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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	Tiotropium bromide
(Proposed) Trade Name	Spiriva Respimat
Therapeutic Class	Anticholinergic bronchodilator
Applicant	Boehringer-Ingelheim
Formulation(s)	Inhalation spray
Dosing Regimen	5mcg once daily (2 actuations of 2.5mcg)
Indication(s)	Long-term, once daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations
Intended Population(s)	adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action for this New Drug Application (NDA) resubmission is Approval of tiotropium bromide for oral inhalation (Spiriva Respimat) for long-term, once daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations at a dose of 5mcg (two actuations of 2.5mcg) once daily.

1.2 Risk Benefit Assessment

The potential benefits of Spiriva Respimat 5mcg in COPD patients for long-term, once daily maintenance treatment of bronchospasm associated with COPD, and for reducing COPD exacerbations outweigh potential safety concerns. Efficacy in terms of lung function has been clearly demonstrated in five clinical trials and in terms of exacerbation in two clinical trials. The safety concerns raised during the initial review cycle that lead to the initial Complete Response action have been adequately addressed by the new data included in this resubmission.

Efficacy
Support for efficacy is derived from two 12-week trials (205.251 and 205.252) that assessed lung function (bronchodilation) and three 48-week exacerbation trials (205.254, 205.255, and 205.372). All trials except the new exacerbation trial, 205.372, were submitted and reviewed with the initial NDA submission. At the conclusion of the first review cycle, a Complete Response action was taken primarily due to safety concerns. It was also noted in the response that there was a lack of replicate evidence for demonstration of an exacerbation reduction benefit. Trial 205.372 has been included in this resubmission to provide replicate evidence of exacerbation reduction and additional support for bronchodilation.

To support bronchodilation, all 5-trials included a primary spirometric endpoint of trough FEV1 response. In trials 205.251 and 205.252, trough FEV1 response was assessed after 12-weeks of treatment. In exacerbation trials 205.254, 205.255, and 205.372, trough FEV1 response was assessed after 48-weeks of treatment. To support exacerbation, trials 205.254 and 205.255 included a co-primary endpoint of rate of exacerbation and trial 205.372 included a co-primary endpoint of time to 1st exacerbation. All three exacerbation trials also included a variety of other exacerbation related secondary endpoints.

<u>Efficacy for Bronchodilation</u>

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In all 5-trials, tiotropium Respimat (SR) 5mcg once daily demonstrated significant improvements in tough FEV1 response. The difference from placebo at the end of the treatment periods for trials 205.251, 205.252, 205.254, 205.255, and 205.372 were 0.11, 0.12, 0.14, 0.11, and 0.10L, respectively. All differences were statistically significant. In the trials that included a SR 10mcg treatment arm (205.251, 205.252, 205.254, and 205.255), the 10mcg dose also demonstrated a statistically significant response compared to placebo in terms of trough FEV1 response. However, there was little incremental benefit of the 10mcg dose over the 5mcg dose (Table 14). Efficacy was further supported by other spirometric secondary endpoints which included trough FEV1 at various times throughout the treatment period and forced vital capacity (FVC). Overall, spirometric data from these trials demonstrate that SR 5mcg has a significant effect on bronchodilation.

Efficacy for Exacerbation Reduction

Efficacy was assessed with respect to exacerbations in 48-week trials 205.254, 205.255, and 205.372. Trials 205.254 and 205.255 were replicate trials. Trial 205.372 was a standalone trial and larger compared to the replicate trials. Exacerbation definitions between the trials were similar. For the replicate trials, only 205.255 demonstrated a statistically significant difference when comparing SR 5mcg to placebo for the primary endpoint of exacerbation rate, although trial 205.254 demonstrated a similar numerical trend. Secondary exacerbation related endpoints were generally consistent with the primary analysis. In trial 205.372, for the primary endpoint of time to first exacerbation a statistically significant difference was demonstrated when comparing SR 5mcg to placebo. The same was true for the secondary endpoint of exacerbation rate. Overall, two of the three exacerbations trials demonstrated statistically significant improvements in SR 5mcg compared to placebo in terms of exacerbation. Overall, the exacerbation data demonstrate that SR 5mcg has a significant effect on exacerbations.

Safety

In the initial NDA review cycle, this application was given a Complete Response (CR) due to a mortality imbalance observed in both 48-week exacerbation trials (205.254 and 205.255) and a potential mortality and stroke risk suggested by a pooled analysis of trials from the SR and Spiriva HandiHaler SHH development programs. In order to address the mortality concern, during the initial review cycle, the Applicant submitted preliminary data from a 4-year, approximately 6000 patient, placebo controlled trial titled Understanding Potential Long-term Impacts of Function with Tiotropium (UPLIFT). This trial included prospective vital status follow-up, a pre-specified mortality endpoint, and all deaths were adjudicated by an independent mortality adjudication committee. Treatment arms were SHH and placebo. While this placebo-controlled trial did not include a SR 5mcg treatment arm, as the both SHH and SR contain the same active pharmaceutical ingredient, mortality data from UPLIFT were thought to be potentially applicable to the SR program, provided that SR 5mcg had similar/lower systemic exposure. However, as the UPLIFT data was preliminary at the time of action, it was

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insufficient to address the mortality concerns and the NDA was given a complete response. Once the final report was available, it was reviewed by the Agency. UPLIFT demonstrated that there was no increased mortality risk when comparing SHH to placebo. The rate ratio for all-cause mortality (SHH: placebo) at day 1470 was 0.89 [95% CI (0.79, 1.01)]. For fatal COPD exacerbations, fatal myocardial infarction, and fatal stroke the rate ratios were 0.79 [95%CI (0.62, 1.01)], 1.00 [95% CI (0.43, 2.30)], and 0.82 [95% CI 0.40, 1.66)], respectively. The rate ratio for deaths falling under the cardiac disorders system organ class (SOC) was 0.81 [95% CI (0.48, 1.36)]. For serious adverse events (on-treatment +30days), the rate ratios for MI, and stroke were 0.71 [95% CI (0.52, 0.99)] and 0.92 [95% CI(0.55, 1.56)]. The rate ratio for SAEs in the cardiac disorders SOC was 0.84 [95% CI (0.73, 0.98)].[1] In addition to the UPLIFT data, the Applicant also submitted data from a third 48-week exacerbation trial (205.372). As with the previous two 48-week exacerbation trials, trial 205.372 again demonstrated a numerical mortality imbalance favoring placebo. Data from these trials were discussed at a Pulmonary Allergy Drug Advisory Committee (PADAC) held on 11/19/2009. While the PADAC concluded that SHH carried no increased mortality risk compared to placebo based on UPLIFT there were still concerns regarding the persistent mortality imbalances observed in the SR exacerbation trials (205.254, 205.255, and 205.372). Given the continued mortality concerns for SR, at the PADAC, the Applicant decided to perform a large safety trial (205.452) to definitively address the mortality concern for SR.

Trial 205.452, titled Tiotropium Safety and Performance in Respimat (TIOSPIR) was a multicenter, multinational, randomized, double-blind, double dummy parallel group trial to compare the efficacy and safety of SR 2.5 mcg and 5 mcg with SHH 18 mcg (SHH) in patients with COPD. This trial was designed to end after approximately 1,266 fatal adverse events and included approximately 17,000 patients. All patients were followed until the end of the trial for vital status, regardless of whether trial medication was discontinued. The total patient year exposure to SR 5mcg was 11,343 years. The primary endpoint was all-cause mortality with an agreed to non-inferiority margin of 1.25. Results demonstrated a hazard ratio of 0.957 [95 % CI (0.837, 1.094)]. As such, non-inferiority of SR 5mcg to SHH was clearly demonstrated in terms of all-cause mortality. While the trial met its primary mortality endpoint, sub-analyses showed that deaths due to myocardial infarction (MI) were more frequent in SR 5mcg patients [n=11 (0.2%)] compared to SHH [n=3 (0.1%)] with a rate ratio of 3.64 [95% CI (1.02, 13.06)]. However, the observation was noted only for mortality due to MI and was not supported by results for MI-related serious adverse events or MACE and stroke related deaths.

