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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	September 24, 2014
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	21-936, Seq 003
Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission:	March 24, 2014 (original submission was on November 16, 2007)
PDUFA Goal Date:	September 24, 2014
Proprietary Name:	Spiriva Respimat
Established Name:	Tiotropium bromide
Dosage form:	Inhalation Spray
Strength:	2.5 mcg per spray
Proposed Indications:	Long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbation
Action:	Approval

1. Introduction

Boehringer Ingelheim (BI) Pharmaceuticals submitted the initial New Drug Application (NDA) under 505(b)(1) on November 16, 2007, for use of Spiriva Respimat in patients with chronic obstructive pulmonary disease (COPD). The proposed dose was 5 mcg (2 inhalation of 2.5 mcg per spray). A Complete Response was issued on September 16, 2008, citing two deficiencies – safety concerns of death and stroke, and lack of replicate finding to support reduction of COPD exacerbation claim. BI addresses these deficiencies in this NDA resubmission. The safety concerns of death and stroke are addressed by a new study (205.452 or TIOSPIR that compares Spiriva Respimat and Spiriva HandiHaler), and pooled data of previously conducted Spiriva Respimat studies (205.251, 205.252, 205.254, and 205.255) and some other studies. The reduction of COPD exacerbation is addressed by a new study (205.372) to complement data from previously provided pooled analysis from two studies (205.254, and 205.255). BI also conducted another study (205.458) to firmly establish pharmacokinetic link between Spiriva Respimat and Spiriva HandiHaler. BI had previously discussed with the Division the plan to conduct these three new studies to supplement the previous studies to address the deficiencies. This was acceptable to the Division. This summary review will provide an overview of the application including studies submitted with the original NDA and with this NDA resubmission.

2. Background

There are several drug classes approved for relief of airflow obstruction in patients with COPD. These include short- and long-acting beta-2 adrenergic agonists, short- and long-

acting anticholinergics, combination products containing beta-2 adrenergic agonists and anticholinergics, combination of long-acting beta-2 adrenergic agonists and corticosteroids, methylxanthines, and phosphodiesterase-4 (PDE4) inhibitors. There are a smaller number of drug classes available for reducing exacerbations in COPD. These include long-acting anticholinergics, combination products containing long-acting beta-2 adrenergic agonists (LABA) and inhaled corticosteroids (ICS), and PDE inhibitors. With the exception of methylxanthines and PDE-4 inhibitors, all others are inhalation products.

Tiotropium bromide is a long-acting anticholinergic with specificity for muscarinic receptors that is currently approved as Spiriva HandiHaler (tiotropium bromide inhalation powder) for use in patients with COPD. Spiriva HandiHaler was approved on January 30, 2004 (NDA 21-395). The approved product consists of a dry powder containing tiotropium bromide in the Spiriva capsule, and the inhalation device, the HandiHaler, which is used to deliver the dry powder from the capsule. With this application BI proposes to introduce a reservoir type device, called the Respimat, to deliver tiotropium bromide.

Inhaled anticholinergics are widely available in the US and worldwide for the treatment of COPD. In the US, one short-acting anticholinergic, ipratropium bromide, and three long-acting anticholinergics, tiotropium bromide (Spiriva HandiHaler), aclidinium bromide (Tudorza Pressair), and umeclidinium (in combination with vilanterol as Anoro Ellipta, and as single ingredient Incruse Ellipta) are currently available. All of these products have anticholinergic adverse effects, such as dry mouth, constipation, and urinary retention. A meta-analysis of various studies suggested a concern regarding increased risk of stroke, cardiovascular death, and myocardial infarction associated with the use of short-acting and long-acting anticholinergics.[1] A pooled analysis of 29 studies conducted by BI in 2007 (25 studies with Spiriva HandiHaler, and 4 studies with Spiriva Respimat) suggested an increased risk of stroke with tiotropium bromide.[2] In contrast, a 6,000 patient, 4-year study with Spiriva HandiHaler conducted by BI in COPD patients (The UPLIFT Study – Understanding Potential Long-term Impacts on Function with Tiotropium) did not show increased mortality or cardiovascular safety risk with Spiriva HandiHaler.[3, 4] A more recent study conducted by BI involving 17,135 COPD patients followed for a mean of 2.3 years (The TIOSPIR study – Tiotropium Safety and Performance in Respimat) showed comparable all-cause mortality between Spiriva Respimat and Spiriva HandiHaler.[5] The TIOSPIR study is submitted with this NDA. The TIOSPIR study, along with previously conducted studies will help address the

[1] Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008; 300:1439-50.
[2] FDA Early Communication about an Ongoing Safety Review of Tiotropium. Http://ww.fda.gov/cder/drug/early_comm/tiotropium.htm
[3] Tashkin 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.
[4] Michele TM, Pinheiro S. Iyasu S. The safety of tiotropium – The FDA conclusions. N Eng J Med 2010; 363: 1097-99.
[5] 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.

concerns regarding excess mortality and cardiovascular safety risks with the long-acting anticholinergic, tiotropium.

In the intervening time period between initial submission of the Spiriva Respimat NDA and the NDA resubmission after Complete Response action on March 24, 2014, two inhaled long-acting anticholinergics were approved for marketing in the US. These were aclidinium bromide, and umeclidinium as mentioned above. Relevant regulatory history related to cardiovascular safety for these two products are briefly discussed below.

The Tudorza Pressair (aclidinium bromide) review noted major cardiovascular adverse events as a potential safety signal. The Agency asked the Applicant to conduct a required post-marketing requirement study (PMR) to evaluate the risk of these events in patients with COPD. The Agency reviews noted that while the actual number of MACE events was low in the Tudorza program, the overall size of the safety database was relatively small compared to other COPD development programs, patients with cardiovascular history were excluded, and noted that pending the results of the ongoing TIOSPIR trial, uncertainty remained regarding cardiovascular adverse events and stroke for this drug class. Therefore, a PMR to expand the safety database and further evaluate cardiovascular safety in an enriched population with cardiovascular risk factors was deemed to be reasonable and was generally consistent with the recommendations of the PADAC meeting convened earlier in February 2013 to discuss the aclidinium program.

The available evidence regarding cardiovascular safety for the Anoro Ellipta (umeclidinium and vilanterol) product was discussed at the September 2013 PADAC meeting and at a subsequent CDER Regulatory Briefing. While small imbalances in the Anoro Ellipta safety database were observed, most notably for nonfatal myocardial infarctions, the FDA review concluded that the clinical program was adequate to support safety without further post-marketing safety study. Unlike the Tudorza program, the Anoro Ellipta program did not exclude patients with a history of cardiovascular disease. Cardiovascular safety analyses based on the pooled COPD trials of 12-weeks duration or longer were mostly unremarkable, including evaluations for death and other MACE events (ischemia/infarction, stroke, and cardiovascular death), and the total number of cardiovascular-related events in the program was fairly low. Based on the totality of the evidence, a post-marketing safety study was not requested for the Anoro Ellipta product.

