# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**021936s000**

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Cross-Discipline Team Leader Review

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| **Date** | September 10, 2014 |
| **From** | Anthony G. Durmowicz, M.D. |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA # Supplement#** | NDA 21936 |
| **Applicant** | Boehringer-Ingelheim |
| **Date of Submission** | June 2, 2014 |
| **PDUFA Goal Date** | March 24, 2014 |
| | |
| **Proprietary Name / Established (USAN) names** | Spiriva Respimat/tiotropium inhalation spray |
| **Dosage forms / Strength** | Inhalation Spray/2.5 mcg/actuation |
| **Proposed Indication(s)** | …for long-term, once daily maintenance treatment of bronchospasm associated with COPD and for reduction of COPD exacerbations |
| **Recommended:** | Approval |

# 1. Introduction

Boehringer Ingelheim (BI) originally submitted the NDA for Spiriva Respimat (tiotropium bromide inhalation spray) 5 mcg once daily for the long-term, once daily maintenance treatment of bronchospasm associated with COPD and for reduction of COPD exacerbations on November 16, 2007. A Complete Response was issued on September 16, 2008, citing two deficiencies: safety concerns of death and stroke, and lack of substantial evidence to support a reduction of COPD exacerbation claim. In the resubmission, BI submitted the results of a large safety study (205.452 or TIOSPIR) that compares Spiriva Respimat and the related tiotropium product, Spiriva HandiHaler, to support the safety of Spiriva Respimat. In addition, BI submitted the results of new study 205.372 to support the COPD exacerbation claim. This review will summarize the Spiriva Respimat program with a focus on new data submitted to support the safety of the product. For a more detailed discussion of the entire development program, please see the primary clinical review by Dr. Robert Lim, the statistical safety review by Dr. Bo Li, and the previous CDTL review from the original NDA submission by Dr. Sally Seymour.

# 2. Background

Spiriva Respimat inhalation spray is a new formulation of tiotropium bromide, which is the active pharmaceutical ingredient in the currently approved dry powder inhaler, Spiriva HandiHaler. Spiriva HandiHaler consists of tiotropium bromide in a dry powder formulation contained in capsules and administered with the HandiHaler inhalation device. Spiriva HandiHaler was approved on January 30, 2004, for the long term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. The regulatory history that is relevant to this application involves both formulations of tiotropium. While both products contain tiotropium, each device has different delivery characteristics with different delivered dose and efficacy is dependent on the local effects in the lungs. Therefore, each product requires a clinical development program to assess efficacy and safety. For safety, local adverse reactions (e.g. cough and dry mouth) are common, but systemic adverse reactions (e.g. urinary retention) are also seen as tiotropium is also absorbed systemically. Below the potential systemic safety signals that were identified for tiotropium after approval of Spiriva HandiHaler and the regulatory history of these safety issues are outlined.

*Stroke and Cardiovascular Safety Concerns*

- In November 2007, BI voluntarily submitted a document to the Agency that described a potential stroke safety signal with tiotropium. As part of routine safety monitoring, BI pooled safety data from clinical trials with tiotropium and noted a numerical increase in stroke adverse events. The pooled data included results from 29 controlled clinical trials, 25 with Spiriva HandiHaler and 4 with Spiriva Respimat, which reflected 13,544 patients contributing 4572 person years of exposure to tiotropium. Based upon BI's analysis, there was a numerical increase in the risk ratio for stroke of 1.37 (95% CI: 0.73, 2.56) with use of tiotropium. Although there was uncertainty of the risk and the analyses were not adjusted for multiplicity, because of the seriousness of stroke and the

Agency's commitment to inform the public about ongoing safety reviews, on March 18, 2008, the Agency released an Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler) that described the preliminary information regarding stroke.[1]

- In September 2008, a meta-analysis was published in the Journal of the American Medical Association evaluating cardiovascular risk of the inhaled anticholinergics, tiotropium and ipratropium.[2] The authors analyzed 17 randomized, controlled clinical trials for the primary combined outcome of cardiovascular death, myocardial infarction (MI), or stroke, and showed a relative risk of 1.58 (95% CI 1.21, 2.06) for inhaled anticholinergics compared to placebo and concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke.

*Spiriva Respimat NDA – 1st Cycle*

- BI submitted the original NDA for Spiriva Respimat in November 2007. Review of clinical data from the clinical program for this new formulation showed that there was a numerical increase in deaths favoring placebo in the two 48-week clinical trials, Studies 254 and 255. There was a numerical trend in dose response for the 5 mcg and 10 mcg dose and the death imbalance. Pharmacokinetic data suggested the possibility of higher systemic exposure of tiotropium with Spiriva Respimat compared to Spiriva HandiHaler. In addition to the death imbalance noted in the clinical program for Spiriva Respimat, the above concerns regarding stroke and cardiovascular safety had been raised for tiotropium during the review cycle and were not resolved. Therefore, a Complete Response was issued on September 16, 2008, citing two deficiencies, safety concerns of death and stroke, and lack of substantial evidence to support the reduction of COPD exacerbation claim. The safety concern was the main issue that precluded approval.

*UPLIFT*

- In November 2008, BI submitted the results of a 4-year, placebo-controlled, parallel group trial with Spiriva HandiHaler in approximately 6000 patients with moderate-severe COPD. The trial is called Understanding Potential Long-term Impacts on Function with Tiotropium or UPLIFT. UPLIFT was designed to assess the effects of Spiriva HandiHaler on the rate of decline of lung function in patients with COPD. While primarily an efficacy study, UPLIFT also provided a substantial amount of controlled long-term safety data for Spiriva HandiHaler as it doubled the existing safety database. To improve the collection and assessment of safety data, BI amended the UPLIFT protocol to specify a Mortality Adjudication Committee that centrally adjudicated all reported deaths and to collect vital status on prematurely discontinued patients. Overall, the results showed that Spiriva HandiHaler did not increase the risk of overall death, MI, or stroke compared to placebo.

*Pulmonary Allergy Advisory Committee (PADAC) – November 19, 2009*

- Because of the ongoing concerns with tiotropium regarding stroke, MI, and cardiovascular death, a PADAC meeting was held on November 19, 2009, to discuss the results of UPLIFT. The AC panel voted that the UPLIFT study adequately

addressed the potential safety signal of stroke and cardiovascular events. Based upon the input from the PADAC and FDA review of UPLIFT, FDA issued a follow up to the Early Communication in January 2010, which noted that UPLIFT showed that there was no significant increase in stroke, MI, or cardiovascular death with Spiriva HandiHaler. [3]

During the PADAC meeting, the Agency also presented information on the death imbalance noted in the Spiriva Respimat program. The presentation included not only the pivotal phase 3 trials from the original NDA submission (Studies 254 and 255), but also Study 372, which was a third 48 week placebo controlled study with Spiriva Respimat 5 mcg that on preliminary review also showed a numerical imbalance in mortality, favoring placebo. As a result, collection of additional safety data for Spiriva Respimat was suggested. During the AC meeting, BI noted its plans to conduct a large safety trial with Spiriva Respimat.