In addition to the large safety trial (TIOSPIR), the Applicant also included analyses of two placebo controlled databases as additional support for safety. These were termed the vital status database and clinical safety database. The vital status database was

1 NDA 21395; trial 205.235 (UPLIFT) CSR; tables 15.3.2.2.1.1:2 and 15.3.2.1.1.2:3; pp1031-1035 and 735-761

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used for mortality analysis and consisted of randomized, double-blind, placebo controlled trials that were ≥24 weeks in length, included a SR 5mcg treatment arm, and had vital status follow-up at the end of the planned treatment period for all patients (including those who had prematurely discontinued). This included the three 48-week exacerbation trials (205.254, 205.255, and 205.372) and a 24-week trial from a different drug development program (1205.14). This database included 6096 patients and represented 2395 patient years of exposure to SR 5mcg.

The clinical safety database was used for analysis of serious adverse events and common adverse events. It consisted of randomized, double-blind, placebo controlled trials that were ≥4-weeks in length and included a SR 5mcg treatment arm. Seven trials were included in this pool. This included the four trials from the vital status database, two 12-week bronchodilator trials (205.251 and 205.252), and one 4-week dose-ranging trial from a different drug development program (trial 1205.04). This database included 6565 patients and represented 2440 patient years of exposure to SR 5mcg. This database was used for analysis of SAEs and AEs.

In the pooled mortality analysis (vital status database), a numerical difference was observed when comparing SR 5mcg [n=68 (2.2%)] to placebo [n=51 (1.7%)] with a hazard ratio of 1.33 [95% CI (0.93, 1.92)]. This is not surprising as numerical differences in mortality had been previously identified in three of the four trials in the vital status database. A numerical difference was also observed in terms of MI related deaths with a SR 5mcg: placebo rate ratio of 4.49 [95% CI (0.96, 20.96)]. Fatal MACE also occurred in more SR 5mcg patients compared to placebo with SR 5mcg: placebo rate ratio of 2 [95% CI (1.03, 2.89]. This was driven by the already mentioned MI related death imbalance. In the analysis of the clinical safety database for all MACE and MI related SAEs, no differences were noted between treatment groups. No differences in stroke deaths and overall stroke events were observed when comparing SR 5mcg to placebo.

The mortality data when comparing trial 205.452 (TIOSPIR) and the vital status database are not entirely consistent. The TIOSPIR data clearly demonstrate that SR 5mcg is non-inferior to SHH in terms of all-cause mortality, which given the UPLIFT data would imply that SR 5mcg should not carry an increased mortality risk compared to placebo. However, a numerical mortality difference favoring placebo was noted in the vital status database. While this was observed, it should be noted that TIOSPIR was specifically designed to address the observed mortality imbalance in three of the four trials in the vital status database. Additionally, TIOSPIR represents a 5-fold larger exposure compared to the vital status database. As such, one may argue that the TIOSPIR data outweighs that of the pooled analysis. With regard to specific causes of death, in both TIOSPIR and the vital status database, numerical differences were noted in deaths related to MI. However, this was not observed for SAEs related to MI. Additionally, the overall number of events was small and these observed differences may have been related to chance and multiple comparisons.

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1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

This NDA resubmission is submitted in support of tiotropium bromide (Spiriva) inhalation spray delivered via the Respimat device. Tiotropium is a specific antagonist at muscarinic acetylcholine receptors, often called anticholinergic. It is delivered via the Respimat device. Throughout this review, the product will be referred to as Spiriva Respimat (SR). The proposed indication for SR is for the long-term, once daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations.

The SR drug product exists as an aqueous solution of tiotropium bromide monohydrate delivered via the Respimat device. The aqueous solution contains 0.023% (g/100mL) tiotropium drug substance and is contained in a plastic container in an aluminum cartridge. The proposed dosing for treatment of COPD is 5mcg (2 actuations) once daily. The product is shown in Figure 1.

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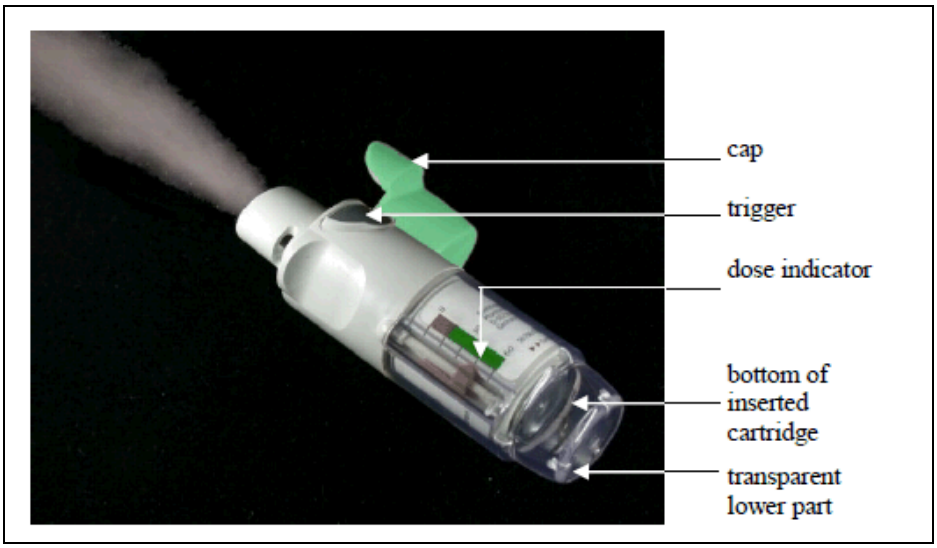
Figure 1. Respimat device with cartridge inserted and aerosol generated



Source: Overall quality summary; figure 3; pg13

To use the SR product the patient initially removes the transparent base on the Respimat device and inserts the cartridge containing the formulation. The clear base is replaced and the patient turns the base until a 'click' is heard, then primes the device by spraying until a mist is observed and then another 3 times into the air. To administer a dose, the cap is then opened and the patient seals his lips around the mouthpiece. During inhalation, the patient presses the trigger button while continuing to inhale.

The Respimat device and cartridge are approved in the United States for use with the Combivent Respimat (albuterol/ipratropium) drug product (NDA 21-747; October 7, 2011). SR is approved in Europe.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are several classes of drug currently used to treat patients with COPD (Table 1). These include bronchodilator products (short and long acting beta-2 adrenergic agonists); anticholinergic agents such as ipratropium, tiotropium and more currently, aclidinium and umeclidinium; and combinations of inhaled corticosteroids and anticholinergics and long-acting beta-2 agonists and anticholinergics. Some anticholinergics, combinations of inhaled corticosteroids and beta-2 agonists, and the methyl xanthines and PDE-4 inhibitors are approved for reducing exacerbations of COPD.

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Table 1. Approved treatments for COPD

Class		Generic Name	Brand Name
Beta$_2$-adrenergic agonists	Short-acting (SABA)*	Albuterol sulfate	Accuneb, ProAir HFA, Proventil HFA, Ventolin HFA
		Levalbuterol tartrate	Xopenex HFA
		Pirbuterol	Maxair autoinhaler
		Terbutaline sulfate	
	Long-acting (LABA)	Salmeterol	Serevent Diskus
		Formoterol	Foradil Aerolizer
		Arformoterol	Brovana
		Formoterol Solution	Perforomist
		Indacaterol maleate	Arcapta Neohaler
Anti-cholinergics	Short-acting	Ipratropium bromide	Atrovent HFA
	Long-acting	Tiotropium bromide	Spiriva Handihaler
		Aclidinium bromide	Tudorza Pressair
		Umeclidium bromide	Incruse Ellipta
Combination	SABA/anti-cholinergic	Albuterol/Ipratropium Albuterol/Ipratropium	Combivent Combivent Respimat
	Corticosteroid/LABA	Fluticasone/Salmeterol	Advair Diskus
		Budesonide/Formoterol	Symbicort
		Fluticasone/Vilanterol	Breo Ellipta
	LABA/anticholinergic	Vilanterol/umeclidinium	Anoro Ellipta
Xanthines		Theophylline	Multiple
Phosphodiesterase Inhibitors	PDE4 Inhibitor	Roflumilast	Daliresp

*not specifically approved for COPD

2.3 Availability of Proposed Active Ingredient in the United States

Tiotropium is available in a dry powder formulation for inhalation under the trade name Spiriva Handihaler, abbreviated in this review as SHH.

