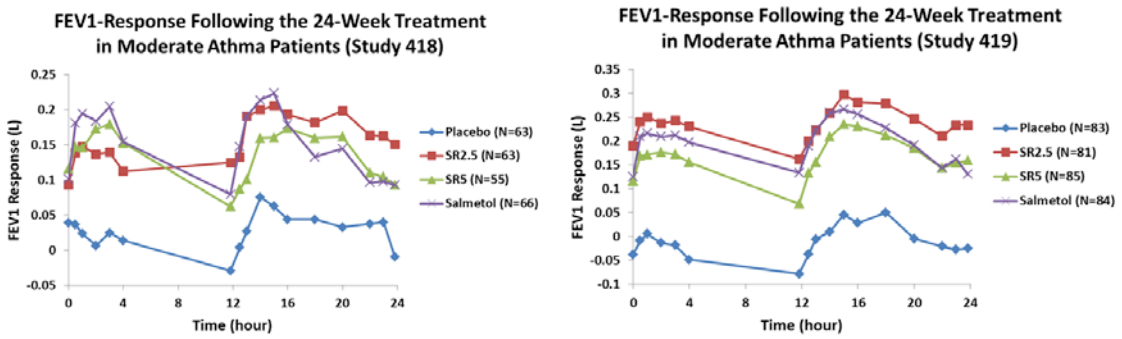

Figure 2. Adjusted mean post-evening dose FEV_1 (L) response over 24 hours in patients with asthma following 24 weeks of treatment in Study 418 (left panel) and Study 419 (right panel). (Source: FDA Clinical Pharmacology Team).

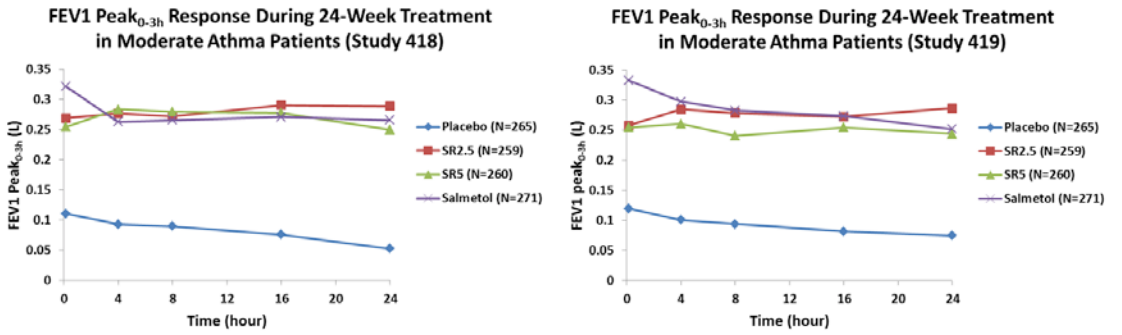

Figure 3. Adjusted mean FEV_1 peak 0-3 hr (L) response at the end of treatment of day 1, weeks 4, 8, 12, 16, and 24 in patients with asthma in Study 418 (left panel), and Study 419 (right panel). (Source: FDA Clinical Pharmacology Team).