*TIOSPIR (Study 205.452)*

- While the safety issues of stroke and cardiovascular events for Spiriva HandiHaler were addressed by UPLIFT, the safety of Spiriva Respimat remained an open issue. In September 2009, BI proposed a large outcome study, non-inferiority design comparing Spiriva Respimat 2.5 mcg, 5 mcg, and Spiriva HandiHaler (Study 205.452). The Division provided feedback on the protocol and recommended an event driven trial with the primary endpoint of mortality and requested justification of the proposed non-inferiority margin. The final protocol was submitted March 2010 and found acceptable by the Division. This study is also known as Tiotropium Safety and Performance in Respimat or TIOSPIR. Given that TIOSPIR compares Spiriva Respimat to Spiriva HandiHaler, the safety of Spiriva Respimat relies on the safety of Spiriva HandiHaler and the results of UPLIFT. Therefore, the safety section will also include a brief discussion of UPLIFT.

To further link the safety of Spiriva Respimat to Spiriva HandiHaler, BI conducted a dedicated pharmacokinetic study (Study 205.458) comparing the two products. The results of the study show that systemic exposure to tiotropium following the use of Spiriva Respimat 5 mcg was slightly lower compared to Spiriva HandiHaler.

# 3. Chemistry, Manufacture, and Controls

As noted above, tiotropium bromide is the active pharmaceutical ingredient in the currently approved Spiriva HandiHaler. For Spiriva Respimat, tiotropium bromide is formulated as a sterile aqueous solution with standard excipients benzalkonium chloride, edetate disodium, water for injection, and hydrochloric acid (to adjust pH). There is no propellant. Each actuation delivers 2.5 mcg of tiotropium from the mouthpiece. The proposed dose is two actuations (5 mcg) once daily.

The formulation is contained in a cartridge, which will be supplied with the Respimat inhaler (Figure 1). 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. 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 on October 2011 and another, Striverdi Respimat (olodaterol hydrochloride), approved for marketing on August 2, 2014.

**Figure 1: Spiriva Respimat**

# 4. Nonclinical Pharmacology/Toxicology

The general nonclinical pharmacology and toxicology considerations for tiotropium bromide were addressed in the Spiriva HandiHaler application (NDA 21-395). Those studies are adequate for this application because the nominal dose of Spiriva Respimat is 5 mcg, which is lower than the nominal dose of Spiriva HandiHaler (18 mcg), and the exposure to tiotropium in humans from these two products are similar.

# 5. Clinical Pharmacology/Biopharmaceutics

The general clinical pharmacology and biopharmaceutics considerations for tiotropium bromide were addressed in the Spiriva HandiHaler application (NDA 21-395). The Spiriva HandiHaler program also included a thorough QT study with Spiriva HandiHaler doses of 18 mcg and 54 mcg. The results did not show significant QT prolongation.

*Original NDA Submission*

Pharmacokinetic sampling performed in the two 4-week safety and efficacy studies 205.249 and 205.250 showed that mean systemic exposure (AUC) and urinary excretion of tiotropium were numerically higher with Spiriva Respimat 5 mcg and 10 mcg doses compared to Spiriva HandiHaler 18 mcg dose, but in Study 205.250, exposure from the Spiriva Respimat 5 mcg dose was close to exposure from the Spiriva HandiHaler 18 mcg dose (Table 1). Based on the results of this pharmacokinetic comparison, and efficacy findings, BI proposed 5 mcg of Spiriva Respimat as the recommended dose that matches the 18 mcg dose of Spiriva HandiHaler.

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

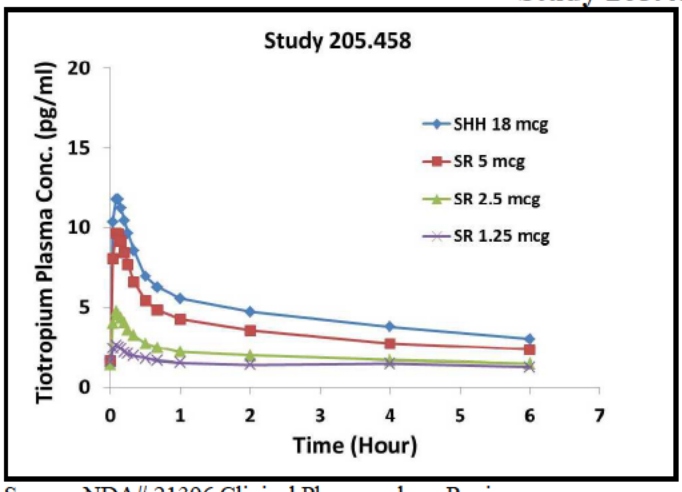
| | Spiriva Respimat 5 mcg | Spiriva Respimat 10 mcg | Spiriva HandiHaler 18 mcg |
|---|---|---|---|
| **Study 205.249** | | | |
| AUC 0-6 ss, pg.hr/mL | 26.1 | 64.6 | 20.2 |
| AUC 0-24 ss, pg.hr/mL | 63.5 | 148 | 52.2 |
| Urinary excretion 0-12 hrs, ng | 561 | 1230 | 428 |
| **Study 205.250** | | | |
| 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 |

Source: NDA#21936, CSR u05-1949 (Study 205.249), Tables 11.5.2:3 & 11.5.2:4;
CSR u04-2041 (Study 205.250),Tables 11.5.2:2 & 11.5.2:3

*Resubmission*

BI conducted a dedicated PK study 205.458 to provide more robust information on the comparative pharmacokinetics of Spiriva Respimat and Spiriva HandiHaler, which was included in this NDA resubmission package. Study 205.458 was a 4 week, randomized, placebo and active-controlled, 5-way crossover trial in 113 patients with COPD. Three doses of Spiriva Respimat were included: 1.25 mcg, 2.5 mcg, and 5 mcg as well as Spiriva HandiHaler 18 mcg. 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 corresponding 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 as shown below in Figure 2. Study 205.458 provides more reliable and robust pharmacokinetic data due to the nature of the rich-PK sampling design and a more sensitive analytical assay.

**Figure 2: Geometric Mean Tiotropium Plasma Concentration Profiles Study 205.458**




Source: NDA# 21396 Clinical Pharmacology Review

# 6. Clinical Microbiology

Not applicable

# 7. Clinical/Statistical- Efficacy

BI conducted a clinical program for the original NDA submission that included studies comparing Spiriva Respimat to Spiriva HandiHaler primarily for dose selection of Spiriva Respimat. The original NDA submission also included two 12-week and two 48-week efficacy and safety studies with Spiriva Respimat. The key clinical studies submitted in the original NDA are shown in the beginning of Table 2 while the clinical studies submitted in the Complete Response are shown at the end of Table 2. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the section 8.