2.4 Important Safety Issues With Consideration to Related Drugs

Class effects of anticholinergic agents include worsening of narrow angle glaucoma and worsening of urinary retention.

The Agency has also historically been concerned with the cardiovascular safety of these agents. The concerns have been discussed extensively both in the medical literature and in open public forums[2]. For example, a meta-analysis of various studies suggested a concern regarding increased risk of stroke, cardiovascular death, and myocardial

2 November 2009 FDA Pulmonary-Allergy Drugs Advisory Committee Meeting.

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infarction associated with the use of short-acting and long-acting anticholinergics.[3] Additionally, a case control study of patients treated with inhaled medications, including anticholinergics, for the treatment of COPD also reported an increased risk for mortality and/or cardiovascular events in patients who received tiotropium or inhaled anticholinergics[4]. A pooled analysis of 29 studies conducted by BI in 2007 (25 studies with SHH, and 4 studies with SR) suggested an increased risk of stroke with tiotropium bromide.[5] As a result of these concerns, the Agency released Early Communications on March 18, 2008 and October 7, 2008 about the ongoing safety review of SHH that described these observations. Following the Early Communication, BI submitted data from a 6,000 patient, 4-year study with the SHH [Understanding Potential Long-term Impacts on Function with Tiotropium trial (UPLIFT[6], trial 205.235)] which was analyzed by the Agency and discussed at a Pulmonary Allergy Drug Advisory Committee (PADAC) in November of 2009. As a result, in January 2010 the Agency provided a Follow-Up[7] to the previous Early Communications regarding the safety of tiotropium marketed as the SHH. In this update, the Agency communicated its conclusion that the available data, including results from UPLIFT do not support an association between the use of SHH (tiotropium) and an increased risk for stroke, heart attack, or death from a cardiovascular cause. A summary of the Agency's conclusions regarding the safety of tiotropium may also be found in the medical literature[8].

2.5 Summary of Presubmission Regulatory Activity Related to Submission

At the time of the initial submission, this NDA was given a complete response (September 2008). During the review cycle, the Division noted concern over the data submitted to support safety of SR in patients with COPD. The most notable concerns related to potential stroke risk and increased death. The stroke concern stemmed from analysis of the pooled data from the SR and SHH programs, for which the Agency had already released an Early Communication as discussed above. The mortality concern arose due to an observed imbalance in deaths in the two 48-week exacerbation trials (205.254 and 205.255) completed at the time of NDA submission. By the end of the review NDA review cycle, these concerns were not sufficiently addressed.

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3 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.
4 Lee TA, Pickard S, Au DH et al. Risk of Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease. *Annals of Internal Medicine* 2008;149:380-390.
5 FDA Early Communication about an Ongoing Safety Review of Tiotropium. Http://ww.fda.gov/cder/drug/early_comm/tiotropium.htm
6 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
7 Follow-Up to the October 2008 Updated Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler), January 14, 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm197429.htm
8 Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. *NEJM* 2010;363(12):1097-9.

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With regard to efficacy, there was substantial evidence for a bronchodilator effect based on two 12-week bronchodilator trials (205.251 and 205.252) and spirometric endpoints in two 48-week exacerbation trials (205.254 and 205.255); and that the 10mcg dose offered no significant incremental benefit compared to 5mcg. However, the evidence submitted to support a reduction in COPD exacerbation claim was not adequate to support approval. Of the two 48-month exacerbation trials (205.254 and 205.255), only one (205.255) demonstrated a statistically significant reduction in exacerbations. However, by design, the trials were not powered to detect a reduction in exacerbations. The Applicant had pre-specified that the data be pooled and analyzed. They had planned to reference SHH exacerbation data from trial 205.266 as evidence for replication. As efficacy is related to local delivery, and the local delivery may not be same between the two products, this was not accepted by the Division. As such, the Division concluded that there was no replication of the exacerbation effect.

Due to these conclusions, this application was given a Complete Response (CR). The following safety and efficacy deficiencies were conveyed to the Applicant:

> Deficiency 1 (Safety)
> Increased frequencies of death were observed in patients treated with SR compared to placebo in the two 48-week studies submitted with this application and increased frequencies of stroke were observed in patients treated with tiotropium bromide compared to placebo in a pooled analysis of clinical study data with SHH and SR.
>
> To resolve the deficiency, the Applicant was asked to provide additional data from an adequate and well-controlled study to address the concerns of death and stroke and that if study 205.235 (The UPLIFT study) was to be used to address these safety concerns, BI should provide justification for use of safety data from SHH to support SR.
>
> Deficiency 2 (Efficacy)
> The submitted data do not provide substantial evidence to support the proposed claim of reduction of COPD exacerbation….replication of the finding is necessary to support a labeling claim. Results of the two individual 48-week studies are not sufficient for replication because only one of the two studies showed a statistically significant difference from placebo.
>
> To resolve the deficiency and to support the proposed claim of reduction of COPD exacerbation, the Applicant was asked to provide data from an adequate and well controlled clinical study that shows statistically significant reduction in COPD exacerbation with SR compared to placebo.

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Near the end of the initial NDA review cycle, the Applicant submitted a preliminary report for a recently completed large phase 4 trial for SHH titled Understanding Potential Long-term Impacts on Function with Tiotropium Handihaler trial (UPLIFT, Protocol 205.235). Preliminary results demonstrated neither an increased stroke nor mortality risk when comparing SHH to placebo.

Once the complete UPLIFT data was available, the Division brought the safety concerns to the Pulmonary Allergy Drug Advisory Committee meeting (PADAC, November 2009). The committee concluded that the UPLIFT data were compelling, with SHH demonstrating generally beneficial effects on mortality. The committee also felt that the potential stroke signal for SHH had been adequately addressed. These results were somewhat reassuring for SR. However, mortality data from a 1-year SR exacerbation trial (205.372) also became available at the time of the PADAC. This trial included approximately 4000 COPD patients, more than doubling the size of the SR safety database. Mortality data from this trial again demonstrated an imbalance in favor of placebo. As such, the mortality concern for SR remained.

As a result, the Applicant proposed an additional large safety trial to specifically address the mortality concern (Trial 205.452). Trial 205.452 was titled Tiotropium Safety and Performance in Respimat (TIOSPIR). The trial was an event driven multicenter, multinational, randomized, double-blind, parallel group trial comparing the long-term efficacy and safety of SR 5 mcg [2 actuations of 2.5 mcg] and 2.5mcg [2 actuations of 1.25mcg] compared with SHH in patients with COPD. All patients, even those who discontinued medication early were followed until the end of the trial for vital status, i.e., mortality. The primary endpoints were all-cause mortality and time to first exacerbation. For all-cause mortality, SR arms were compared to SHH for non-inferiority with a non-inferiority margin of 1.25. For exacerbations, SR arms were compared to SHH for superiority. Because of the proposed size, scope, and implications of the trial 205.452 (TIOSPIR), the protocol was reviewed in detail by the Agency. The protocol design and non-inferiority margin were felt to be acceptable (correspondence dated February 1, 2010). The data from this trial was included in this resubmission as primary support of safety.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

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3.1 Submission Quality and Integrity

This submission was appropriately indexed and complete to permit review

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each clinical study report.

3.3 Financial Disclosures

The Applicant has submitted a statement certifying that no debarred individuals were used in the conduct of the trials included in this NDA. From trials 205.372 and 205.452, BI certified the absence of financial arrangement for 5189 primary and sub-investigators. From trial 205.372, the 48-week exacerbation trial meant to provide replicate evidence for exacerbation reduction to address the efficacy deficiency, there were (b) (6) investigators with significant payments of other sorts: (b) (6) . These significant payments of other sorts were determined to not have significant impact upon the conduct of this clinical trial, given that the study was randomized, double-blinded, placebo-controlled trial, with objective spirometric and exacerbation related endpoints, and since each investigator was only responsible for enrolling a small number of patients to this multi-center trial.