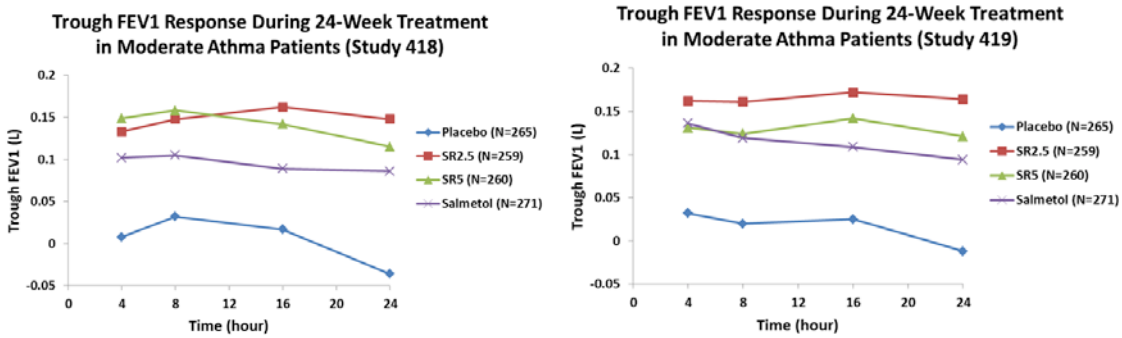

Figure 4. Adjusted mean trough FEV_1 (L) response at the end of treatment of weeks 4, 8, 12, 16, and 24 in patients with asthma in Study 418 (left panel), and Study 419 (right panel). (Source: FDA Clinical Pharmacology Team).

Spiriva Respimat, exacerbation effects:

Asthma exacerbation results were supportive of the FEV_1 results. Pooled analysis of asthma exacerbation for studies 416 and 417 (essentially COPD patients) showed statistically significant difference between Spiriva Respimat 5 mcg (only dose studied) and placebo (Table 7, Figure 4). The exacerbation benefit as defined by steroid use (Table 2 footnote) did not translate to asthma exacerbation benefit by hospitalizations for asthma exacerbation. The percentage of patients with at least 1 hospitalization for asthma exacerbation 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 8). The numbers of asthma exacerbation were higher in studies 416 and 417 compared to studies 418 and 419 because of the differing baseline severity of the patients in these two study groups. Studies 416 and 417 enrolled patients with limited bronchodilator reversibility and relatively fixed airway obstruction, and studies 418 and 419 enrolled patients with large bronchodilator reversibility typical of asthma (Table 5). The exacerbation benefit supports the FEV_1 benefit observed across studies.

Table 7. Asthma exacerbation and asthma worsening, study 416 and 417 (severe asthma in adults) pooled, all patients (ITT)

	TioR 5 (n=453)	**Placebo (n=454)**
Time to first asthma exacerbation		
Number of patients with at least 1 event (n) % TioR5 vs Placebo, Hazard ratio (95% CI), p-value	122 (27%)	149 (32%) 0.79 (0.62, 1.00), 0.03
Rate of asthma exacerbation		
Mean rate of events TioR5 vs Placebo, Ratio (95% CI), p-value	0.53	0.66 0.80 (0.64, 1.00), 0.05
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		