**Table 2 Summary of Spiriva Respimat Clinical Development Program**

| Original NDA Submission | | | | | | |
|---|---|---|---|---|---|---|
| **Study No.** | **Description** | **Subjects** | **Design** | **Dose** | **Duration** | **Endpoints** |
| 205.127<br>France<br><br>Mar 1998 - Apr 1999 | P2a PD and PK dose ranging study | 202 subjects with COPD | R, DB, PC, AC, PG | 1.25 mcg Spiriva Respimat QD<br>2.5 mcg Spiriva Respimat QD<br>5 mcg Spiriva Respimat QD<br>10 mcg Spiriva Respimat QD<br>20 mcg Spiriva Respimat QD<br>18 mcg Spiriva HandiHaler QD<br>Placebo Respimat QD<br>Placebo HandiHaler QD | 3 weeks | Trough $FEV_1$ |
| 205.249<br>United States<br>Canada<br>Nov 2002-Apr 2004 | P3 cross over comparison of Spiriva Respimat and Spiriva HandiHaler | 131 subjects with COPD | R, DB, DD, AC, PC, XO | 5 mcg Spiriva Respimat QD<br>10 mcg Spiriva Respimat QD<br>18 mcg Spiriva HandiHaler QD<br>Placebo Respimat QD<br>Placebo HandiHaler QD | 4 weeks | Trough FEV1 (non-inferiority) |
| 205.250<br>Netherlands<br>Belgium<br>Aug 2002 – July 2003 | P3 cross over comparison of Spiriva Respimat and Spiriva HandiHaler | 76 subjects with COPD | R, DB, DD, AC, PC, XO | 5 mcg Spiriva Respimat QD<br>10 mcg Spiriva Respimat QD<br>18 mcg Spiriva HandiHaler QD<br>Placebo Respimat QD<br>Placebo HandiHaler QD | 4 weeks | Trough FEV1 (non-inferiority) |
| 205.251<br>Multinational<br>Nov 2002-Dec 2003 | P3 12-week safety and efficacy trial | 361 subjects with COPD | R, DB, DD, PC, AC, PG | 5 mcg Spiriva Respimat QD<br>10 mcg Spiriva Respimat QD<br>36 mcg ipratropium bromide QID<br>Placebo Respimat QD<br>Placebo MDI QID | 12 week | Trough FEV1 |
| 205.252<br>Multinational<br>Nov 2002-Dec 2003 | P3 12-week safety and efficacy trial | 358 subjects with COPD | R, DB, DD, PC, AC, PG | 5 mcg Spiriva Respimat QD<br>10 mcg Spiriva Respimat QD<br>36 mcg ipratropium bromide QID<br>Placebo Respimat QD<br>Placebo MDI QID | 12 week | Trough FEV1 |
| 205.254<br>Multinational<br>Feb 2003 – June 2005 | P3 48 week safety and efficacy trial | 983 subjects with COPD | R, DB, PC, PG | 5 mcg Spiriva Respimat QD<br>10 mcg Spiriva Respimat QD<br>Placebo Respimat QD | 48 week | Trough FEV1, SGRQ, TDI, exacerbations (combined) |
| 205.255<br>Multinational<br>Mar 2003 – | P3 48 week safety and efficacy trial | 1007 subjects with COPD | R, DB, PC, PG | 5 mcg Spiriva Respimat QD<br>10 mcg Spiriva Respimat QD<br>Placebo Respimat QD | 48 week | FEV1, SGRQ, TDI exacerbations (combined) |

| | | | | | | |
|---|---|---|---|---|---|---|
| June 2005 | | | | | | |
| **Complete Response Submission** | | | | | | |
| 205.458<br>Europe<br>Oct 2010-<br>June 2011 | 4 week pharmacokinetic trial | 154 subjects with COPD | R, DB, PC, AC, XO | 1.25 mcg Spiriva Respimat QD<br>2.5 mcg Spiriva Respimat QD<br>5 mcg Spiriva Respimat QD<br>18 mcg Spiriva HandiHaler QD<br>Placebo Respimat QD | 4 week | Plasma and urine for tiotropium<br>FEV1 $AUC_{0-6h}$ |
| 205.372<br>Multinational (31 countries)<br>Oct 2006-<br>Jan 2009 | One year efficacy and safety trial | 3991 subjects with COPD | R, DB, PC, PG | 5 mcg Spiriva Respimat QD<br>Placebo Respimat QD | 48 weeks | Trough FEV1<br>Time to 1st COPD exacerbation |
| 205.452<br>Multinational<br>May 2010-<br>May 2013 | Comparative safety trial (TIOSPIR) | 17116 subjects with COPD | R, DB, AC, DD, PG | 2.5 mcg Spiriva Respimat QD<br>5 mcg Spiriva Respimat QD<br>18 mcg Spiriva HandiHaler QD<br>Placebo Respimat QD<br>Placebo HandiHaler QD | 3.5 years | Mortality<br>Time to 1st COPD exacerbation |
| **Additional studies in Complete Response with Spiriva Respimat as comparator in other development program for safety only** | | | | | | |
| 1205.14<br>Multinational<br>Sept 2007-<br>May 2009 | Dose ranging trial for another development program | 389 subjects with COPD | R, DB, PC, PG | 5 mcg Spiriva Respimat QD<br>Placebo Respimat QD<br>Investigational therapy | 4 weeks | Trough FEV1 |
| 1205.04<br>United States, Netherlands, Belgium<br>July 2005 – May 2006 | Safety and efficacy trial for another development program | 2080 subjects with COPD | R, DB, PC, PG | 5 mcg Spiriva Respimat QD<br>Placebo Respimat QD<br>Investigational therapy | 24 weeks | Trough FEV1 |
| R=randomized, DB = double-blind, PC = placebo-controlled, PG = parallel group, DD = double dummy, XO= cross over, AC = active controlled | | | | | | |

*Dose Ranging*

To support dose selection for the phase 3 development program, BI conducted a randomized, double-blind, placebo controlled, 3 week, dose-ranging trial in 200 patients with COPD (Study 205.127). Patients were randomized to Spiriva HandiHaler, placebo, or one of 5 Spiriva Respimat treatment groups. Safety assessments included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, and ECG. The primary efficacy endpoint was change from baseline trough FEV1 and the results are shown in Table 3.

**Table 3 Results of Dose Ranging Study 205.127**

| Treatment Group | n | Mean Change from Baseline Trough $FEV_1$ (L)* 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† |
| Placebo Respimat QD | 24 | 0.02 | |
| Spiriva HandiHaler 18 mcg QD | 25 | 0.23 | 0.32† |
| Placebo HandiHaler QD | 23 | -0.09 | |

*adjusted for baseline †statistically significant
Source: NDA 21936, CSR u00-0077.pdf (Study 205.127), page 49

The results showed that the 5 mcg and 20 mcg Spiriva Respimat treatment group responses were statistically significant compared to placebo, but there is no clear dose response. The 1.25 and 2.5 mcg doses were not significantly different from placebo and the 20 mcg dose did not appear to show a benefit over the 5 and 10 mcg doses; however, there was an increase in AEs (dry mouth) with higher doses. Based upon the results of this study, BI chose to carry forward the 5 mcg and 10 mcg dose into the phase original 3 program.

*Efficacy Study Design*

Unless otherwise noted, the phase 3 studies were randomized, double-blind, placebo controlled and parallel group design in patients with moderate-to-severe COPD. The phase 3 clinical studies enrolled patients with a diagnosis of moderate to severe COPD, with the following pertinent entry criteria: a) 40 years of age and older; b) FEV1/FVC $\leq$ 70% and FEV1 $\leq$ 60%; and c) current or ex-smokers with a smoking history of > 10 years. Pertinent exclusion criteria included a recent history of myocardial infarction (6 months or less) and unstable or life-threatening cardiac arrhythmia. Unless otherwise noted, the primary efficacy variable was trough FEV1 at the end of the treatment period. Trough FEV1 was defined as FEV1 measured at -10 minutes at the end of the 24-hour dosing interval. Safety assessments generally included recording of adverse events, vital signs, physical examinations, clinical laboratory measures, and ECG. Holter monitoring was assessed in a subset of patients in Studies 254 and 255 (24 hours) and in patients in Study 458 (6.5 hours).