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 (as preservative), edetate disodium (as stabilizer), water for injection, and hydrochloric acid (to adjust pH (b) (4)). The formulation is contained in a cartridge, which will be supplied separately from the Respimat Inhaler. 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 and compress a spring. The patient then presses a trigger, which releases the spring to provide mechanical energy that propels the formulation through a nozzle with two outlets that form two jets of solutions. The two jets converge on each other and create an aerosol cloud that emits gently from the mouthpiece of the product. 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. BI submitted adequate stability data to support the proposed expiry of (b) (4) for the drug product that consists of the Respimat device and the unassembled cartridge containing the formulation (stored separately), and three months after the cartridge is assembled with the Respimat Inhaler or first patient use, whichever comes first.

The steps needed to use the product and the internal mechanisms of the product are rather complex. 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. A consultation with CDRH was obtained because of the complexity of the product. The CDRH review did not raise any concern with the manufacturing and quality of the product, but raised concerns on performance testing with regards to human factors. BI has performed adequate specific patient handling studies with Respimat. In addition, in two phase 3 studies patient handling of the device was assessed and representative devices used in clinical studies were tested for in vitro performance characteristics. These assessments did not suggest any significant problems with patient handling, performance, and robustness of the Respimat device. The only issue that was 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.

One point of note is that the device had undergone some changes during clinical studies. The phase 3 clinical studies were conducted with the A4 version of the Respimat, and the to-be-marketed product is the A5 version. The changes between the two versions are minor, with the most important change being incorporation of a locking mechanism after 60 actuations. BI has submitted adequate in vitro data to link the two versions of the device.

The drug substance and drug product including the Respimat device are manufactured at a BI facility in Ingelheim am Rhein, Germany. All manufacturing and testing facilities associated with this drug product have acceptable establishment evaluation status. All DMFs associated with this application were also found to be acceptable.

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 5 mcg, which is lower than the nominal dose of Spiriva HandiHaler, which is 18 mcg, and the exposure to tiotropium in humans from these two products are similar.

BI submitted results from one safety pharmacology study. The study 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. This study did not show any safety issues.

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. Pharmacokinetic sampling done in the two 4-week safety and efficacy studies 249 and 250 showed that systemic exposure and urinary excretion of tiotropium were higher with Spiriva Respimat 5 mcg and 10 mcg doses compared to Spiriva HandiHaler 18 mcg dose, but exposure from the Spiriva Respimat 5 mcg dose was close to exposure from the Spiriva HandiHaler 18 mcg dose (Table 1). Studies 249 and 250 are described in section 7. Based on the results of this pharmacokinetic comparison and efficacy findings (to be discussed in section 7), BI proposed 5 mcg of Spiriva Respimat as the recommended dose that matches the 18 mcg recommended dose of Spiriva HandiHaler.

Table 1. Mean tiotropium plasma concentration and mean tiotropium urinary excretion from patients treated with Spiriva Respimat and Spiriva HandiHaler

	Spiriva Respimat 5 mcg	Spiriva Respimat 10 mcg	Spiriva HandiHaler 18 mcg
Study 249			
AUC 0-6 ss, pg.hr/mL	26.1	64.6	20.2
AUC 0-24 ss, pg.hr/mL	63.5	148	52.2
Urinary excretion 0-12 hrs, ng	561	1230	428
Study 250			
AUC 0-6 ss, pg.hr/mL	26.8	58.1	24.2
AUC 0-24 ss, pg.hr/mL	67.4	143	62.3
Urinary excretion 0-12 hrs, ng	479	892	410

BI conducted study 458 after review of the initial NDA and submitted with this NDA resubmission. The aim of the study was to provide detailed information on the pharmacokinetics of Spiriva Respimat and Spiriva HandiHaler to address potential differences between the two formulations and confirm dose selection. The results of the study show that systemic exposure to tiotropium following the use of Spiriva Respimat was slightly lower compared to Spiriva HandiHaler. 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.

BI submitted results from a thorough QT study in the Spiriva HandiHaler application (NDA 21-395), and the study results were cross-referenced in this 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) and sealed aseptically. Once the cartridge is inserted into the Respimat Inhaler the formulation is open to contamination from the environment. The formulation contains benzalkonium chloride as a preservative, which is adequate to address this concern.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

BI conducted studies comparing Spiriva Respimat to Spiriva HandiHaler, and also a full stand alone clinical program with Spiriva Respimat to support this application. Some characteristics of the selected studies that form the basis of review and regulatory decision for this application are shown in Table 2. The studies are shown in two groupings – those submitted with the initial NDA, and those submitted with this NDA resubmission. BI also submitted studies 1205.14 and 1205.04 as support for safety. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section. For brevity, the studies are referred to later in this review by the last three digits of the study number.

Table 2. Relevant clinical studies

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study objective, design** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy endpoint ¶**	**Regions and Countries //**
Submitted with the initial NDA					
Comparability assessment to Spiriva HandiHaler					
205.127 [1999]	- ≥ 40 yr - COPD by ATS criteria - Dose-ranging, PG - 3 weeks	SR 1.25 mcg QD SR 2.5 mcg QD SR 5.0 mcg QD SR 10 mcg QD SR 20 mcg QD SH 18 mcg QD Pbo R QD Pbo H QD	25 28 25 26 26 25 24 23	FEV_1 trough at day 21	France
205.249 [2004]	- ≥ 40 yr - COPD - Efficacy and safety, XO - 4 weeks	SR 5 mcg QD SR 10 mcg QD SH 18 mcg QD Pbo QD	131 131 131 131	FEV_1 trough at end of each 4-week treatment period	US (92%), Canada
205.250 [2003]	- ≥ 40 yr - COPD by ATS criteria - Efficacy and safety, XO - 4 weeks	SR 5 mcg QD SR 10 mcg QD SH 18 mcg QD Pbo QD	76 76 76 76	FEV_1 trough at end of each 4-week treatment period	Belgium, Netherlands
Stand alone pivotal efficacy and safety studies for Spiriva Respimat					