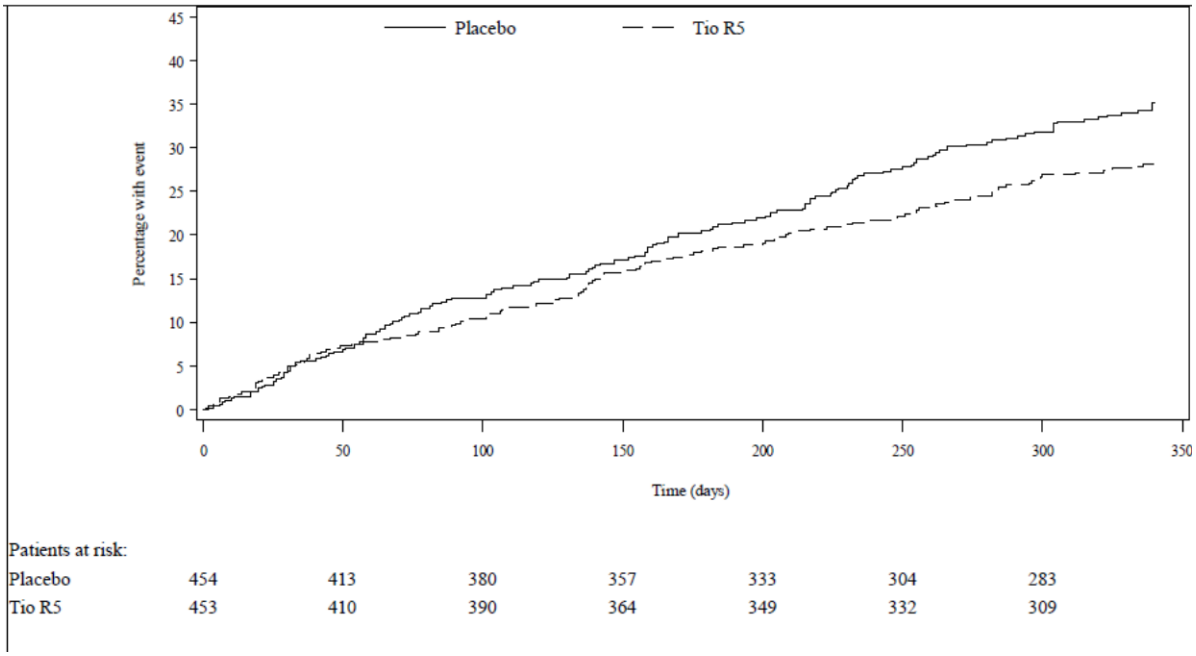

Figure 5. The cumulative percentage of patients with at least 1 asthma exacerbation for studies 416 and 417 combined, Kaplan Meier method (source: BI Clinical Overview of Efficacy, Figure 3.2.1.2.1:1)

Table 8. Asthma exacerbation and asthma worsening, Study 418, Study 419, and Studies 418 and 419 (moderate asthma in adults) pooled (pooling was not pre-specified), all patients (ITT)

Study 418:	**TioR 5 (n=261)**	**Tio R 2.5 (n=259)**	**Placebo (n=265)**
Time to first asthma exacerbation			
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)
Rate of asthma exacerbation			
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)
Study 419:	**TioR 5 (n=252)**	**Tio R 2.5 (n=256)**	**Placebo (n=253)**
Time to first asthma exacerbation			
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)
Rate of asthma exacerbation			
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)
Study 418 and Study 419 pooled:	**TioR 5 (n=513)**	**Tio R 2.5 (n=515)**	**Placebo (n=518)**
Time to first asthma exacerbation			
Number of patients with at least 1 event (n) %	31 (6%)	22 (4%)	43 (8%)

Study 418:	TioR 5 (n=261)	Tio R 2.5 (n=259)	Placebo (n=265)
TioR5 vs Placebo, Hazard ratio (95% CI)			0.7 (0.5, 1.1)
TioR2.5 vs Placebo, Hazard ratio (95% CI)			0.5 (0.3, 0.8)
Rate of asthma exacerbation			
Mean rate of events	0.16	0.10	0.21
TioR5 vs Placebo, Ratio (95% CI), p-value			0.8 (0.6, 1.0)
TioR2.5 vs Placebo, Ratio (95% CI), p-value			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			

Spiriva Respimat, Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) effects:

ACQ and AQLQ are commonly used measurements tools for asthma with defined measurement properties,[12] and listed in common asthma treatment guidelines, [13, 14] and elsewhere.[15]

ACQ is a questionnaire to measure the adequacy of asthma control and change in asthma control that occur either spontaneously or as a result of treatment. There are 7 items in ACQ: 5 items of self-administered questions (breathlessness, nocturnal waking due to asthma, asthma symptoms upon waking, activity limitation, and wheeze), 1 item of self-administered rescue bronchodilator use, and 1 item of FEV_1 completed by clinic staff. The 7 item complete ACQ is commonly used. There are shortened versions of ACQ, including a 5 item version that do not use rescue bronchodilator use and FEV_1. The shortened versions have good measurement qualities but not quite as good as those of the complete ACQ versions. 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.

AQLQ is a disease specific health-related instrument that measures physical and emotional impact of disease. There are 32 items in AQLQ that are in 4 domains – symptoms, activity limitation, emotional function, and environmental stimuli. A change in score of 0.5 on the 7-point scale is the smallest change that is considered clinically important, which is the minimal important difference for AQLQ.