Studies 249 and 250 were 4 weeks duration, cross-over design and also included Spiriva HandiHaler as a comparator. Studies 251 and 252 were 12 weeks duration. Studies 254 and 255 were 48 weeks duration and the pivotal efficacy studies in the original NDA submission. These studies 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 included the Mahler TDI for the purpose of registration in EU and no claims are being requested based on the SGRQ. Therefore, for the purpose of US review, the endpoints for consideration are trough FEV1 and COPD exacerbation.

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 $\geq$ 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 generally closely follows the definitions used in the literature.[4] Exacerbations were categorized as mild, moderate, and severe:

- mild – treated at home without visit to health care facility

- moderate – visit to outpatient facility or ER
- severe – hospital admission or ER visit greater than 24 hours

Study 372 was 48 weeks duration. Patients were allowed to continue LABA and ICS/LABA use. The study had two co-primary efficacy variables: trough FEV1 at the end of the 48-week treatment period, and time to first COPD exacerbation. The definition of COPD exacerbation was similar to studies 254 and 255. All patients were to be followed for vital status and deaths were adjudicated by an independent panel.

Study 452 (TIOSPIR) had a different design and objective, so it is important to describe the study design. Study 452 was 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. Two doses of Spiriva Respimat were included: 2.5 mcg and 5 mcg. The study was event driven and designed to end after approximately 1266 fatal events (approximately 3.5 years). Patients were excluded if recent history of MI, unstable/life-threatening cardiac arrhythmia, and hospitalization for cardiac failure NYHA Class III or IV during the last year. Patients were allowed to continue stable baseline respiratory medications (except anticholinergics), including LABA and ICS/LABA.

The first primary endpoint was time to all-cause mortality and the second primary endpoint was time to first COPD exacerbation. There were 3 hypotheses tested comparing Spiriva Respimat to Spiriva HandiHaler in the following order: 1) non inferiority time to death 5 mcg; 2) non-inferiority time to death 2.5 mcg; and 3) superiority time to 1st COPD exacerbation. For the non-inferiority analysis, the upper limit of the 95% CI was to exclude 1.25. The definition of COPD exacerbation was similar to studies 254 and 255. The study also included a PFT sub-study in which a randomized subset of patients had spirometry every 24 weeks until study close-out. The PFT sub study was analyzed through week 120 and also specified a non-inferiority analysis with the lower limit of the 95% CI to exclude -50mL.

Safety assessments included analysis of adverse events. All patients were to be followed up until the end of the study for vital status regardless of continuation of study treatment. All causes of death were adjudicated by an independent adjudication committee. The following were protocol defined outcome events: COPD exacerbations, pneumonias, myocardial infarctions, strokes, and transient ischemic attacks. The protocol defined outcome events were centrally monitored to determine if the events met the pre-specified definition outlined in the protocol. Analyses of major adverse cardiovascular events (MACE) were specified using the following definition:

- Fatal events in system organ classes cardiac and vascular disorders
- Sudden death, cardiac death, or sudden cardiac death preferred terms
- Myocardial infarction (serious and non-serious)
- Stroke (serious and non-serious)
- TIA (serious and non-serious)

However, MACE events were not adjudicated by an independent committee.

*Efficacy Results - Bronchodilator Effect*

Use of Spiriva Respimat 5 mcg for maintenance treatment of bronchospasm associated with COPD is supported by studies submitted with the initial NDA and study 372 submitted with this NDA resubmission. The results for the trough FEV1 from the 4 week (active controlled) studies are shown in Table 4 and the results for the remainder of the phase 3 studies are shown in Table 5. As shown in the tables, improvement in trough FEV1 for patients treated with Spiriva Respimat 5 mcg was significant compared to placebo in multiple studies at 4 weeks, 12 weeks, and 48 weeks and provided similar treatment effect compared to Spiriva HandiHaler in Study 250. Spiriva Respimat 10 mcg did not provide a consistent benefit over Spiriva 5 mcg.

**Table 4 Mean trough FEV1 (L) treatment difference at 4 weeks**

| | 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 18 mcg 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 | -0.01 | -0.05, 0.03 | 0.028 |
| Spiriva HandiHaler 18 mcg QD | 0.13 | 0.09, 0.17 | <0.001 | | | |

* superiority; p-values are one-sided; † non-inferiority; p-values are one sided
Source: NDA 21936 CSR u05-1949 (Study 205.249), page 89; CSR u04-2041 (Study 205.250), page 85

**Table 5 Mean Trough $FEV_1$ (L) at End of Treatment Period**

| Full analysis set | Spiriva Respimat 5mcg | Spiriva Respimat 10mcg | Placebo |
|---|---|---|---|
| **Study 205.251** | | | |
| Trough $FEV_1$* | 1.34 | 1.41 | 1.23 |
| Difference from Placebo (95% CI) | 0.11 (0.04, 0.18) p = 0.003 | 0.18 (0.11, 0.25) p < 0.0001 | |
| **Study 205.252** | | | |
| Trough $FEV_1$* | 1.11 | 1.10 | 0.99 |
| Difference from Placebo (95% CI) | 0.12 (0.07, 0.18) p < 0.0001 | 0.12 (0.06, 0.17) p = 0.0001 | |
| **Study 205.254** | | | |
| Trough $FEV_1$* | 1.17 | 1.19 | 1.03 |
| Difference from Placebo (95% CI) | 0.14 (0.10, 0.18) p < 0.0001 | 0.16 (0.12, 0.20) p < 0.0001 | |
| **Study 205.255** | | | |
| Trough $FEV_1$* | 1.14 | 1.16 | 1.02 |
| Difference from Placebo (95% CI) | 0.11 (0.08, 0.15) p < 0.0001 | 0.14 (0.11, 0.18) p < 0.0001 | |
| **Study 205.372** | | | |
| Trough $FEV_1$§ | 1.23 | | 1.13 |
| Difference from Placebo (95% CI) | 0.10 (0.09, 0.12) p < 0.0001 | | |

* adjusted for center, smoking status, and baseline
§ adjusted for baseline, pooled center, and LABA use at randomization
Source: NDA 21936, CSR u04-3400 (Study 251), page 93, 175; CSR u04-3343 (Study 252), page 96, 183; CSR u05-2112-01 (Study 254), page 117, 239; CSR u05-2113 (Study 255), page 114, 238; CSR 0205-0372-01-15 (Study 372), page 86

TIOSPIR (Study 452) also included a PFT sub-study in which a randomized subset of patients had spirometry every 24 weeks until study close-out. As in Study 250, the results for Spiriva Respimat 5 mcg were similar to Spiriva HandiHaler.

*SGRQ*

BI did not seek an SGRQ benefit statement in the product label. The submitted data from multiple studies show numerical benefit on total SGRQ score with Spiriva Respimat, and the differences over placebo are statistically significant, but the minimum clinically important difference of 4 was not achieved for the 5 mcg dose. The submitted data provide secondary support for efficacy of Spiriva Respimat, but the data do not support an SGRQ labeling claim.