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study objective, design** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy endpoint ¶**	**Regions and Countries //**
205.251 [2003]	- ≥ 40 yr - COPD by ATS criteria - Efficacy and safety, PG - 12 weeks	SR 5 mcg QD SR 10 mcg QD A 36 mcg QID Pbo	88 93 89 91	ΔFEV_1 trough baseline to wk 12	Germany, Italy, Switzerland, South Africa
205.252 [2003]	- ≥ 40 yr - COPD by ATS criteria - Efficacy and safety, PG - 12 weeks	SR 5 mcg QD SR 10 mcg QD A 36 mcg QID Pbo	92 87 89 90	ΔFEV_1 trough baseline to wk 12	US (57%), Canada
205.254 [2003]	- ≥ 40 yr - COPD by ATS criteria - Efficacy and safety, PG - 48 weeks	SR 5 mcg QD SR 10 mcg QD Pbo QD	332 332 319	ΔFEV_1 trough baseline to week 48 SGRQ at week 48 TDI at week 48 Number of COPD exacerbations	US (16%), Canada, Europe
205.255 [2005]	- ≥ 40 yr - COPD by ATS criteria - Efficacy and safety, PG - 48 weeks	SR 5 mcg QD SR 10 mcg QD Pbo QD	338 335 334	ΔFEV_1 trough baseline to week 48 SGRQ at week 48 TDI at week 48 COPD exacerbation	US (16%), Canada, Europe
205.392 [2005]	- ≥ 40 yr - COPD by ATS criteria - Follow up from 254, 255 - 48+ weeks	SR 5 mcg QD SR 10 mcg QD Pbo	456		US (16%), Canada, Europe, Africa, Australia
Submitted with this NDA resubmission					
205.372 [2009]	- ≥ 40 yr - COPD by ATS criteria - Efficacy and safety, PG - 48 weeks	SR 5 mcg QD Pbo QD	1952 1965	ΔFEV_1 trough baseline to week 48 Time to 1st COPD exacerbation	US (14.7%), Canada, Europe, Asia, Africa, Australia, Non-U.S. Americas
205.452 [2013]	- ≥ 40 yr - COPD by ATS criteria - Safety - 3.5+ years	SR 2.5 mcg QD SR 5 mcg QD SH 18 mcg QD	5724 5705 5687	All cause mortality Time to 1st COPD exacerbation	US (20.9%), Canada, Europe, Asia, Africa, Australia, Non-U.S. Americas, Israel
205.458 [2011]	- ≥ 40 yr - COPD by ATS criteria - Comparative PK PD, XO - 4 weeks	SR 2.5 mcg QD SR 5 mcg QD SH 18 mcg QD Placebo	154 154 154 154	PK parameters	Europe

* Study ID shown (top to bottom) as BI's study number, and [Year study subject enrollment ended]
† XO=cross over, PG=parallel group
‡ SR = Spiriva Respimat; SH: Spiriva HandiHaler; A = Atrovent MDI; Pbo R = Placebo Respimat: Pbo H = Placebo HandiHaler;
§ Intent to treat (ITT)
¶ FEV1 trough is measured 23:50 hours after dosing. Primary efficacy variables for the bronchodilator studies were analyzed using mixed model for repeated measure (MMRM) in the ITT population.
// Europe included: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Georgia, Greece, Hungary, Ireland, Italy, Lativa, Lithuania, Netherlands, Norway, Portugal, Poland, Romania, Russia, Slovakia, Spain, Sweden, Switzerland, UK, Ukraine.
Asia included: China, Hong Kong, India, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, Tunisia, Turkey
Non-U.S. Americas: Argentina, Columbia, Guatamala, Mexico, Panama

b. Design and conduct of the studies

Study 127 was randomized, double-blind, placebo-controlled, parallel-group in design, conducted in patients with COPD. The objective of this study was to determine pharmacodynamic and pharmacokinetic profiles of a range of doses of Spiriva Respimat and compare those to the approved dose of Spiriva HandiHaler. The study had a 1-week screening period, followed by 3-week double-blind treatment period. Primary efficacy variable was trough FEV1 response on day 21 of treatment. Safety assessments included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, and ECG.

Studies 249 and 250 were randomized, double-blind, double-dummy, active- and placebo-controlled, parallel group in design, conducted in patients with moderate-to-severe COPD. The study had four randomized 4-week treatment periods separated by 4-week washout periods. Primary efficacy variable was trough FEV1 at the end of each 4-week treatment period. Trough FEV1 was defined as FEV1 measured at -10 minutes at the end of the 24-hour dosing interval. Serial blood samples and urine were collected for pharmacokinetic analyses. Safety assessments included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, and ECG.

Studies 251 and 252 were randomized, double-blind, double-dummy, active- and placebo-controlled, parallel group in design, conducted in patients with moderate-to-severe COPD. The study had a 2-week run-in period followed by a 12-week randomized treatment period. Primary efficacy variable was trough FEV1 at the end of the 12-week treatment period. Trough FEV1 was defined as FEV1 measured at -10 minutes at the end of the 24-hour dosing interval. Safety assessments included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, and ECG.

Studies 254 and 255 were randomized, double-blind, placebo-controlled, parallel group in design, conducted in patients with moderate-to-severe COPD. These studies had a 2-week run-in period followed by 48-week randomized treatment period, and then a 3-week follow-up period. Each study had four co-primary efficacy variables pre-declared to be tested sequentially (in order to control the type I error for multiple endpoints) as follows: trough FEV1 at the end of 48-week treatment period, total SGRQ score at the end of 48-week treatment period, Mahler TDI at the end of 48-week treatment period, and number of COPD exacerbations occurring during the year of randomized treatment. The protocol specified that trough FEV1 and SGRQ were to be analyzed separately for each study, and Mahler TDI and COPD exacerbation to be analyzed by pooling the studies. BI stated that the Mahler TDI was included for the purpose of registration in EU and that no claims were being requested based on the SGRQ. Therefore, for the purpose of US review, the endpoints for consideration are trough FEV1 and COPD exacerbation. The protocol specified that demonstration of statistical significance with the first primary endpoint (FEV1) would be adequate for demonstration of efficacy. This was acceptable to the Agency. Safety assessments included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, ECG and 24-hour Holter monitoring in a subset of patients.

COPD exacerbation in studies 254 and 255 were defined as "a complex of respiratory events or symptoms with duration of 3 days or more requiring treatment." A complex of respiratory events/symptoms means ≥ 2 of the following (increase of symptom or new onset): shortness of breath/dyspnea/shallow, rapid breathing, sputum production (volume), occurrence of purulent sputum, cough, wheezing, and chest tightness. A change in or requirement of treatment included the following: prescription antibiotics and/or systemic corticosteroids, and/or a significant change of the prescribed respiratory medication (bronchodilators including theophylline). There is no generally accepted definition of COPD exacerbations, but it usually includes some combination of symptoms and a change of treatment. The definition used in these studies is as precise as practicable and generally closely follows the definitions used in the literature.[6]

Study 372 was randomized, double-blind, placebo-controlled, parallel group in design, conducted in patients with moderate-to-severe COPD. The study had a 4-week run-in period followed by 48-week randomized treatment period, and then a 4-week follow-up period. Patients were allowed to continue LABA use. The study had two co-primary efficacy variables: trough FEV1 at the end of 48-week treatment period, and time to first COPD exacerbation. The definition of COPD exacerbation was similar to studies 254 and 255. Safety assessments included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, and ECG.