ACQ was assessed in Studies 416, 417, 418, 419, and 442. Results of studies 418 and 419 were planned to be analyzed for the studies combined. AQLQ was assessed in

[12] Measurement of Health-Related Quality of Life & Asthma Control. At: https://qoltech.co.uk/index htm
[13] National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. At: http://www nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines
[14] Global Initiative for Asthma (GIINA): Global strategy for asthma management and prevention, Updated 2015. At: http://www.ginasthma.org/
[15] ATS website: http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/acq.php

Studies 416, 417, 418, and 419. ACQ was to be completed prior to other questionnaire and before the pre-dose spirometry was conducted. Results are shown in Table 9 and Table 10. 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 5 mcg and 2.5 mcg dose. The ACQ and AQLQ data are supportive of the 2.5 mcg dose as the appropriate dose for asthma.

Table 9. ACQ-7 responder analysis at ≥0.5 threshold

	TioR 5 (n=261)	**Tio R 2.5 (n=259)**	**Placebo (n=265)**
Study 416 (severe asthma), ACQ-7			
Week 24	55.5%	-	53.6%
TioR5 vs Placebo, odds ratio (95% CI)			1.07 (0.73, 1.57)
Study 417 (severe asthma), ACQ-7			
Week 24	52.3%	-	40.5%
TioR5 vs Placebo, odds ratio (95% CI), p-value			1.61 (1.09, 2.38)
Study 418 (moderate asthma). ACQ-7			
Week 24	66.7%	62.5%	53.2%
TioR5 vs Placebo, odds ratio (95% CI)			1.76 (1.22, 2.45)
TioR2.5 vs Placebo, odds ratio (95% CI)			1.47 (1.02, 2.11)
Study 419 (moderate asthma). ACQ-7			
Week 24	61.9%	66.4%	62.5%
TioR5 vs Placebo, odds ratio (95% CI)			0.98 (0.67, 1.42)
TioR2.5 vs Placebo, odds ratio (95% CI)			1.19 (0.81, 1.74)
Study 442 (mild asthma), ACQ-7			
Week 12	58.1%	59.1%	58.7%
TioR5 vs Placebo, odds ratio (95% CI)			0.97 (0.60, 1.57)
TioR2.5 vs Placebo, odds ratio (95% CI)			1.02 (0.63, 1.64)
Study 416 (severe asthma), ACQ-5			
Week 24	58.2%	-	56.3%
TioR5 vs Placebo, odds ratio (95% CI)			1.08 (0.73, 1.59)
Study 417 (severe asthma), ACQ-5			
Week 24	55.6%	-	42.7%
TioR5 vs Placebo, odds ratio (95% CI), p-value			1.68 (1.14, 2.48)
Study 418 (moderate asthma). ACQ-5			
Week 24	68.2%	65.3%	61.5%
TioR5 vs Placebo, odds ratio (95% CI)			1.34 (0.92, 1.95)
TioR2.5 vs Placebo, odds ratio (95% CI)			1.18 (0.81, 1.70)
Study 419 (moderate asthma). ACQ-5			
Week 24	67.1%	67.2%	66.8%
TioR5 vs Placebo, odds ratio (95% CI)			1.01 (0.69, 1.49)
TioR2.5 vs Placebo, odds ratio (95% CI)			1.02 (0.69, 1.50)
TioR = tiotropium administered via Respimat			

Table 10. AQLQ responder analysis at ≥0.5 threshold

	TioR 5 (n=261)	Tio R 2.5 (n=259)	Placebo (n=265)
Study 416 (severe asthma)			
Week 24 TioR5 vs Placebo, odds ratio (95% CI)	41.4%	-	44.1% 0.89 (0.61, 1.31)
Study 417 (severe asthma)			
Week 24 TioR5 vs Placebo, odds ratio (95% CI), p-value	44.4%	-	36.2% 1.41 (0.95, 2.10)
Study 418 (moderate asthma)			
Week 24 TioR5 vs Placebo, odds ratio (95% CI) TioR2.5 vs Placebo, odds ratio (95% CI)	57.1%	57.5%	50.2% 1.32 (0.92, 1.89) 1.34 (0.94, 1.93)
Study 419 (moderate asthma)			
Week 24 TioR5 vs Placebo, odds ratio (95% CI) TioR2.5 vs Placebo, odds ratio (95% CI)	57.5%	57.4%	55.3% 1.09 (0.76, 1.58) 1.09 (0.76, 1.57)
TioR = tiotropium administered via Respimat			