From the large safety trial (TIOSPIR, 205.452), one investigator received significant payments of other sorts (b) (6) and one investigator's spouse is employed by the Applicant (b) (6)). Given that the study was randomized, double-blinded, double-dummy, active controlled trial, with an objective mortality endpoints and since each investigator was only responsible for enrolling a small number of patients to this large (>17,000 patient), multi-center trial; it was determined to that this financial disclosure information did not significantly affect trial conduct.

From trials 205.372 and 205.452, BI performed due diligence on 183 primary investigators and financial interest was not certified. For 181 primary investigators, the reasons that this information was not certified was the site did not initiate the trial or the site did not enroll any patients. For the two remaining primary investigators, both from 205.372, the reason given was "unable to contact" and "deceased."

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4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The recommendation from the Chemistry, Manufacturing, and Controls reviewer is Approval. In the complete response letter for the original submission, no CMC issues were identified. For a more in depth review of the original submission, see the review written by Dr. Alan Schroeder dated 8/15/2008. In this resubmission, the Applicant has made several changes since the original submission. These included a new route for synthesis for tiotropium bromide, an additional market presentation (14 dose), extended shelf life, and changes to drug product specifications. These changes were reviewed by the CMC reviewer and found to be acceptable (see review by Dr. Eugenia Nashed dated and 7/25/2014)

4.2 Clinical Microbiology

The recommendation from Clinical Microbiology is Approval. In the complete response letter for the original submission, no Clinical Microbiology issues were identified. For a more in depth review of the original submission, see the review written by Dr. Lolas 7/3/08 and 8/14/2008) dated 8/15/2008. In this resubmission, the Applicant has included additional data to support extended shelf life. These changes were reviewed by the Clinical Microbiology reviewer and found to be acceptable (see review by Dr. Mello dated 08/22/2014).

4.3 Preclinical Pharmacology/Toxicology

No new data was submitted

4.4 Clinical Pharmacology

The recommendation from the Clinical Pharmacology reviewer is Approval. A brief review of the clinical pharmacology findings for Spiriva Respimat relevant to this Complete Response resubmission can be found below. Complete details of the full program can be found in the Clinical Pharmacology reviews for the initial NDA and Complete Response resubmission by Drs.Yun Xu (dated 7/31/2008) and Yunzhao Ren reviews, respectively

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4.4.1 Mechanism of Action

Tiotropium is a long-acting anticholinergic agent that binds muscarinic receptors M_1 to M_5. When applied locally to the airways, it exhibits its pharmacologic effect through inhibition of M_3-receptors at the smooth muscle leading to bronchodilation.

4.4.2 Pharmacodynamics

No new data was submitted

4.4.3 Pharmacokinetics

Absorption: Following inhalation of tiotropium bromide approximately one-third of the inhaled dose reaches the systemic circulation. Maximum tiotropium plasma concentrations were observed 5 to 7 minutes after inhalation. Tiotropium systemic exposure increases proportionally from 1.25 µg to 10 µg.

Distribution: The drug has a plasma protein binding of 72% and shows a volume of distribution of 32 L/kg. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung.

Metabolism: The extent of metabolism appears to be small, evident from a urinary excretion of 74% of unchanged substance after an intravenous dose.

Elimination: The effective half-life of tiotropium ranges between 27 to 45 h following inhalation.

Systemic Exposure Comparison between SR5 and SHH:
The Applicant included data from a new PK trial (205.458) in this resubmission. This trial was meant to provide more comprehensive PK data as compared to the PK trials submitted with the initial NDA (205.249 and 205.250). These previously submitted duplicate trials were randomized, double-blind, double-dummy, placebo controlled cross-over trials comparing systemic exposure to tiotropium following 4-weeks of treatment with SR 5mcg, SR 10mcg, SHH, and placebo. It should be noted that these trials were not designed as dedicated bioavailability/bioequivalence (BA/BE) studies for PK profile comparison between SR 5 mcg and SHH. There were only three post-dosing PK samples (post-dose 10 minutes, 1 hour, and 6 hours) and tiotropium concentrations from majority of samples taken at 6 hours were below the limit of quantification (BLQ) Figure 2 shows that the systemic exposure ($AUC_{0\text{-}6,ss}$) is slightly higher following SR 5mcg treatment in study 205.249 (N=49) and no different between two treatments in study 205.250 (N=34). It is important to note there is considerable variability in the PK profiles, rendering it difficult to ascertain differences in the PK between products.

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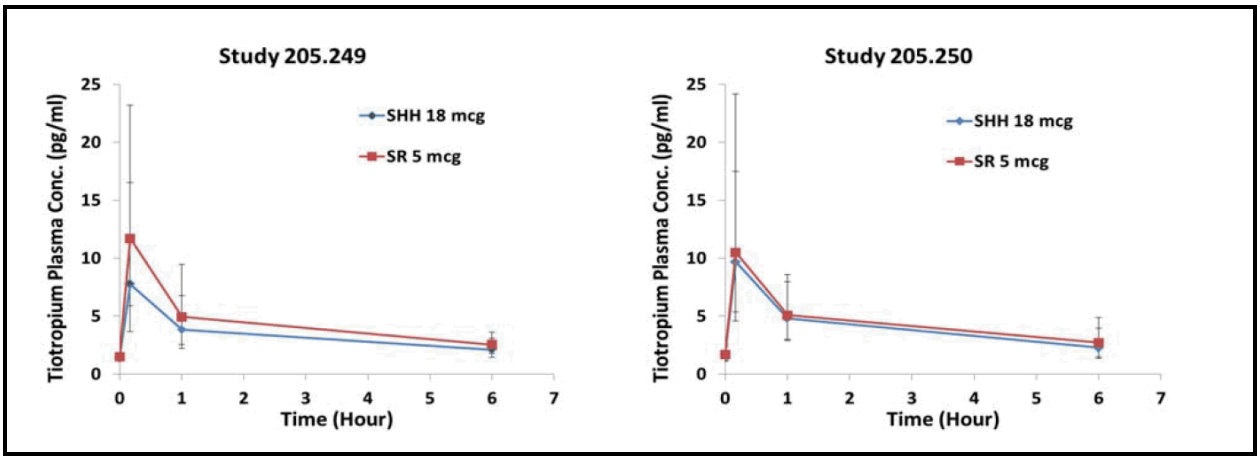
Figure 2. Tiotropium plasma concentration-time profile at steady state following 4-weeks of treatment with SR 5mcg or SHH 18mcg from study 205.249 (left panel) and 205.250 (right panel). Observations represent the geometric mean for each time-point +/- standard deviation.