Study 452 was a randomized, double-blind, active-controlled, parallel group in design, conducted in patients with moderate-to-severe COPD. The main objective of the study was to compare safety of Spiriva Respimat to Spiriva HandiHaler. The study was event driven and designed to end after approximately 1266 fatal events that were predicted to occur within 3.5 years. All patients were to be followed up until the end of the study for vital status regardless of continuation of study treatment. Patients were allowed to continue stable baseline respiratory medications other than anticholingergics, and LABA use was allowed. The first primary variable of the study was time to all-cause mortality planned as non-inferiority analysis with the upper limit of the 95% CI <1.25. The second primary variable of the study was time to first COPD exacerbation. The definition of COPD exacerbation was similar to studies 254 and 255. The study also included a PFT sub-study where a randomized subset of patients had spirometry every 24 weeks until study close-out. The sub-study was projected to included 1305 patients. Safety assessments included analysis of adverse events with the following as protocol defined outcome events: COPD exacerbations, pneumonias, myocardial infarctions, strokes, and transient ischemic attacks. The protocol defined outcome events were centrally monitored to determine of the events met the pre-specified definition outlined in the protocol. The definitions for events used in the protocol were acceptable to the Agency. Analyses of major adverse cardiovascular events (MACE) were conducted using standard accepted definition.

Study 458 was randomized, double-blind, active- and placebo-controlled, 5-way crossover in design, conducted in patients with moderate-to-severe COPD. The study

[6] Cazzola M, MacNee W, Martinez FJ, et al. ATS/ERS Task Force Report: Outcomes for COPD pharmacological trials, from lung function to biomarkers. Eur Resp J 2008; 31: 416-468.

was designed to characterize the PK as the primary objective and evaluate bronchodilator efficacy as a secondary objective. The aim of the study was to provide detailed information on the pharmacokinetics of Spiriva Respimat and Spiriva HandiHaler to address potential differences between the two formulations and confirm dose selection.

c. Efficacy findings and conclusions

The clinical program submitted with this application is large for a product for COPD. The program was designed to establish a link between Spiriva Respimat and the currently marketed Spiriva HandiHaler, and further demonstrate efficacy for Spiriva Respimat in stand-alone studies (Table 2).

There are four components of efficacy assessment relevant to this application. These are airflow obstruction or bronchodilator effect, SGRQ, Mahler TDI, and COPD exacerbation. These four components are briefly discussed below, although for the purpose of US registration, BI stated that airflow obstruction and COPD exacerbation are relevant.

Airflow Obstruction or Bronchodilator Effect

Use of Spiriva Respimat 5 mcg for maintenance treatment of bronchospasm associated with COPD is supported by studies 127, 249, 250, 251, 252, 254, and 255, submitted with the initial NDA and study 372 submitted with this NDA resubmission. In study 127 Spiriva Respimat at doses of 5 mcg and above had numerically larger improvement in trough FEV1 compared to lower doses. The trough FEV1 response tended to be flat at doses 5 mcg and above (Table 3). BI carried the 5 mcg and 10 mcg doses in further clinical studies submitted with the initial NDA, and the 5 mg dose in the study 372 conducted later and submitted with this NDA resubmission (Table 2). In studies 249 and 250, both 5 mcg and 10 mcg doses were statistically significantly superior to placebo, and both doses provided numerically similar trough FEV1 response over placebo (Table 4). In study 249 both doses of Spiriva Respimat provided slightly larger numerical response compared to Spiriva HandiHaler 18 mcg. In the stand-alone studies 251, 252, 254, and 255, both 5 mcg and 10 mcg doses were consistently statistically superior to placebo (Table 5). The 10 mcg doses tended to provide slightly larger numerical response compared to 5 mcg dose (Table 5). In study 372 the 5 mg dose was also statistically superior to placebo (Table 5). FEV1 time-response curve for these studies also provided similar results (data not shown in this review). The overall data support BI's proposal to seek approval for the 5 mcg dose. The numerical superiority of 10 mcg over 5 mcg is not consistent and minimal. Furthermore, systemic exposure from Spiriva Respimat 5 mcg was close to systemic exposure from Spiriva HandiHaler 18 mcg (Table 1).

The clinical program explored various doses of Spiriva Respimat as mentioned above, but did not explore any dosing frequency other than once daily. Once daily dosing for Spiriva Respimat is reasonable because Spiriva HandiHaler is approved at once daily dosing and the submitted clinical studies provides adequate link between Spiriva Respimat and Spiriva HandiHaler. In studies 249 and 250 both doses of Spiriva Respimat were at least nearly non-inferior to Spiriva HandiHaler (with a non-inferiority margin of 0.05L) and in fact provided slightly larger numerical response compared to

Spiriva HandiHaler 18 mcg (Table 4). The FEV1 time-response curves for both products were also similar (data not shown in this review). Furthermore, in studies 251 and 252, the trough FEV1 response for both doses of Spiriva Respimat was numerically greater than Atrovent Inhalation Aerosol dosed four times daily (Table 5).

Table 3. Results of dose ranging study 127

Treatment groups	n	Mean Trough FEV1 (L) Response on Day 21	Difference from placebo (L)
Spiriva Respimat 1.25 mcg QD	25	0.10	0.08
Spiriva Respimat 2.5 mcg QD	28	0.05	0.03
Spiriva Respimat 5 mcg QD	25	0.15	0.13 *
Spiriva Respimat 10 mcg QD	26	0.13	0.11
Spiriva Respimat 20 mcg QD	26	0.15	0.13 *
Spiriva HandiHaler 18 mcg QD	25	0.23	0.32 *
Placebo Respimat QD	24	0.02	
Placebo HandiHaler QD	23	-0.09	
* Statistically significant			

Table 4. Mean trough FEV1 (L) treatment differences between Spiriva Respimat and the comparators at the end of treatment periods from two comparative studies