*Exacerbations*

During the initial NDA review it was concluded that reduction of COPD exacerbation was not supported by the submitted data. Of the two studies that assessed exacerbation, only Study 255 showed statistically significant superiority for Spiriva Respimat over placebo (Table 6). Although pre-specified combined analyses of the two studies showed statistical significance, this was not deemed to be adequate because the pooled studies were considered as one study.

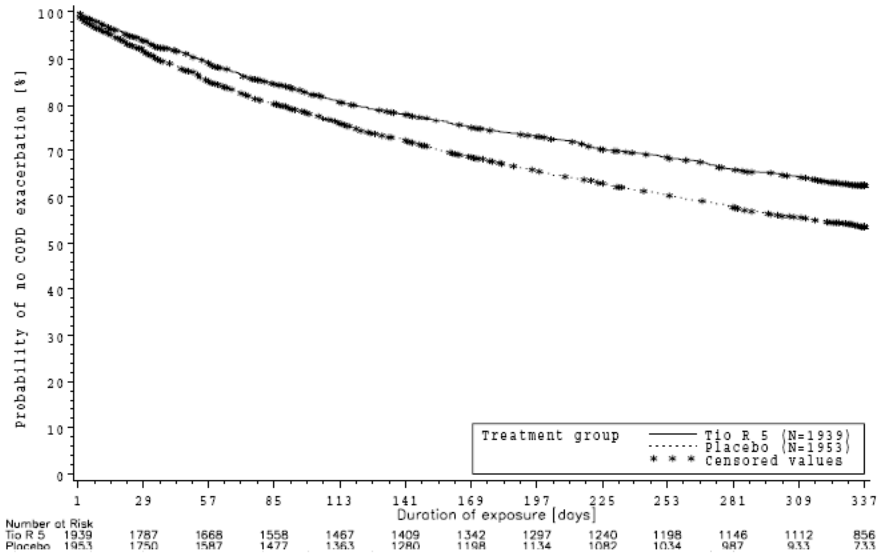
**Table 6 Mean Exacerbation Rate* Per Year**

| | Study 205.254 | | | Study 205.255 | | | Pooled | | |
|---|---|---|---|---|---|---|---|---|---|
| | SR5 n=332 | SR10 n=332 | Pbo n=319 | SR5 n=338 | SR10 n=335 | Pbo n=334 | SR5 n=670 | SR10 n=667 | Pbo n=653 |
| Exacerbation rate* | 0.7 | 0.8 | 1.9 | 1.1 | 1.2 | 2.0 | 0.93 | 1.02 | 1.91 |
| p value vs. pbo | 0.2 | 0.07 | | 0.003 | 0.004 | | 0.002 | 0.0008 | |

SR = Spiriva Respimat, Pbo = placebo; *(number of exacerbations/number of days of treatment) per year of exposure
Wilcoxon Mann Whitney test
Source: NDA 21936, Statistical Review from 1st cycle dated August 26, 2008

With this NDA resubmission, BI submitted results of study 372 to support a reduction of COPD exacerbation claim. The study showed superiority of Spiriva Respimat 5 mcg over placebo for time to first 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, presented graphically in Figure 3, shows separation between Spiriva Respimat 5 mcg and placebo. Other secondary analyses also were supportive, including time to first moderate or severe COPD exacerbation, time to 1st hospitalization, and number of COPD exacerbations.

**Figure 3: Kaplan-Meier plot of time to first COPD exacerbation during randomization treatment period in study 372**



Source: NDA#21936, CSR Study 372, Figure 15.2.2.1

The results of Study 452 (TIOSPIR) are also supportive of the exacerbation findings for Spiriva Respimat. In TIOSPIR, time to 1st COPD exacerbation was a pre-specified second primary endpoint. The hazard ratio for Spiriva Respimat 5 mcg compared to Spiriva HandiHaler was 0.98 (95% CI: (0.93, 1.03). Although Spiriva Respimat 5 mcg did not achieve statistical significance compared to Spiriva HandiHaler, the results suggest that the effects on exacerbation are similar across products.

***Summary of Efficacy***

The submitted studies provide replicate evidence of statistically significant effect of Spiriva Respimat 5 mcg compared to placebo on trough FEV1 at 12 and 48 weeks. The mean treatment effect size ranges from 100-140 mL and appears to be similar to the effect size for Spiriva HandiHaler. With the data from Study 205.372, there is now replicate evidence of statistically significant effect of Spiriva Respimat 5 mcg on COPD exacerbations (rate and time to first COPD exacerbation). The results of TIOSPIR suggest that the effects on COPD exacerbation are similar for Spiriva Respimat 5 mcg and Spiriva HandiHaler.

# 8. Safety

*Background on Safety Issues*

As discussed in the background section, concerns regarding stroke were raised during the first review period. In addition, a published meta-analysis suggested a significantly increased risk of cardiovascular death, MI, or stroke for inhaled anticholinergics compared to placebo.[2]

During review of the initial NDA, the two 48-week studies (254 and 255) showed a mortality imbalance against Spiriva Respimat (see top portion of Table 7). The results were most notable in Study 205.255, in which there were no deaths in the placebo group. The most common causes were unknown and neoplasm, primarily lung cancer, followed by COPD exacerbation and myocardial infarction. Based upon review of cause of death, there was no obvious pattern that could explain the imbalance.

**Table 7 Fatal Adverse Events in 48 Week Clinical Trials with Spiriva Respimat**

| Number Fatal Adverse Events (%)* | Spiriva Respimat 5 mcg | Spiriva Respimat 10 mcg | Placebo | Relative Risk vs. Placebo (95% CI) † | |
|---|---|---|---|---|---|
| | | | | Spiriva Respimat 5 mcg | Spiriva Respimat 10 mcg |
| **Original NDA Submission** | | | | | |
| **Study 254 (n)** | 332 | 332 | 319 | | |
| Within Study | 7 (2.2%) | 8 (2.4%) | 5 (1.9%) | 1.2 (0.4, 3.8) | **1.4 (0.4, 4.2)** |
| With Vital Status | 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 | 5 (1.6%) | 8 (2.7%) | 0 (0.0%) | undefined | **undefined** |
| With Vital Status | 7 (1.8%) | 10 (2.8%) | 2 (0.6%) | 3.4 (0.7, 16.5) | **5.0 (1.1, 22.9)** |
| **Results available for November 2009 PADAC Meeting & Resubmission** | | | | | |
| **Study 372 (n)** | 1952 | | 1965 | | |
| Within Study | 30 (1.5%) | | 19 (1.0%) | 1.5 (0.9, 2.7) | **NA** |
| With Vital Status | 52 (2.7%) | | 38 (1.9%) | 1.4 (0.9, 2.1) | **NA** |

***Kaplan Meier estimates at 48 weeks; †Estimated by Cox proportional hazards regression with treatment as independent variable, stratified by study for pooled analysis**
**Source: FDA Briefing Document PADAC Meeting November 19, 2009**
**http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM190463.pdf [accessed July 15, 2014]**

The safety concerns of death and stroke precluded approval of Spiriva Respimat during the initial NDA review. At the time of the initial NDA review, the Agency was aware that BI had completed UPLIFT and that UPLIFT would provide a large safety database for tiotropium. However, UPLIFT would require Agency review and the study report had not been submitted to the Agency prior to the PDUFA date for the Spiriva Respimat NDA. Therefore, a Complete Response action was issued on September 16, 2008.