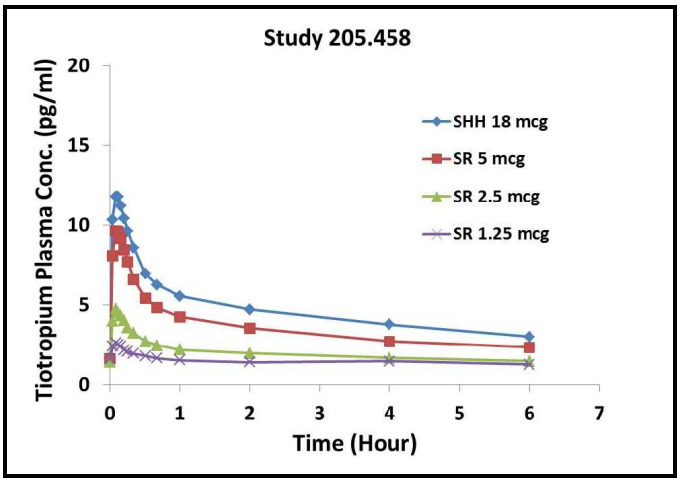


Trial 205.458 was the first dedicated rich PK sampling BA/BE study to compare the systemic exposure between SR5 and SHH. The trial was a 4-week treatment period, randomized, placebo and active controlled, cross-over trial comparing systemic exposure between SR 1.25mcg, 2.5mcg and 5mcg to SHH. This trial included COPD patients (FEV1 <80% predicted and FEV1/FVC ratio <0.7) ≥40 years of age. Patients were also current smokers or had a smoking history of >10 pack-years. Patients were excluded if they had had a myocardial infarction in the past 6-months, hospitalization for cardiac failure in the past year, or had been hospitalized for an unstable/life threatening cardiac arrhythmia in the past year. Following initial informed consent and a 1-2 week run-in period, patients attended a screening visit. Eligible patients then had a further 7-10 day run-in period, followed by randomization. Patients received 4 weeks of each trial treatment (SR 1.25mcg, 2.5mcg, 5mcg, placebo Respimat, and SHH 18) in succession. At the end of each treatment period, serial blood draws at 13 post-dose time points (up to 6-hours post-dose) were performed for PK analysis. There was no washout period between 4-week treatment periods. The primary PK endpoints were maximum measured concentration of tiotropium in plasma at steady state ($C_{max,ss}$) and area under the curve of tiotropium in plasma over the interval 0-6 hours after inhalation at steady state ($AUC_{0-6,ss}$).

This trial randomized 154 patients. Similar numbers of patients participated in each of the cross-over treatment groups (145-150 patients across groups). Patients were predominantly white (99.4%) male (76%) with a mean age of 63 years. Results of this trial demonstrated that the adjusted geometric mean for $AUC_{0-6,ss}$ and $C_{max,ss}$ for SR 5mcg were approximately 20 – 25% % lower than that of SHH. The ratio (SR 5mcg:

SHH) for $AUC_{0-6,ss}$ was 0.75 (90% CI= 0.69, 0.81, N=103) and for $C_{max,ss}$ was 0.80 (90% CI= 0.73, 0.88, N=109). Consistent with these findings, urinary excretion was also higher in SR groups compared to SHH. For this study, there was improvement for both analytical methodology for plasma concentration determination and study design compared to trials 205.249 and 205.250. Tiotropium concentrations from majority of the post-dose samples, including the last time point (6 hours), were precisely and accurately measured. Plasma concentrations over time are summarized graphically in Figure 3.

Figure 3. Tiotropium plasma concentration-time profile at steady state following 4-weeks of treatment with SR 5mcg or SHH 18mcg from study 205.458. Observations represent the geometric mean for each time-point.



The lower exposure of tiotropium in SR5 suggests that the UPLIFT systemic safety data for SHH is applicable to SR 5mcg and support the systemic safety comparison between SHH and SR in the TIOSPIR trial.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The sources of clinical data used in this review are summarized in Table 2. Trials highlighted in grey were submitted and reviewed in the initial NDA review cycle.

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Table 2. Sources of clinical data

Study	Description	Subjects	Design	Treatments	Endpoint
Dose Selection Trial					
205.127	3-week treatment period dose ranging trial	202 COPD patients	R, DB, PC, AC	SR 1.25 mcg SR 2.5 mcg SR 5mcg SR 10mcg SR 20mcg SHH 18 mcg PBO	Trough FEV1
Phase 3 Efficacy/Safety Trials					
Exacerbation					
205.372	48-week safety/efficacy exacerbation trial	3991 COPD patients	R, DB, PC, PG	SR 5mcg Placebo LABA allowed	Trough FEV1 Time to 1st exacerbation
205.254	48-week safety/efficacy exacerbation trial	983 COPD patients	R, DB, PC, PG	SR 5 mcg SR 10 mcg PBO	Trough FEV1 SGRQ, TDI Exacerbation (pooled with 205.255)
205.255	48-week safety/efficacy exacerbation trial	1007 COPD patients	R, DB, PC, PG	SR 5 mcg SR 10 mcg PBO	Trough FEV1 SGRQ, TDI Exacerbation (pooled with 205.254)
Bronchodilation					
205.251	12-week safety/efficacy bronchodilation trial	361 COPD patients	R, DB, PC, PG	SR 5 mcg SR 10 mcg PBO	Trough FEV1
205.252	12-week safety/efficacy bronchodilation trial	358 COPD patients	R, DB, PC, PG	SR 5 mcg SR 10 mcg PBO	Trough FEV1
Phase 3 Safety Trial (TIOSPIR)					
205.452 (TIOSPIR)	Event driven comparative safety and efficacy trial. 3.5 years or until 1266 fatal events	17,183 COPD patients	R, AC, DB, DD, PG	SR 2.5 mcg SR 5 mcg SHH 18 mcg LABA allowed	Mortality Time to 1st exacerbation
Pharmacokinetic Trial					
205.458	4-week treatment period pharmacokinetic (PK) trial	154 COPD patients	R, PC, AC, 5-way XO	SR 1.25 mcg SR 2.5 mcg SR 5mcg SHH 18 mcg (OL) PBO	PK $C_{max,ss}$ $AUC_{0-6,ss}$
205.249	4-week treatment period PK and lung function trial	131 COPD patients	R, PC, AC, DD 4-way XO	SR 5 mcg SR 10mcg SHH 18 mcg	PK FEV1 AUC(0-12hr)

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				PBO (double dummy	
205.250	4-week treatment period PK and lung function trial	76 COPD patients	R, PC, AC, DD, 4-way XO	SR 5 mcg SR 10mcg SHH 18 mcg PBO (double dummy	PK FEV1 AUC(0-12hr)
Other trials included in pooled safety analyses					
1205.04	4-week dose ranging trial	389 COPD patients	R, DB, PC, PG	SR 5mcg PBO Experimental drug	Trough FEV1
1205.14	24-week safety/efficacy trial	2080 COPD patients	R, DB, PC, AC, PG	SR 5mcg PBO Experimental drug	Trough FEV1

SR=tiotropium Respimat, SHH=tiotropium Handihaler, R=randomized, DB=double-blind, PC=placebo controlled, DD=double dummy, AC=active controlled, FEV1=force expiratory volume in 1 second, Pbo=placebo, SGRQ=St. George's Respiratory Questionnaire, TDI= transitional dyspnea index

5.2 Review Strategy

Assessment of safety with regard to mortality and serious adverse events is based primarily on the analysis of the large safety trial 205.452 (TIOSPIR); the design of which was agreed upon with the Division to address the safety deficiency outlined in the Complete Response letter dated September 6, 2008. As this trial was specifically designed to address the safety concerns raised in the initial NDA submission, this trial will be the focus of this review.

Additional safety information is derived from two different pooled safety databases designated the vital status database and the clinical safety database. The vital status database is meant as supportive safety information with regard to mortality and included placebo controlled, parallel group trials ≥24 weeks in length which included a SR 5mcg treatment arm and vital status follow-up at the end of the planned treatment period. This database included three 48-week exacerbations trials (205.254, 205.255, and 205.372) and one 24-week trial (1205.14) from a different drug development program.

The clinical safety database is meant to provide supportive safety information with regard to nonfatal adverse events, both serious and non-serious. This database included the same 4 trials in the vital status database as well as two 12-week bronchodilator trials (205.251 and 205.252) and one 4-week dose-ranging trial (1205.04) from a different drug development program.

Assessment of efficacy with regard to exacerbation relies on data from the newly submitted 48-week exacerbation trial 205.372, as well as the Division's previous review of 48-exacerbation trials 205.254 and 205.255 which were submitted with the initial NDA. Data to support efficacy with regard to bronchodilation is derived from the 12-week bronchodilator trials 205.251 and 205.252 and spirometric data from the 48-week

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exacerbation trials 205.254 and 205.255 which were reviewed at initial NDA submission.

In-depth protocol reviews for exacerbation trial 205.372 and mortality trial 205.452, as well as the individual safety results for trial 205.372 are included in section 5.3 Discussion of Individual Studies/Clinical Trials. Efficacy data from exacerbation trial 205.372 are discussed in section 6 Review of Efficacy. Safety data from mortality trial 205.452 are discussed in section 7 Review of Safety, and exacerbation data in section 6.1.10 Additional Efficacy Issues/Analyses.