Treatment groups	Difference from placebo			Difference from HandiHaler		
	Point estimate	95% CI	p-value*	Point estimate	95% CI	p-value†
Study 249						
Spiriva Respimat 5 mcg QD	0.12	0.08, 0.15	<0.001	0.05	0.01, 0.08	<0.001
Spiriva Respimat 10 mcg QD	0.13	0.09, 0.16	<0.001	0.06	0.02, 0.09	<0.001
Spiriva HandiHaler 18mcg QD	0.07	0.04, 0.10	<0.001			
Study 250						
Spiriva Respimat 5 mcg QD	0.13	0.09, 0.17	<0.001	0.00	-0.04, 0.04	0.006
Spiriva Respimat 10 mcg QD	0.12	0.08, 0.16	<0.001	-0.10	-0.51, 0.03	0.028
Spiriva HandiHaler 18mcg QD	0.13	0.09, 0.17	<0.001			
* superiority; p-values are one-sided † non-inferiority; p-values are one sided						

Table 5. Mean trough FEV1 (L) results at the end of treatment period from four pivotal studies

Treatment groups	n	Baseline	End of Treatment	Difference from placebo		
				Point estimate	95% CI	p-value vs placebo
Study 251						
Spiriva Respimat 5 mcg QD	85	1.15	1.34	0.11	0.04, 0.18	0.0034
Spiriva Respimat 10 mcg QD	89	1.26	1.41	0.18	0.11, 0.25	<0.0001
Atrovent MDI 36 mcg QID	84	1.25	1.29	0.06	-0.01, 0.13	0.1045
Placebo	87	1.24	1.23			
Study 252						
Spiriva Respimat 5 mcg QD	90	0.99	1.11	0.12	0.07, 0.18	<0.001
Spiriva Respimat 10 mcg QD	84	0.98	1.10	0.12	0.06, 0.17	0.0001
Atrovent MDI 36 mcg QID	86	0.96	1.03	0.04	-0.01, 0.10	0.1373
Placebo	84	1.11	0.99			
Study 254						

Treatment groups	n	Baseline	End of Treatment	Difference from placebo		
				Point estimate	95% CI	p-value vs placebo
Spiriva Respimat 5 mcg QD	326	1.05	1.17	0.14	0.10, 0.18	<0.0001
Spiriva Respimat 10 mcg QD	320	1.09	1.19	0.16	0.12, 0.20	<0.0001
Placebo	196	1.07	1.03			
Study 255						
Spiriva Respimat 5 mcg QD	324	1.09	1.14	0.11	0.08, 0.15	<0.0001
Spiriva Respimat 10 mcg QD	324	1.04	1.16	0.14	0.11, 0.18	<0.0001
Placebo	307	1.05	1.02			
Study 372						
Spiriva Respimat 5 mcg QD	1939	1.11	1.23	0.10	0.09, 0.12	<0.0001
Placebo	1953	1.11	1.13			

SGRQ

BI did not seek SGRQ benefit statement in the product label. The submitted data show numerical benefit on total SGRQ score with Spiriva Respimat, and the differences over placebo are statistically significant, but the minimum important difference of 4 was not achieved in either study for the 5 mcg dose (Table 6). The submitted data provide support for efficacy of Spiriva Respimat, but the data do not support any labeling claim specific to SGRQ.

Table 6. Mean total SGRQ score at the end of 48 weeks of treatment

Treatment groups	n	LS Mean	Difference from placebo		
			Point estimate	95% CI	p-value
Study 254					
Spiriva Respimat 5 mcg QD	318	39.6	-3.3	-5.2, -1.3	0.001
Spiriva Respimat 10 mcg QD	315	38.7	-4.2	-6.2, -2.3	<0.0001
Placebo	275	42.9			
Study 255					
Spiriva Respimat 5 mcg QD	310	39.8	-3.7	-5.8, -1.6	0.0004
Spiriva Respimat 10 mcg QD	304	40.0	-3.4	-5.5, -1.4	0.001
Placebo	276	43.5			

Mahler TDI

The Division has concluded previously that Mahler TDI is not adequate for labeling claim and BI is also not seeking a dyspnea claim for Spiriva Respimat. Nevertheless, the instrument is widely used and worth mentioning. The submitted data show that both doses of Spiriva Respimat were statistically superior over placebo in both studies (Table 7). The submitted data provide support for efficacy of Spiriva Respimat.

Table 7. Mean Mahler TDI score at the end of 48 weeks of treatment

Treatment groups	n	LS Mean	Difference from placebo		
			Point estimate	95% CI	p-value
Study 254					
Spiriva Respimat 5 mcg QD	318	1.9	1.1	0.7, 1.5	<0.0001
Spiriva Respimat 10 mcg QD	313	2.0	1.3	0.8, 1.7	<0.0001
Placebo	273	0.8			
Study 255					
Spiriva Respimat 5 mcg QD	310	1.9	1.0	0.5, 1.5	<0.0001
Spiriva Respimat 10 mcg QD	305	1.8	0.9	0.4, 1.4	0.0002
Placebo	279	0.9			

Exacerbation

During the initial NDA review it was concluded that reduction of COPD exacerbation statement in label was not supported by the submitted data. Of the two studies that assessed exacerbation, one showed statistically significant superiority for Spiriva Respimat over placebo (Table 8). Although pre-specified combined analyses of the two studies showed statistical significance, this was not deemed to be adequate because the pooled studies are considered as one study. With the original NDA, BI submitted results of a study conducted in Veterans Affairs patients with Spiriva HandiHaler (study 205.266) to show replication of COPD exacerbation. That study was not adequate for the purpose of replication because it was conducted with a different product.

Table 8. Mean COPD exacerbations data

Treatment groups	n	Exacerbation Rate per patient	Exacerbation rate ratio versus placebo	
			Point estimate	p-value*
Study 254				
Spiriva Respimat 5 mcg QD	332	0.8	-1.1	0.20
Spiriva Respimat 10 mcg QD	332	0.8	-1.1	0.07
Placebo	319	1.9		
Study 255				
Spiriva Respimat 5 mcg QD	338	1.1	-0.9	0.003
Spiriva Respimat 10 mcg QD	335	1.2	-0.8	0.004
Placebo	334	2.0		
* p-value determine using the Wilcoxin-Mann-Whitney test				

With this NDA resubmission, BI submitted results of study 372 to support a reduction of COPD exacerbation claim. The study showed statistically significant superiority of Spiriva Respimat 5 mcg over placebo for COPD exacerbation. The Cox proportional hazard ratio for Spiriva Respimat 5 mcg versus placebo for time to first exacerbation was 0.69 (95% CI 0.63, 0.77, p<0.0001). Time to first COPD exacerbation is presented graphically in Figure 1 and shows clear separation between Spiriva Respimat 5 mcg and placebo. Time to first moderate-to-severe COPD exacerbation in study 372 also showed

statistically significant superiority of Spiriva Respimat 5 mcg over placebo with a hazard ratio of 0.70 (95% CI 0.63, 0.78, p<0.0001).