Spiriva Respimat, subgroup population analysis:

Efficacy data were analyzed based on various subgroups, such as gender, age, ethnicity, and geographical regions. In general, bronchodilator benefit and exacerbation benefit numerically trended in favor of Spiriva Respimat for these subgroups, but the confidence intervals for some were large because of small numbers, particularly for the pediatric age group and those of African ethnicity.

Spiriva Respimat, efficacy summary:

The efficacy data reviewed above shows consistent bronchodilator efficacy for Spiriva Respimat 5 mcg and 2.5 mcg across studies as add-on maintenance treatment in patients who were symptomatic on ICS. (b) (4) there was a consistent numerical trend of a higher response of 2.5 mcg over 5 mcg for lung functions parameters in asthma studies in adult patients (Table 6). The exacerbation data also showed numerical benefit for both 5 mcg and 2.5 mcg doses (Table 7 and Table 8). 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 (Table 2, Table 6) is more informative than the dedicated dose-ranging studies (Table 1, Table 4) because the pivotal studies were longer in duration and larger in size. The reason for apparent reduction of FEV_1 with 5 mcg compared to 2.5 mcg is not clear. It is possible that increased drying of airways with a higher dose of an anticholinergic may negatively impact the bronchodilator effect.

8. Safety

a. Safety database

The safety assessment of Spiriva Respimat for asthma is based on studies shown in Tables 1, and 2. The asthma safety database is large and adequate. In addition extensive safety information on tiotropium is available from the COPD programs of Spiriva HandiHaler and Spiriva Respimat.

b. Safety findings and conclusion

The submitted data support the safety of Spiriva Respimat for the treatment of asthma in patients 12 years of age and older.

BI conducted a comprehensive safety analysis of the available data. Safety assessment in the clinical studies included evaluation of deaths, serious adverse events (SAEs[16]), common adverse events (AEs), vital signs, physical examination, clinical laboratory and hematology measures, ECGs, and analysis of major cardiovascular events (MACE). Events related to anticholinergic, such drying effects of mucosal surface, urinary retention, ocular effects, and analysis of MACE events were of interest.

Deaths, SAEs, dropouts and discontinuations:

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

Serious adverse events (SAEs) 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 commonest cause of discontinuation was asthma, which was rare (less than 1%), and occurred with numerically lower frequency in tiotropium treatment arms compared to placebo treatment arm.

[16] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Common adverse events:

Common adverse events seen in the program were typical of asthma studies, and 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 (frequencies about 2 times to 3 times higher compared to placebo), but the overall frequency was low at about 0.3 to 0.7%. 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. This drying effect could partly explain the dose-related decrease of FEV_1 seen across clinical studies (Table 6).

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 was no patient with fatal MACE 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.

c. REMS/RiskMAP

There will be no REMS for this product related to the asthma indication. BI submitted a risk management plan consisting of a pharmacogivilance plan with focus on events of interest.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application because the safety and efficacy data of Spiriva Respimat for asthma did not raise any issues that would warrant an Advisory Committee discussion. The decision not to have an Advisory Committee meeting was discussed with BI, and BI was in agreement.

10. Pediatric

This development of Spiriva Respimat for asthma triggered PREA because of the new asthma indication. In the initial Pediatric Study Plan (iPSP) for asthma, BI agreed to complete three studies in adolescents 12 to 17 years of age (Studies 424, 444, and 456), which would be submitted with the adult studies to the original NDA. All other pediatric studies were deferred until efficacy was established in adults and adolescents.