*UPLIFT (Study 205.235)*

Study 205.235 was a 4 year, randomized, double-blind, parallel group, placebo controlled trial to assess the rate of decline of lung function with Spiriva HandiHaler in 5993 patients with COPD. Entry criteria were similar to the Spiriva Respimat clinical studies. Background medications of LABAs, and ICS were allowed. While UPLIFT was designed as an efficacy study to evaluate the effects of Spiriva HandiHaler on decline in lung function, the results provided a large amount of safety data that essentially doubled the safety database for Spiriva HandiHaler. Protocol amendments specified obtaining vital status on patients who discontinued and established an independent adjudication committee for death. Results of selected endpoints are shown below in Table 8. Overall, UPLIFT did not show increased risk of mortality, stroke, cardiovascular death and myocardial infarction with Spiriva HandiHaler.

**Table 8 Selected Endpoints in UPLIFT (Study 205.235)**

| | Spiriva HandiHaler N=3006 | Placebo N=2986 | Rate Ratio (95% CI) |
|---|---|---|---|
| **Fatal Events – adjudicated, Vital Status (Day 1470) dataset** | | | |
| Mortality – all cause | 446 (14.9) | 495 (16.5) | 0.89 (0.79, 1.01) |
| COPD Exacerbation – fatal | 120 (4.0) | 150 (5.0) | 0.79 (0.62, 1.01) |
| Cardiac disorders – fatal | 26 (0.9) | 32 (1.1) | 0.81 (0.48, 1.36) |
| Myocardial infarction – fatal | 11 (0.4) | 11 (0.4) | 1.00 (0.43, 2.30) |
| Stroke (CVA) – fatal | 14 (0.5) | 17 (0.6) | 0.82 (0.40, 1.66) |
| **Serious adverse events, on treatment+30 days dataset** | | | |
| Serious Adverse Events | 1540 (51.6) | 1509 (50.2) | 0.95 (0.88, 1.02) |
| Cardiac Disorder SAEs | 322 (10.8) | 350 (11.6) | 0.84 (0.73, 0.98) |
| Myocardial Infarction SAEs | 65 (2.2) | 84 (2.8) | 0.71 (0.52, 0.99) |
| Stroke SAEs | 28 (0.9) | 28 (0.9) | 0.92 (0.55, 1.56) |

Source: NDA 21395, CSR 0205-0235-01-15 (Study 235), pages 735-761, 1031-1035;

*PADAC – November 2009*

As discussed in the Background section, on November 19, 2009, a PADAC meeting was held to discuss the ongoing safety concerns with tiotropium and the results of UPLIFT.[5] During the AC meeting, the Agency also presented the mortality imbalance data in the Spiriva Respimat program and presented not only the mortality results from Studies 254 and 255, but also the results of Study 372, which was a third 48 week study that showed a mortality imbalance against Spiriva Respimat and was available prior to the PADAC meeting (see bottom portion of Table 7). At the PADAC, there was a consensus that safety concerns for Spiriva HandiHaler were alleviated by UPLIFT; however, the safety of Spiriva Respimat remained an open issue and further data was suggested. At the PADAC meeting, BI noted its plans to conduct a large safety trial with Spiriva Respimat.

*Complete Response*

In this Complete Response, BI provided additional safety data from placebo controlled clinical trials and the large TIOSPIR study.

Overall, the safety database for Spiriva Respimat is quite large as shown by the clinical development program in Table 2. Safety data from the placebo controlled trials were analyzed using different datasets, the vital status database and the clinical safety database as described in Table 9 below. The vital status database included all trials that had vital status follow up at

the end of the treatment period (prospectively and retrospectively), including patients who prematurely discontinued. This included the three 48 week studies (254, 255, and 372) and a 24 week placebo controlled study in 2080 patients with COPD for another development program in which Spiriva Respimat 5 mcg was included as an active comparator (Study 1205.14). The clinical safety database included more studies of shorter duration and this dataset was used to assess common AEs and SAEs. The clinical safety database included an additional study from another development program, Study 1205.04, which was a 4 week dose ranging study in 389 patients with COPD in which Spiriva Respimat 5 mcg was an active comparator.

**Table 9 Placebo Controlled Safety Datasets**

| | Types of studies included | Studies | Spiriva Respimat 5 mcg N | Placebo N | Safety Endpoints |
|---|---|---|---|---|---|
| **Vital Status** | R, DB, PG, PC, vital status available (EOT) | 254, 255, 372, 1205.14 | 3049 | 3047 | Mortality (EOT); adjudication only in 372 |
| **Clinical Safety** | R, DB, PG, PC, ≥4 weeks | Same as vital status + 251, 252, 1205.04 | 3282 | 3283 | SAEs & AEs (EOT+30 days) |

R=randomized, DB = double-blind, PC = placebo-controlled, PG = parallel group, DD = double dummy, EOT = end of treatment, SAE = serious adverse events, AE= adverse events

Table 10 shows the analysis of overall death in the vital status database. In these 4 studies, vital status was obtained in 98-99% of patients. There was a numerical imbalance favoring placebo, which is not surprising, given the known imbalance in deaths in the three 48 week studies (Table 7). Notable imbalances in primary system organ class were cardiac disorders with 0.5% in the Spiriva Respimat 5 mcg group compared to 0.2% in the placebo group and neoplasms with 0.3% in the Spiriva Respimat 5 mcg group compared to 0.1% in the placebo group.

To further explore the cardiac disorder imbalance, BI conducted a MACE analysis and there was an imbalance favoring placebo with a HR of 2.0 (95% CI 1.0, 3.9). In the vital status database, fatal MI and sudden death were the main components driving the fatal MACE results. There was no imbalance in death due to stroke. The results for fatal MACE and the components are shown in Table 11. It is important to note that deaths were not adjudicated in most of these studies, thus, the cause of death is based upon investigator preferred term, and these studies were not designed to prospectively assess cardiovascular safety.

**Table 10 Analysis of Death in Vital Status Database**

| | Spiriva Respimat 5 mcg QD | Placebo QD |
|---|---|---|
| Number of patients | 3049 | 3047 |
| Vital status complete | 99% | 98% |
| Deaths, n (%) | 68 (2.2) | 51 (1.7) |
| Comparison vs. Placebo HR (95% CI) | 1.33 (0.93, 1.92) | |
| MACE - fatal | 26 (0.9) | 13 (0.4) |
| Cardiac Disorder - fatal | 16 (0.5) | 7 (0.2) |

| | | |
|---|---|---|
| Ischemic heart disease - fatal MI | 9 (0.3) | 2 (0.1) |
| Stroke - fatal | 1 (0) | 1 (0) |
| Sudden death | 9 (0.3) | 5 (0.2) |

MACE = Major Adverse Cardiac Events
Source: NDA# 21936, Summary Clinical Safety, page 45-55, SCS-supplement-study-report-body, page 287

SAEs were analyzed using the safety database. Total SAEs were balanced between Spiriva Respimat 5 mcg and placebo. The most common system organ class for SAEs was respiratory, thoracic, and mediastinal disorders, which was numerically less in the Spiriva Respimat 5 mcg group (6.8%) vs. placebo (7.5%). Table 11 shows some SAEs with numerical imbalance favoring placebo. Chest pain and death were the main drivers for the imbalance in the general system organ class. The renal and urinary disorders imbalance was driven by urinary retention, which is an expected adverse event and the imbalance in neoplasm was driven primarily by lung cancer. The table also shows the results for MACE and the relevant components of MACE. Total MACE, stroke, and MI did not show an imbalance. The SAEs were not adjudicated in these studies, thus, the analyses are based upon investigator preferred term.