Because trials 1205.14 and 1205.04 were part of another experimental drug development program, only brief summaries of these trials are included in section 5.3.2 Trials from a different drug program that included Spiriva Respimat treatment arms (1205.14 and 1205.04). Safety data from these trials are also discussed in the context of the pooled placebo controlled databases in section 7 Review of Safety.

A brief summary of trials 205.127, 205.249 and 205.250 are also included in section 5.3. Only brief protocol summaries for trials 205.254, 205.255, 205.251, and 205.252 are included in this review, as these trials have been previously reviewed by the agency in depth. Efficacy and safety data from these trials are summarized in the context of the entire development program in section 6 Review of Efficacy and section 7 Review of Safety, respectively.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 New Exacerbation Trial (205.372)

Administrative Information

- **Study title**: A randomized, double-blind, placebo-controlled, parallel group study to assess long term (one-year) efficacy and safety of treatment of tiotropium inhalation solution 5 mcg [2 puffs of 2.5 mcg] delivered by the Respimat inhaler in patients with chronic obstructive pulmonary disease (COPD)
- **Study dates:** 10/06/2006-1/22/2009
- **Study sites:** Multinational (31 countries, 336 sites)
- **Study report date:** 6/05/2009

Objectives/Rationale

- To evaluate the long-term (1-year) safety and efficacy of SR compared to placebo in patients with COPD

Study Design and Conduct

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Overview
The trial was a multicenter, multinational, randomized, double-blind, parallel group Phase 3b study to compare the long-term efficacy and safety of SR 5 mcg [2 actuations of 2.5 mcg] compared with placebo in patients with COPD. All patients also received albuterol MDI inhalers for rescue use and were permitted to use stable baseline respiratory medications other than anticholinergics (usual care). LABAs were allowed as background therapy. Patients who prematurely withdrew from trial were followed-up at what would have been their exit date.

This trial consisted of a screening assessment, treatment period, and follow-up period. There were a total of 16 clinic visits (visits 0-15). At visit 0 (day -28), patients gave informed consent and prohibited medications were discontinued. If the patient was on tiotropium, this was discontinued at this time. Based on physician discretion, these patients were started on alternative bronchodilator medications. At visit 1 (day -7), patients were screened for eligibility and baseline data was obtained. Patients were also assessed for reversibility. At visit 2 (day 0), eligible patients returned and were randomized to placebo or SR. Thereafter patients were seen in clinic every 4-weeks until the conclusion of the trial. Note that only visits 0, 1, 2, 3, 4, 6, 8, 10, 12, and 14 required that patients be in clinic. For visits, 5, 7, 9, 11, and 13; while coming into clinic was strongly encouraged, telephone ‘visits’ were permitted. The Applicant did not state if for visit 15 (follow-up visit) clinic attendance was mandatory. The assessment schedule is summarized in Table 3.

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Table 3. Trial 205.372 assessment schedule

Visit Number	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Week			0	4	8	12	16	20	24	28	32	36	40	44	48	52
Date	-28	-7	1	29	57	85	113	141	169	197	225	253	281	308	337	+30
Informed consent	X															
Demographics		X														
Medical History		X														
Inclusion / exclusion criteria		X														
Physical examination		X													X	
Vital signs (seated)		X	X	X					X						X	
Laboratory tests (fasted)		X														
12-lead ECG		X		X											X	
Training in use of Respimat®		X	X	X	X		X		X		X		X			
Conclusion of screening			X													
Randomisation			X													
Medication washout check		X	X	X					X						X	
Dispense Respimat® inhaler			X	X	X		X		X		X		X			
Collect Respimat® inhaler				X	X		X		X		X		X		X	
Drug accountability				X	X		X		X		X		X		X	
PFTs (FEV_1 / FVC)		X	X	X					X						X	
SGRQ			X						X						X	
Review smoking status			X						X						X	
Review exacerbation status			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Termination of trial medication															X	

* The interval between Visit 0 and Visit 1 may be between 2 and 28 days depending on medication washout requirements; Visit 3 should take place within ± 3 days of the scheduled date; Visits 4-14 should take place within ± 7 days of the scheduled date.

Trial Population

The trial consisted of 3991 randomized COPD patients. Randomization was stratified by study center and within the center.

Key Inclusion Criteria

1. Signed informed consent consistent with ICH GCP guidelines prior to participation in the trial, including medication washout and restrictions
2. Male or female patients 40 years of age or older
3. Current or ex-smoker with a smoking history of ≥10 pack years; patients who had never smoked cigarettes were to be excluded
4. Diagnosis of COPD; patients must have met the following criteria at Visits 1 and 2:

- Relatively stable, moderate to severe airway obstruction with a pre-bronchodilator FEV1 ≤60% of predicted normal and FEV1 ≤70% of FVC. Predicted normal values were calculated according to the European Community for Coal and Steel (ECSC)

5. Patients must have been able to perform all study related procedures including technically acceptable pulmonary function tests (PFTs)
6. Patients must have been able to use the Respimat inhaler correctly

Key Exclusion Criteria

1. Significant diseases other than COPD. A significant disease was defined as a disease or condition which, in the opinion of the investigator, may have put the patient at risk because of participation in the study or may have influenced either the results of the study or the patients' ability to participate in the study
2. Patients with clinically significant abnormal baseline hematology, blood chemistry, or urinalysis, if the abnormality defined a significant disease as defined above
3. Patients with a recent history (i.e. 6 months or less) of myocardial infarction (MI)
4. Patients with any unstable or life-threatening cardiac arrhythmia requiring intervention or change in drug therapy during the last year
5. Hospitalization for cardiac failure during the past year
6. Malignancy for which the patient had undergone resection, radiation, or chemotherapy within the last 5 years; patients with treated basal cell carcinoma were allowed
7. Known narrow angle glaucoma
8. Patients with a history of asthma, allergic rhinitis, or who had a blood eosinophil count ≥600/mm3; a repeat eosinophil count was not conducted in these patients
9. Patients with a life-threatening pulmonary obstruction, or a history of cystic fibrosis, or clinically evident bronchiectasis
10. Known active tuberculosis
11. Patients with a history of and/or active significant alcohol or drug abuse
12. Patients who had undergone thoracotomy with pulmonary resection; patients with a history of thoracotomy for other reasons should have been evaluated as per the first exclusion criterion
13. Patients who had completed a pulmonary rehabilitation program in the 6 weeks prior to the screening visit (Visit 1) or patients who were currently in a pulmonary rehabilitation program that was not maintained throughout the duration of the study
14. Patients who regularly used daytime oxygen therapy for more than 1 h per day and in the investigator's opinion were unable to abstain from the use of daytime oxygen therapy; night-time oxygen use was allowed
15. Patients who had taken an investigational drug within 30 days or 6 half-lives (whichever was greater) prior to the screening visit (Visit 1)
16. Use of cromolyn sodium or nedocromil within 3 months of screening visit (Visit 1)

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17. Use of antihistamines (H1 receptor antagonists), anti-leukotrienes, or leukotriene receptor antagonists for asthma or excluded allergic conditions
18. Use of systemic corticosteroid medication at unstable doses (i.e. less than 6 weeks on stable dose) or at doses in excess of the equivalent of 10 mg prednisolone per day or 20 mg every other day
19. Known hypersensitivity to anticholinergic drugs, BAC, EDTA, or any other components of the Respimat inhalation solution delivery system
20. Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e. oral contraceptives, intrauterine devices, diaphragm. or subdermal implants e.g. Norplant) for at least 3 months prior to and for the duration of the trial
21. Previous participation (receipt of randomized treatment) in this study
22. Previous participation (receipt of randomized treatment) in any other study of tiotropium inhalation solution delivered by the Respimat inhaler
23. Patients who were currently participating in another study

Enrollment Cautions:

1. SR should be used with caution in patients with prostatic hypertrophy or bladder neck obstruction.
2. As SR is renally excreted, SR use should be monitored closely in patients with moderate to severe renal impairment
3. The randomization of patients with any respiratory infection or COPD exacerbation in the 6 weeks prior to the Screening Visit (Visit 1) or during the baseline period should be postponed. Patients may be randomized 6 weeks following recovery from the infection or exacerbation.