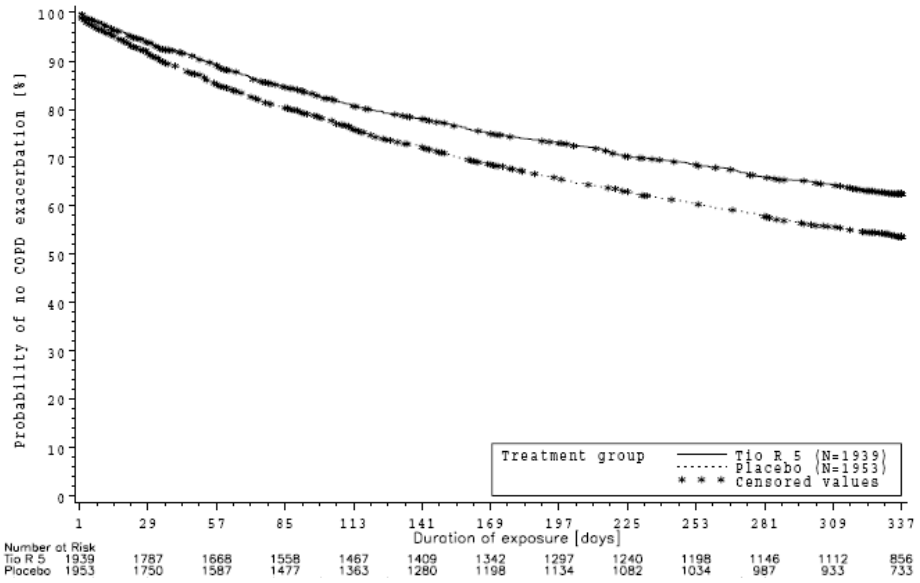

Figure 1. Kaplan-Meier plot of time to first COPD exacerbation during randomization treatment period in study 372

The active controlled study 452 also supports the exacerbation findings. The median number of days to first COPD exacerbation was 756 for Spiriva Respimat and 719 for Spiriva HandiHaler, with a hazard ratio of 0.98 (95% CI 0.93, 1.03, p=0.42).

8. Safety

a. Safety database

The safety database for Spiriva Respimat is large. There is a large amount of safety data from studies that formed the basis of approval for Spiriva HandiHaler for maintenance treatment of airflow obstruction and reduction of COPD exacerbation, which provides support for the systemic safety of tiotropium. This application contains additional safety data with Spiriva Respimat, including a large safety study that compared Spiriva Respimat to Spiriva HandiHaler (Table 2).

b. Safety findings and conclusion

The submitted data support the safety of Spiriva Respimat for use as maintenance treatment of bronchospasm associated with COPD, and for reduction of COPD exacerbation. Safety analysis of particular interest for Spiriva Respimat was death, cardiovascular safety, and stroke as discussed in section 2 above. Assessment of anticholinergic effects was also of interest because of known effect for this class of drug.

The Agency has previously concluded that tiotropium bromide administered by the inhalation route is safe for use in COPD patients, which was the basis for approval of Spiriva HandiHaler. Subsequently, safety concerns with inhaled anticholinergics were

raised as discussed in section 2 above. During review of the initial NDA, two potential safety signals emerged for Spiriva Respimat. These were increased frequency of death seen in Spiriva Respimat 48-week studies, and increased frequency of stroke seen in Spiriva HandiHaler and Spiriva Respimat studies. The safety findings of death and stroke as seen in the initial NDA review are discussed in the following section, followed by review of data with this NDA resubmission that addresses these concerns.

As discussed above, the Agency has been concerned about the increased risk of stroke and cardiovascular safety of inhaled anticholinergic products. In November 2007, BI submitted pooled analyses of 29 placebo-controlled clinical studies with Spiriva HandiHaler (25 clinical studies) and Spiriva Respimat (4 studies) that showed a potential increased risk of stroke (Table 9).

Table 9. Risk of stroke in pooled clinical studies with tiotropium

Event	Spiriva patients with event per 1000 patients treated for one year	Placebo patients with event per 1000 patients treated for one year	Excess events expressed per 1000 patients treated for one year period	Risk Ratio (95% confidence interval)
Any Stroke	8	6	2	1.4 (0.7, 2.6)
Serious Stroke	7	5	2	1.6 (0.9, 3.1)

During review of the initial NDA, it was noted that the two 48-week studies showed a mortality imbalance against Spiriva Respimat (Table 10). Review of the cases of death did not point to a particular cause. The causes of death were generally what would be expected in older patients with COPD, such as cardiac and respiratory system diseases.

Table 10. Death in 48 week studies with Spiriva Respimat in original NDA submission

	Spiriva Respimat		Placebo	Relative risk vs placebo (95% CI)	
	5 mcg	10 mcg		5 mcg	10 mcg
Study 254 (n)	332	332	319		
Within study period	7 (2.2%)	8 (2.4%)	5 (1.9%)	1.2 (0.4, 3.8)	1.4 (0.4, 4.2)
With retrospective follow-up	8 (2.5%)	8 (2.1%)	7 (2.3%)	1.1 (0.4, 3.0)	1.1 (0.4, 2.9)
Study 255 (n)	338	335	334		
Within study period	5 (1.6%)	8 (2.7%)	0 (0.0%)	undefined	undefined
With retrospective follow-up	7 (1.8%)	10 (2.8%)	2 (0.6%)	3.4 (0.7, 16.5)	5.0 (1.1, 22.9)
Study 254 + 255 (n)	670	667	653		
Within study period	12 (1.9%)	16 (2.5%)	5 (0.9%)	2.1 (0.7, 5.9)	2.9 (1.1, 8.0)
With retrospective follow-up	15 (2.1%)	18 (2.5%)	9 (1.4%)	1.6 (0.7, 3.6)	1.9 (0.9, 4.3)

These safety concerns of death and stroke precluded approval of Spiriva Respimat during the initial NDA review (initial NDA was submitted on November 16, 2007, and Complete Response action was issued on September 16, 2008). At the time of the initial NDA review, the Agency was aware that BI concluded a 6000 patient 4-year study with Spiriva HandiHaler in COPD patients (the UPLIFT Study – Understanding Potential Long-term Impacts on Function with Tiotropium, study 205.235). Since that study would

provide a large safety database, a final call on the safety risk with tiotropium was deferred until formal Agency review of the UPLIFT study results.