**Table 11 Serious Adverse Events of Interest in Clinical Safety Database**

| | **Spiriva Respimat 5 mcg QD N=3282** | **Placebo QD N=3283** |
|---|---|---|
| SAEs n (%) | 491 (15.0) | 496 (15.1) |
| Cardiac disorder | 84 (2.6) | 69 (2.1) |
| General d/o, administration site d/o | 32 (1.0) | 17 (0.5) |
| Neoplasm | 66 (2.0) | 44 (1.3) |
| Renal and urinary d/o | 19 (0.6) | 11 (0.3) |
| Total MACE | 46 (1.4) | 49 (1.5) |
| SMQ ischemic heart disease (sub-SMQ MI, broad, fatal and non-fatal) | 16 (0.5) | 21 (0.6) |
| Stroke PVE (fatal and non-fatal, includes TIA) | 13 (0.4) | 17 (0.5) |
| SOC Cardiac Disorder (fatal) | 23 (0.7) | 12 (0.4) |
| Sudden death PT | 2 (0.1) | 1 (0) |
| SOC Vascular disorder (fatal) | 0 | 1 (0) |

MACE = Major Adverse Cardiac Events; SMQ = Standardized MedDRA Query; SOC = system organ class; PVE= pharmacovigilance endpoint; PT = preferred term
Source: NDA# 21936, Summary Clinical Safety, page 67, 80; SCS-supplement-study-report-body, page 319,336-337,368-369, 571

A detailed review of common AEs is not included in summary review, but the primary clinical review by Dr. Robert Lim of the submitted data noted common AEs typical for an inhaled anticholinergic, including dry mouth, cough, and other upper respiratory symptoms, such as nasopharyngitis.

*TIOSPIR*

Study 205.452 (TIOSPIR) was a large comparative safety study conducted to specifically address the safety concern for Spiriva Respimat noted in the Complete Response action. The design is described in the Clinical/Efficacy section. In terms of safety, all patients were to be followed up until the end of the study for vital status regardless of continuation of study treatment. All causes of death were adjudicated by an independent adjudication committee. There were protocol defined outcome events: COPD exacerbations, pneumonias, myocardial

infarctions, strokes, and transient ischemic attacks. The protocol defined outcome events were centrally monitored to determine if the events met the pre-specified definition outlined in the protocol. Analyses of major adverse cardiovascular events (MACE) were specified.

A total of 17,135 patients were randomized in TIOSPIR and received at least one dose of study medication. Twenty-three percent of patients discontinued study medication prematurely and similarly across treatment groups, but vital status was confirmed for 99.7% of treated patients. The majority of patients were male (72%), white (82%), with a mean age of 65 years, mean FEV1 48% predicted, and 15% of patients had a history of ischemic heart disease. The mean exposure was 727 days.

The first primary endpoint was time to all-cause mortality. There were a total of 1302 deaths in the study with similar number of events across treatment groups. For both of the Spiriva Respimat doses, the upper limit of the 95% confidence intervals were <1.25 and within the pre-specified non-inferiority margin (Table 12). 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.

**Table 12 All-cause mortality including vital status - TIOSPIR (Study 205.452)**

| Death Analysis Dataset | **Spiriva Respimat 2.5 mcg QD** | **Spiriva Respimat 5 mcg QD** | **Spiriva HandiHaler 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) | 1.00 (0.87, 1.14) | 0.96 (0.84, 1.09) | |
| vs, SR 5 mcg, HR (95% CI) | 1.04 (0.91, 1.19) | | |

SH = Spiriva HandiHaler; SR = Spiriva Respimat; HR = Hazard Ratio
Source: CSR Study 205.452, page 102

The causes of death in TIOSPIR 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 death included complications from COPD, lung cancer, and death/sudden death/sudden cardiac death. Selected causes of death of interest are shown in Table 13. The various causes of death were generally balanced across treatment groups. Within the cardiac disorders, there was a small numerical imbalance in myocardial infarction and cardiac death favoring Spiriva HandiHaler when comparing Spiriva Respimat to Spiriva HandiHaler, but no dose response with the 2 doses of Spiriva Respimat. On the other hand, for sudden death, there was a small numerical imbalance that favored the Spiriva Respimat over Spiriva HandiHaler. As such, and given the small number of events for these subpopulations, it is difficult to conclude there are true differences between the two products.

**Table 13 Adjudicated cause of death at vital status follow up for selected events of interest TIOSPIR (Study 205.452)**

| Death Analysis Dataset | **Spiriva Respimat 2.5 mcg QD** | **Spiriva Respimat 5 mcg QD** | **Spiriva HandiHaler 18 mcg QD** |
|---|---|---|---|
| Total number of patients | 5730 | 5711 | 5694 |
| Total number of deaths, n (%) | 440 (7.7) | 423 (7.4) | 439 (7.7) |
| COPD | 110 (1.9) | 115 (2.0) | 117 (2.1) |

| | | | |
|---|---|---|---|
| Pneumonia | 23 (0.4) | 24 (0.4) | 24 (0.4) |
| Sudden death | 45 (0.8) | 38 (0.7) | 46 (0.8) |
| Death | 35 (0.6) | 27 (0.5) | 37 (0.6) |
| Sudden cardiac death | 37 (0.6) | 29 (0.5) | 22 (0.4) |
| Cardiac disorders | 22 (0.4) | 27 (0.5) | 17 (0.3) |
| Myocardial infarction | 9 (0.2) | 6 (0.1) | 2 (0) |
| Vascular disorders | 5 (0.1) | 3 (0.1) | 5 (0.1) |
| Nervous system disorders | 13 (0.2) | 16 (0.3) | 13 (0.2) |
| Cerebrovascular accident | 6 (0.1) | 10 (0.2) | 9 (0.2) |
| Fatal MACE | 119 (2.1) | 113 (2.0) | 101 (1.8) |
| Comparison | | | |
| vs, SH 18 mcg, HR (95% CI) | 1.17 (0.90, 1.53) | 1.11 (0.85, 1.45) | |
| vs, SR 5 mcg, HR (95% CI) | 1.05 (0.81, 1.36) | | |
| Source: NDA# 21936, CSR Study 205.452, pages 148-150, 327-335 | | | |

In addition to death, the following were protocol defined outcome events: COPD exacerbations, pneumonias, myocardial infarctions (serious and non-serious), strokes, and transient ischemic attacks. These were generally similar across the 3 treatment groups. The only numerical trend was for myocardial infarction, in which there were 0.9%, 1.2%, and 1.3% of patients with MI in the Spiriva HandiHaler, Spiriva Respimat 2.5 mcg and Spiriva Respimat 5 mcg groups, respectively with a hazard ratio of 1.41 (95% CI: 0.98, 2.0) for Spiriva Respimat 5 mcg vs. Spiriva HandiHaler. MACE was evaluated as a secondary endpoint. The definition is described in the Clinical-Efficacy section. The incidence of MACE (on treatment) was 3.9% in both Spiriva Respimat groups vs. 3.6% in the Spiriva HandiHaler group. For MACE, the HR for comparison between Spiriva HandiHaler and Spiriva Respimat 5 mcg is 1.10 (0.91, 1.33). Fatal MACE (adjudicated) is shown in Table 13.