The trial design is similar to the exacerbation trials submitted with the initial NDA submission (trials 205.254 and 205.255). However, unlike trials 205.254 and 205.255, this trial allowed for background LABA use.

Treatments

Treatment Groups

SR 5mcg qD (2 actuations of 2.5mcg/actuation)
Placebo (administered via Respimat inhaler)

Concomitant/Restricted Medications:

Medications taken by the patient within 2 months of the screening visit were recorded in the electronic case report form (eCRF). All medications used during the trial were also recorded in the eCRF. The following medications were permitted:

- Salbutamol/albuterol inhalation aerosol as needed
- Temporary increases in the dose or the addition of theophylline and oral corticosteroids were permitted during the randomized treatment period.

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Pulmonary function testing (PFT) were not be conducted within 7 days after the last administered dose of an increase or addition.
- The use of antibiotics was not restricted.
- In the case of life-threatening exacerbations, any and all therapies deemed medically necessary were allowed to be prescribed

The following medications were allowed if stabilized for at least 6 weeks prior to and throughout the study period.
- LABA, LABA/ICS, ICS
- Theophylline preparations
- Mucolytic agents not containing bronchodilators
- Salbutamol/albuterol MDI
- Anti-leukotriene and leukotriene receptor antagonists only if prescribed for conditions other than asthma or excluded allergic conditions
- Oral corticosteroids were if the patient were stabilized on minimal doses (≤10mg prednisone daily or 20mg every other day)

The following medications were not allowed for at least 1 month prior to the beginning of the screening period and throughout the study period:
- All other investigational drugs
- Long acting anticholinergic drugs

The following medications were not allowed for at least 3 months prior to the beginning of the screening period and throughout the study period:
- Cromolyn sodium/nedocromil sodium

The following medications were not allowed during the randomized treatment period. Note that a washout may have been required prior to pulmonary function testing.
- Short acting anticholinergic drugs
- Short acting β-adrenergic therapies other than the supplied rescue medication
- Fixed combination anticholinergic/β-adrenergic therapies

Efficacy Parameters

Primary Endpoint

The co-primary endpoints for this trial were trough FEV1 response at day 337 (week 48) and time to first COPD exacerbation. Trough FEV1 response was defined the change from baseline in trough FEV1. Trough FEV1 was defined as pre-treatment FEV1 (10 minutes prior to trial medication). Baseline trough FEV1 was defined as the measurement at visit 2 (day 0).

COPD exacerbation was defined as a complex of respiratory events/symptoms with a duration of ≥3 days with ≥ 2 of the following (increase of symptoms or new onset):
- Shortness of breath / dyspnea / shallow, rapid breathing

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- Sputum production (volume)
- Occurrence of purulent sputum
- Cough
- Wheezing
- Chest tightness

The change in/or requirement of treatment includes the following:

- Prescription of antibiotics and / or systemic corticosteroids
- And / or a significant change of the prescribed respiratory medication (bronchodilators including theophylline).

The onset of an exacerbation was defined by the onset of the first recorded symptom. The end of the exacerbation was recorded as defined by the investigator. Exacerbation severity was defined as follows:

- Mild--Treated at home without seeing a health care provider.
- Moderate--Visit with health care provider (e.g. home visit, visit to an outpatient facility or an emergency department – but not requiring admission to hospital)
- Severe--Hospitalization (an emergency department stay > 24 hours is considered a hospitalization).

Secondary Endpoints

The secondary endpoints included the following:

1. Trough FEV1 response after 4 and 24 weeks.
2. Number of COPD exacerbations per patient.
3. Number of patients with at least one COPD exacerbation.
4. Time to first hospitalization for COPD exacerbation.
5. Number of hospitalizations for COPD exacerbations per patient.
6. Number of patients with at least one hospitalization for COPD exacerbation.
7. St. George's Respiratory Questionnaire (SGRQ) after 24 and 48 weeks (total and domain scores).
8. Trough FVC response after 4, 24 and 48 weeks.

The SGRQ is a self-administered health related quality of life measure divided into three components: symptoms, activity, and impacts. The symptoms component contains items concerned with the level of symptomatology, including frequency of cough, sputum production, wheeze, breathlessness, and the duration and frequency of breathlessness or wheeze. The activity component is concerned with physical activities that either cause of are limited by breathlessness. The impacts component covers such factors as employment, being in control of health, panic, stigmatization, the need for medication and its side effects, expectations for health and disturbance of daily life. Scores ranging from 0 to 100 are calculated for each component, as well as a total score which summarizes the responses to all items. A zero score indicates no impairment of quality of life. An improvement of 4 points is considered the minimal clinically important difference (MCID). The questionnaire takes approximately 10

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minutes to complete. In this trial, the SGRQ was administered at baseline (visit 2) and at weeks 24 and 48. It was administered prior to PFTs.

Safety parameters:
Monitored safety parameters will include the following:

- AEs, physical exam, vital signs and clinical labs were performed as per the schedule listed in Table 3.
- ECGs were performed at visits 1, 3, and 14 (days -7, 28, and 377, respectively) 4, 5, 7, and 10. ECGs were performed prior to pre-dose PFTs.

The co-primary endpoints are acceptable to assess an effect on lung function and exacerbations. The exacerbation definition is the same as used in the 48-week exacerbations trials (205.254 and 205.255) submitted in the initial NDA. Secondary endpoints are also reasonable. The monitored safety parameters are also reasonable and typical for a COPD trial of this duration.

Compliance
Compliance was determined based on dose indicator readings from returned medications.

Ethics:
This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol. No changes were made without the IRB's approval.

Statistical Analysis

Sample Size
Based on the Applicant's previous experience, the standard deviation for trough FEV1 was estimated to be 229mL. The Applicant estimated that a total of 1500 patients/group would yield 99% power to detect a 130mL trough FEV1 response with a one sided alpha of 0.05.

With regard to exacerbations, with a sample size of at least 1,500 patients/group, a 0.050 level two sided log-rank test for equality of survival curves will have 80% power to detect a constant hazard ratio of approximately 0.850 (15% reduced risk) assuming the proportion of patients experiencing at least one exacerbation is 37.2% for SR inhaler and 42.1% for placebo.

Missing Data
Trough FEV1 data missing due to worsening symptoms were replaced with the least favorable prior trough FEV1 value. If missing for other reasons, missing data was

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replaced using last observation carried forward (LOCF). Missing SGRQ data were imputed using LOCF.

Analysis populations
The Applicant pre-specified 3 analysis populations. The randomized set (RAN) consisted of all randomized patients whether treated or not. The treated set (TS) consisted of all patients who took at least one dose of study drug during the treatment period and were not randomized at site 91009. The TS was used for the analysis of safety, concomitant medications and diagnoses, and demographics and other baseline characteristics. Patients from site 91009 were excluded from the TS as the Applicant had concerns regarding the quality of the data from that site. At site 91009 (74 patients randomized), there were issues related to lack of concordance between drug receipt logs and drug dispensing logs. Because this cast doubt on the assignment and administration of study drug, these patients were removed from the TS.

The full analysis set (FAS) consisted of all patients who received at least one dose of study drug during the treatment period and were not at sites 1008, 3314, or 91009. The FAS was used for the analysis of COPD exacerbations and efficacy. Site 91009 was removed for reasons discussed above. At site 3314, which randomized 17 patients, at least 4 patients were also participating in a Novartis trial. At site 1008, which randomized 8 patients, there were issues with randomized treatment accountability. As a result of these issues, The Applicant considered the efficacy data from these sites questionable and removed them from the FAS.