The UPLIFT study was submitted to the Agency to support labeling claims for reduction in COPD exacerbation and long-term effects on lung function for Spiriva HandiHaler (NDA 21-395, S29, submitted on November 17, 2008). The UPLIFT study included pre-specified mortality endpoint with independent adjudication to assess causes of death. Vital status information was available for 98% of Spiriva HandiHaler treated patients and 97% of placebo treated patients including discontinued patients out to at least 45 months post-randomization. The completeness of follow-up makes safety assessment from the UPLIFT study robust. The UPLIFT study did not show increased risk of mortality, stroke, cardiovascular death and myocardial infarction with Spiriva HandiHaler. The hazard ratios for all-cause mortality at 4 years (tiotropium:placebo) was 0.83 (95% CI 0.72, 0.95), fatal stroke was 0.85 (95% CI 0.39, 1.87), stroke SAEs was 0.97 (95% 0.69, 1.37), deaths due to cardiovascular disorder was 0.81 (95% CI 0.48, 1.36), and death due to myocardial infarction was 1.00 (95% CI 0.43, 2.30).[7] The UPLIFT study was presented and discussed at the PADAC meeting held on November 19, 2009. [8] At the PADAC discussion there was a consensus that safety concerns for Spiriva HandiHaler were alleviated.

Study 458 (conducted from October 2010 to June 2011) submitted with this NDA resubmission demonstrated that systemic exposure to tiotropium following the use of Spiriva Respimat was slightly lower compared to Spiriva HandiHaler (see section 5 above). This study supports applicability of the UPLIFT systemic safety data generated with Spiriva HandiHaler to Spiriva Respimat, and also supports systemic safety comparison between Spiriva HandiHaler and Spiriva Respimat as was done in the TIOSPIR study.

Study 452 (The TIOSPIR Study – Tiotropium Safety and Performance in Respimat), submitted with this NDA resubmission, was a comparative safety study conducted to specifically address the safety concern for Spiriva Respimat noted in the Complete Response action issued after the original NDA (original NDA was submitted on November 16, 2007, and Complete Response action was issued on September 16, 2008). Study 452 (conducted from May 2010 to May 2013) compared two doses of Spiriva Respimat to the approved dose of Spiriva HandiHaler (Table 2). There were a total of 1302 deaths in the study with similar number of events across treatment groups. For both the Spiriva Respimat doses, the upper limit of the 95% confidence intervals were <1.25 and within the pre-specified non-inferiority margin. The results of the study are shown in Table 11 and Figure 2. A sensitivity analysis using on treatment deaths (deaths occurring while on randomized treatment and within 30 days of last treatment) was consistent with the primary analysis.

[7] Summary Review and other reviews for Spiriva HandiHaler, Application Number 21-395/S029, Approval Date 12/17/2009; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021395Orig1s029.pdf
[8] FDA PADAC meeting; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021395Orig1s029.pdf

Table 11. All-cause mortality, Study 452

	SR 2.5 mcg QD *	SR 5 mcg QD *	SH 18 mcg QD *
Number of patients	5730	5711	5694
Deaths, n (%)	440 (7.7)	423 (7.4)	439 (7.7)
Comparison			
vs, SH 18 mcg, HR (95% CI)	0.996 (0.872, 1.136)	0.957 (0.837, 1.094)	
vs, SR 5 mcg, HR (95% CI)	1.040 (0.910, 1.189)		
* SR = Spiriva Respimat; SH: Spiriva HandiHaler;			

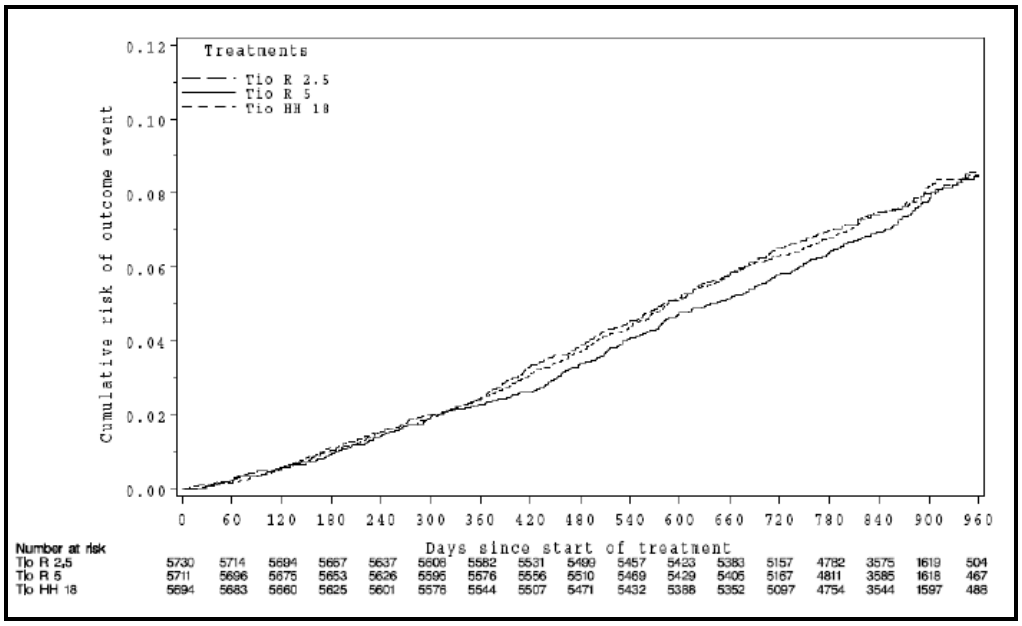

Figure 2. Kaplan-Meier plot of time to death by treatment, study 452 (TioR is Spiriva Respimat, Tio HH is Spiriva HandiHaler)

The causes of death seen in study 452 (TIOSPIR study) were varied and generally consistent with deaths commonly seen in COPD patients, who are elderly, with history of smoking, and with other concurrent medical conditions. Common causes of deaths seen in the study included complications from COPD, various cancers and specifically lung cancer, pneumonia, sudden death, sudden cardiac death, and cardiac disorder in general. The various causes of death were balanced across treatment groups. However, for the cardiac disorders, there was a numerical imbalance comparing Spiriva Respimat groups to the Spiriva HandiHaler group. Within the cardiac disorders, there was a numerical imbalance in myocardial infarction when comparing Spiriva Respimat groups to the Spiriva HandiHaler group (Table 12). On statistical analysis of these events with imbalance, while the point estimates were greater than unity, the 95% confidence intervals spanned unity. There was no evidence of dose response for these events with imbalance, suggesting that these were not related to Spiriva Respimat, but rather chance events. Some related events, such as sudden cardiac death, vascular events, and cerebrovascular accident did not show numerical imbalances. Fatal MACE analysis also did not show difference across treatment groups (Table 12). Analysis of SAEs (occurred

in a total of 5625 patients) did not show any imbalance across treatment groups, including for cardiac events. The SAEs included events that are expected to occur in this patient group. Analysis of dropouts and discontinuations and common adverse events also did not show any noticeable imbalance across treatment groups. Results of this TIOSPIR study, along with the safety data from UPLIFT study, and safety data from other studies alleviate the safety concerns of increased mortality, stroke, and cardiovascular adverse events with Spiriva Respimat.