*Holter*
Holter monitoring was performed in a subset of patients in Studies 205.254 and 205.255 (24 hours) and in all patients in Study 205.458 (6.5 hours). A small increase in patients with ventricular premature beats was observed in the Spiriva Respimat 5 mcg and Spiriva HandiHaler groups compared to placebo and lower doses of Spiriva Respimat in Study 205.458. However, this trend was not observed in the longer duration studies (205.254 and 205.255) and BI's re-analysis of all Holter data from the Spiriva Respimat program did not identify a treatment effect on Holter ECG endpoints.

***Summary of Safety***
The original NDA submission raised concerns regarding a numerical imbalance in deaths favoring placebo in the two 48-week studies (254 and 255). However, there was no pattern to the cause of death. There was also concern regarding stroke for tiotropium as discussed in the Background section, but this was one of many endpoints evaluated and not adjusted for multiplicity. The safety concerns of death and stroke precluded approval of Spiriva Respimat during the initial NDA review.

In this Complete Response, BI provided additional safety and pharmacokinetic data to support the safety of Spiriva Respimat 5 mcg. Regarding safety, BI submitted the results of a large comparative safety study, TIOSPIR (Study 452), comparing Spiriva Respimat 5 mcg, Spiriva Respimat 2.5mcg, and Spiriva HandiHaler to specifically address the safety concern of

mortality for Spiriva Respimat. The results showed the both doses of Spiriva Respimat were non-inferior (NI margin 1.25) to Spiriva HandiHaler for all-cause mortality. TIOSPIR relies indirectly on the results of UPLIFT which did not show a safety signal of death or stroke with Spiriva HandiHaler.

BI also submitted the results of Study 458, which was a dedicated pharmacokinetic study that provided robust data to show that systemic exposure to tiotropium following the use of Spiriva Respimat 5 mcg was slightly lower compared to Spiriva HandiHaler (see Clinical Pharmacology section). Given that the systemic exposure to tiotropium is less with Spiriva Respimat 5 mcg, this helps support the systemic safety comparison between Spiriva HandiHaler and Spiriva Respimat as was done in TIOSPIR.

# 9. Advisory Committee Meeting

A PADAC meeting was held on August 14, 2014 to discuss the safety and efficacy of Spiriva Respimat. Both the efficacy and safety of Spiriva Respimat were discussed. The voting questions were:

- Do the efficacy data provide substantial evidence of a clinically meaningful benefit for tiotropium bromide inhalation spray 5 mcg for the long-term, once-daily maintenance treatment of bronchospasm associated with COPD and for reducing COPD exacerbations? If not, what further data should be obtained?

- Do the safety data adequately address the safety concerns with tiotropium bromide inhalation spray 5 mcg, including the mortality imbalance noted in the 48 week Phase 3 studies? If not, what further data should be obtained?

- Do the data support approval of tiotropium bromide inhalation spray 5 mcg for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations? If not, what further data should be obtained?

With regard to efficacy, the committee voted 14-yes, 0-no that there was substantial evidence of efficacy.

Regarding addressing safety concerns, the committee voted 9-yes and 4-no that previous safety concerns including mortality were adequately addressed. For those who voted “no”, there was concern regarding the small numerical increase in fatal MI subcomponent of cardiovascular deaths in the Spiriva Respimat treated patients.

The committee members subsequently voted 10-yes and 3-no that the data support approval of Spiriva Respimat 5 mcg for the long-term, once-daily, maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations. The 3 members who voted “no” stated that they did not see compelling efficacy benefit of Spiriva Respimat above Spiriva Handihaler, and given their concerns regarding fatal MI, they did not feel that approval was justified.

# 10. Pediatrics

BI is requesting an indication for tiotropium for treatment of patients with COPD only. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required that relate to this action specific to COPD. PeRC had previous agreed that for such COPD applications a full waiver should be granted because studies the disease does not exist in pediatric patients.

# 11. Other Relevant Regulatory Issues

- Financial Disclosure: The applicant submitted acceptable financial disclosure statements certifying that no debarred individuals were used in the conduct of the trials included in this NDA. For trials 205.372 and 205.452, there were a total of 5 investigators with significant payments of other sorts. Given that both trials were large randomized, double-blinded, controlled trials and each investigator was only responsible for enrolling a small number of patients, it was determined to that this financial disclosure information did not significantly affect the conduct of the trials.
- DSI audits information: DSI audited two sites at the time of the original NDA submission. These two sites enrolled the largest number of patients in the pivotal phase 3 trials and one of these two sites had the highest number of deaths. Audit of these sites did not show any major irregularities. No DSI audits were conducted at clinical sites that participated in the clinical trials for the resubmission. Review of the application did not identify any irregularities that would raise concerns regarding data integrity. No ethical issues were present. All trials were conducted in accordance with accepted ethical standards.

# 12. Labeling

- Proprietary Name: The name Spiriva Respimat was judged acceptable
- Physician Labeling: The label was reviewed by various disciplines within DPARP, the Office of Medical Policy Programs (OMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to healthcare providers. The labeling language in the Clinical Trials section (b) (4) was not allowed at the time of the original submission due to lack of efficacy demonstrated for this label claim. A labeling teleconference was held with BI on September 8, 2014, at which time the main discussion was concerning the presentation of exacerbation data and clinical safety data in the label. Labeling discussions are ongoing at the time of finalization of this review.
- Carton and Immediate Container Label: These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

# 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is for approval of Spiriva Respimat (tiotropium inhalation spray) at a dose of 5 mcg once daily for the long-term, once daily maintenance treatment of bronchospasm associated with COPD and for reduction of COPD exacerbations.

- Risk Benefit Assessment

The overall risk-benefit assessment supports approval of tiotropium inhalation spray at a dose of 5 mcg once daily for long-term once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD as well as for reduction in COPD exacerbations. The submitted safety data from the TIOSPIR study does not show a unique mortality signal for Spiriva Respimat when compared to the currently marketed Spiriva HandiHaler tiotropium dry powder inhaler product. From an efficacy standpoint, the clinical program showed that tiotropium at a 5 mcg once-daily dose provided a statistically significant bronchodilator effect as well as a reduction in COPD exacerbations.

1. Recommendation for Post-marketing Risk Management Activities

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

2. Recommendation for other Post-marketing Study Commitments

None

3. Recommended Comments to Applicant

No additional comments are recommended to be conveyed.

## References

1 http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsand Providers/DrugSafetyInformationforHeathcareProfessionals/ucm070651.htm [accessed June 9, 2014]
2 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(12): 1439-1450. Correction: JAMA 2009; 301(12): 1227-1230.
3 http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm197429.htm [accessed June 10, 2014]
4 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.
5 FDA PADAC meeting November 19, 2009; http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm126203.htm

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09/11/2014