(b) (4)

(b) (4) As for 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 at the PeRC meeting on May 27, 2015, and PeRC agreed with the revised pediatric study plan.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited three representative clinic sites from four studies (Studies 416, 418, 419, and 444) in the pivotal asthma studies. The clinical and statistical review teams recommended the sites because these sites enrolled larger number of patients compared to other sites. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Nine investigators had significant financial interest in BI. The number of subjects enrolled in the investigator sites was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proprietary name Spiriva Respimat was previously reviewed by DMEPA with the original application for COPD indication and found to be acceptable.

b. Physician Labeling

BI submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Division of Medical Policy Programs (DMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. The main issue during labeling review was the change (b) (4) that required extensive changes to various sections of the labeling.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Spiriva Respimat will carry a patient labeling to help safe use of the product. There is no Medical Guide for Spiriva Respimat related to the COPD indication, and the new asthma indication does not warrant a Medical Guide.

13. Action and Risk Benefit Assessment

a. Regulatory Action

BI has submitted adequate data to support approval of Spiriva Respimat at a dose of 2.5 mcg once-daily as an add-on maintenance treatment of asthma in patients 12 years of age and older who remain symptomatic on at least inhaled corticosteroids (b) (4) . For administrative reason, the application was split for the 2.5 mcg dose (b) (4) The regulatory action for the 2.5 mcg dose will be approval. (b) (4) .

(b) (4)

b. Risk-Benefit Assessment

Tiotropium was originally developed as an inhaled anticholinergic for the treatment of patients with COPD. This submission provides results from a comprehensive clinical development program with tiotropium in the Respimat device across a broad spectrum of asthma patients on background maintenance treatment consistent with their asthma severity. The submitted efficacy and safety data support use of Spiriva Respimat 2.5 mcg for the treatment of asthma.

The submitted data show consistent efficacy on lung function parameters. In the confirmatory studies in adults with asthma, Spiriva Respimat 5 mcg and 2.5 mcg showed statistically significantly higher FEV_1 response for the primary endpoints, both peak

FEV_1 0-3 hr (primary efficacy variable) and trough FEV_1 (primary or secondary efficacy variable), compared to placebo. Effect sizes for Spiriva Respimat 5 mcg and 2.5 mcg were comparable to that of salmeterol. Dose ordering for FEV_1 parameters was reverse, with the 2.5 mcg showing consistent numerical higher response compared to the 5 mcg dose. Asthma exacerbation data, which places FEV_1 data in context, also showed numerical benefit of Spiriva Respimat 5 mcg and 2.5 mcg doses compared to placebo in studies in adults. Confirmatory studies in adolescent patients 12 to 17 years of age assessed FEV_1 response and showed results generally consistent with results of the adult studies. The studies in adolescent patients were smaller in size than studies in adult patients. Safety findings with Spiriva Respimat in studies in asthma did not show any safety signals of concerns. Adverse events were consistent with those in patients with COPD. Anticholinergic adverse events, such as dry mouth, dry throat, thirst, and dysphonia occurred more in tiotropium treatment arms (frequencies about 2 times to 3 times higher compared to placebo), but the overall frequency was low at about 0.3 to 0.7%.

(b) (4) the 2.5 mcg dose would be the appropriate dose for patients with asthma because of consistent numerical trend of a higher response of 2.5 mcg over 5 mcg for lung functions parameters. The exacerbation data do not support one dose over the other because both doses showed favorable numerical benefit. Dose ranging information from the pivotal studies is robust and more informative because of their larger size and longer duration than the dedicated dose-ranging studies. Also, with the lower 2.5 mcg dose compared to the 5 mcg dose, adverse events, specifically anticholinergic adverse events are expected to be lower.

c. Post-marketing Risk Management Activities

No post-marketing risk management activities are required.

d. Post-marketing Study Commitments

None, other than the PREA required studies.

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/s/

BADRUL A CHOWDHURY
09/11/2015