Table 12. Adjudicated causes of death at vital status follow up for selected events of interest, data shown as number, (percentage), and [Rate per 100 patient exposure years], Study 452

	SR 2.5 mcg QD *	SR 5 mcg QD *	SH 18 mcg QD *
Total number of patients	5730	5711	5694
Total number of deaths, n (%)	440 (7.7)	423 (7.4)	439 (7.7)
Fatal MACE	119 (2.1) [0.91]	113 (2.0) [0.86]	101 (1.8) [0.77]
Selected deaths, n (%) [Rate]			
Sudden death	45 (0.8) [0.3]	38 (0.7) [0.3]	46 (0.8) [0.4]
Sudden cardiac death	37 (0.6) [0.3]	29 (0.5) [0.3]	22 (0.4) [0.4]
Cardiac disorders	22 (0.4) [0.2]	27 (0.5) [0.2]	17 (0.3) [0.1]
Myocardial infarction	9 (0.2) [0.1]	6 (0.1) [0]	2 (0) [0]
Vascular disorders	5 (0.1) [0]	3 (0.1) [0]	5 (0.1) [0]
Nervous system disorders	13 (0.2) [0.1]	16 (0.3) [0.1]	13 (0.2) [0.1]
Cerebrovascular accident	6 (0.1) [0]	10 (0.2) [0]	9 (0.2) [0]
* SR = Spiriva Respimat; SH: Spiriva HandiHaler;			

Review of the safety data from TIOSPIR and other studies did not show any new previously unknown safety signal for tiotropium or Spiriva Respimat. Laboratory data, ECG, and Holter monitoring also did not suggest a safety signal. Adverse events related to anticholinergic effects occurred with Spiriva Respimat as was to be expected, with frequencies generally similar to Spiriva HandiHaler and other inhaled anticholinergic drug products.

c. REMS/RiskMAP

BI submitted a Risk Management plan for Spiriva Respimat that consists of routine pharmacovigilance practices. A REMS is not necessary for Spiriva Respimat.

9. Advisory Committee Meeting

During review of the initial NDA, an advisory committee meeting was not convened. Initially the Division tentatively planned for a Pulmonary and Allergy Drug Advisory Committee (PADAC) meeting for mid-June 2008 to discuss the mortality signal with Spiriva Respimat. The Division later cancelled the PADAC meeting with the reasoning that to fully discuss the mortality and stroke signal, FDA review and analyses of the UPLIFT study results, and other relevant studies that may be conducted by BI were necessary. It was thought that this application would be discussed at a PADAC meeting during review of NDA resubmission when further data were available.

As discussed in section 8 above, the UPLIFT study was submitted to the Agency to support labeling claims for reduction in COPD exacerbation and long-term effects on

lung function for Spiriva HandiHaler (NDA 21-395, S29, submitted on November 17, 2008). The UPLIFT study was presented and discussed at the PADAC meeting held on November 19, 2009. [9] At the PADAC discussion there was a consensus that safety concerns for Spiriva HandiHaler was alleviated.

A meeting of the PADAC was held on August 14, 2014, to discuss this application for Spiriva Respimat. The issues for discussion were the adequacy of the efficacy data to support the use of Spiriva Respimat as maintenance treatment of bronchospasm associated with COPD, and for reduction of COPD exacerbation; and the safety data. The history of the safety concerns of increased mortality, stroke, and cardiovascular adverse events with Spiriva HandiHaler and Spiriva Respimat, and the safety studies, particularly TIOSPIR, were discussed. The panel members concluded that there were sufficient data to support the efficacy of Spiriva Respimat as maintenance treatment of bronchospasm associated with COPD and for reducing of COPD exacerbations (voted 14 yes, 0 no, and 0 abstain), and that the safety data alleviates the safety concerns for Spiriva Respimat (voted 9 yes, 4 no, and 0 abstain). Regarding approvability, which is essentially the sum of the demonstration of efficacy and safety, the panel members concluded in favor of approval of Spiriva Respimat (voted 10 yes, 3 no, 0 abstain).

10. Pediatric

COPD is an adult disease, therefore, specific pediatric studies would not be required that relate to this action specific to COPD.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two sites during the original NDA review. The clinical review team recommended these sites. These sites enrolled the largest number of patients in the pivotal phase 3 studies and one of these two sites had the highest number of deaths. Audit of these sites did not show any major irregularities. Review of the application during the initial NDA review and review of this NDA resubmission did not identify any irregularities that would raise concerns regarding data integrity. No ethical issues were present. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

BI submitted acceptable financial disclosure statements. A total of 25 investigators had significant financial interest in BI or Pfizer (co-marketer for Spiriva). The number of subjects that these investigators enrolled was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that these financial interests 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.

[9] FDA PADAC meeting; http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/021395Orig1s029.pdf

12. Labeling

a. Proprietary Name

There are no issues with the proprietary name as the root name Spiriva was previously reviewed and found to be acceptable, and Respimat is appropriate name for the delivery platform.

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, SEALD, 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 Division and BI have agreed on the final label language.

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 will be no Medication Guide for Spiriva Respimat.

13. Action and Risk Benefit Assessment

a. Regulatory Action

BI has submitted adequate data to support approval of Spiriva Respimat (tiotropium bromide inhalation spray) for maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbation, at the dose of 5 mcg (2 inhalation of 2.5 mcg per spray) once daily. The regulatory action on this application is Approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment supports approval of Spiriva Respimat for use in patients with COPD. The safety concerns of increased mortality, stroke, and cardiovascular adverse events for Spiriva Respimat have been adequately addressed as reviewed in section 8 above. The safety findings related to anticholinergic effects are known safety risks of this class of drug, and occurred in frequencies with Spiriva Respimat that were comparable to Spiriva HandiHaler. The efficacy data submitted were adequate to support the indications of maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbation. The proposed dose of 5 mcg once daily is supported by the safety and efficacy data, and also is comparable to the approved dose of Spiriva HandiHaler based on systemic exposure and FEV1 measures.

c. Post-marketing Risk Management Activities

No post-marketing risk management activities are required.

d. Post-marketing Study Commitments

None.

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/s/

BADRUL A CHOWDHURY
09/24/2014