Efficacy Analyses

Primary Analysis
The co-primary endpoints were analyzed in a hierarchical manner to protect against type 1 error. The analysis first compared trough FEV1 response for the SR 5mcg group to placebo. If superiority was demonstrated then the time to first COPD exacerbation was analyzed. All statistical tests were 2-sided with an alpha of 5%. Trough FEV1 analysis was performed using ANCOVA with center, LABA, and treatment fitted as main effects and baseline trough as a covariate. For time to first COPD exacerbation, regression analysis was performed using the Cox' proportional hazards model with center, LABA use, and treatment fitted as effects.

Secondary Analyses
The analyses of the spirometric secondary endpoints were similar to the first co-primary endpoint. However, the statistical analysis plan did not account for multiplicity.

For the endpoint of number of COPD exacerbations analyses were performed using both a Poisson and negative binomial distribution to account for asymmetry. The proportion of patients experiencing at least one COPD exacerbation was analyzed using logistic regression with center, LABA use, treatment exposure, and treatment fitted as effects and treatment exposure as a covariate. The analysis was performed including

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COPD exacerbations during both the randomized treatment period and the planned 48 week randomized treatment period. COPD exacerbations were also evaluated for those hospitalized due to a COPD exacerbation, and those with moderate or severe exacerbations

The total and component SGRQ scores were analyzed using ANCOVA.

Safety Analyses
Incidence densities, relative risk, confidence interval (CI) of relative risk and time risk for each patient were calculated for all AEs.

The date of the onset of each fatal AE episode was the minimum date of the AE occurrences that were collapsed. For all-cause mortality the earliest onset of all fatal AE episodes was used. Deaths were assigned to treatment periods in 4 ways (in order of importance):

1. planned randomized treatment start and stop dates with no washout period; date of death on or before day 337
2. actual randomized treatment start and stop dates with the 30 day washout period; date of death on or before 30 days after last dose of study medication
3. planned randomized treatment start and stop dates with the 30 day washout period; date of death on or before day 337 + 30 days (i.e. day 367)
4. actual randomized treatment start and stop dates with a 1 day washout period; date of death on or before 1 day after last dose of study medication

Kaplan-Meier and Cox regression analyses were performed for time to death (all cause, lower respiratory and cardiac). Time to death was defined as the time (in days) from the first dose of study medication to the date of death. Patients not experiencing a fatal event were censored at the end of the interval. If a patient died of other causes than the endpoint being investigated they were considered censored at the time of death.

Protocol Amendments
There were two local protocol amendments. These were submitted on July 31, 2007 and January 31, 2007 in Brazil and the UK, respectively. These amendments were similar in content. The amendments added an exclusion criterion that excluded patients currently or previously treated with Spiriva Handihaler, unless they have been discontinued from the medication due to inability to use the device. The amendments also disallowed investigators from taking patients off of Spiriva for the purposes of trials entry.

In addition to the above protocol changes, there were also changes to the planned statistical analysis and study conduct. Notable changes are as follows:

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The LABA user definition was clarified to be defined as patients who were taking a LABA on the date of randomization and continued to at least one or more days after randomization.

The definition for the FAS and TS were also amended, due to trial conduct issues with specific sites. There were concerns regarding data quality at 3 trial sites. At site 3314 (N=17), at least 4 patients were also participating in a Novartis trial. At site 1008 (N=8) there were issues with randomization. At site 91009 (N=74), there were multiple issues. These included lack of concordance between drug receipt and dispensing logs and other evidence that 'other data may be fraudulent.' As a result, of these findings, patients from these sites were removed from the FAS for efficacy analysis. Due to the exclusion of these sites from the FAS, BI performed sensitivity analysis. For the safety analysis, patients from site 91009 was not used, however, patients at sites 3314 and 1008 were (treated set).

The Applicant also made alterations to their statistical analysis plan following database lock. These changes primarily consisted of additional safety analyses and not efficacy analyses.

Given the reported issues with sites 3314, 1008, and 91009, it is reasonable to have removed them from the efficacy analysis (FAS). Inclusion of site 1008 in the safety analysis is reasonable, assuming that the conduct issues were only related to randomization. Inclusion of site 3314 is theoretically problematic as some patients may have been on a Novartis experimental drug product. However, as the total number is low and an additional experimental medication would not likely improve safety, inclusion of this site in the safety analysis is not an issue.

Safety Results

Protocol Violations

A total of 669 patients (17.1%) had important protocol violations (IPV), 316 (16.2%) patients in the SR 5mcg group and 353 (18%) in the placebo group. An important protocol violation was defined as a violation that could potentially affect the interpretation of the efficacy of safety data. The most common violation was 'may not have COPD' (4.1%), followed by incorrect trial medication taken (3.8%), and insufficient trough FEV1 data available (3.4%). This is summarized in Table 4

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Table 4. Trial 205.372. Important protocol deviations

	SR 5mcg n(%)	Placebo n(%)	Total n(%)
Total treated (treated set)	1952 (100.0)	1965 (100.0)	3917 (100.0)
Number of patients with PV	316 (16.2)	353 (18.0)	669 (17.1)
PV description			
Target indication not met − may not have COPD	87 (4.5)	75 (3.8)	162 (4.1)
Target indication not met − evidence of asthma or allergic rhinitis	30 (1.5)	20 (1.0)	50 (1.3)
Unstable baseline for primary endpoint(s) − unstable at randomization visit	17 (0.9)	12 (0.6)	29 (0.7)
Significant other disease/treatment − may obscure treatment response	22 (1.1)	21 (1.1)	43 (1.1)
Significant other disease/treatment − use of tiotropium Respimat may be contraindicated	3 (0.2)	0 (0.0)	3 (0.1)
Taken marketed Spiriva	12 (0.6)	27 (1.4)	39 (1.0)
Incorrect trial medication taken	9 (0.5)	5 (0.3)	14 (0.4)
Non−compliance	62 (3.2)	88 (4.5)	150 (3.8)
Medication code broken	1 (0.1)	0 (0.0)	1 (0.0)
Improper medication wash−out	19 (1.0)	17 (0.9)	36 (0.9)
Prohibited medication use	40 (2.0)	42 (2.1)	82 (2.1)
Insufficient trough FEV1 data available	51 (2.6)	84 (4.3)	135 (3.4)
Incorrect value − trough FEV1 recorded after dosing	26 (1.3)	31 (1.6)	57 (1.5)

source: Trial 205.372 CSR, table 15.1.2:1, p207

Disposition

All of the 3991 patients randomized received at least one dose of trial medication. However, due to trial conduct issues at three clinical site (91009, 3314, and 1008), for the treated set (TS), patients from site 91009 were excluded (n=74) and for the full analysis set (FAS) patients from all three sites were excluded (n=99). This left 3917 patients in the TS and 3892 in the FAS. The TS was used for safety analyses and the FAS for efficacy analysis. The most common reasons for discontinuation were adverse events followed by lack of efficacy. Patient disposition is summarized in Table 5.

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Table 5. Trial 205.372. Disposition

	SR 5mcg n(%)	Placebo n(%)	Total n(%)
Number of patients randomized	1989	2002	3991
Treated Set*	1952 (98.1)	1965 (98.2)	3917 (98.1)
Full Analysis Set**	1939 (97.5)	1953 (97.6)	3892 (97.5)
Not prematurely discontinued trial medication	1671 (84.0)	1629 (81.4)	3300 (82.7)
Prematurely discontinued trial medication	318 (16.0)	373 (18.6)	691 (17.3)
Adverse events	143 (7.2)	156 (7.8)	299 (7.5)
Worsening of disease under study	46 (2.3)	77 (3.8)	123 (3.1)
Worsening of other pre-existing disease	14 (0.7)	7 (0.3)	21 (0.5)
Other AE	83 (4.2)	72 (3.6)	155 (3.9)
Lack of efficacy	28 (1.4)	67 (3.3)	95 (2.4)
Non-compliant with protocol	47 (2.4)	35 (1.7)	82 (2.1)
Lost to follow-up	22 (1.1)	28 (1.4)	50 (1.3)
Consent withdrawn	20 (1.0)	35 (1.7)	55 (1.4)
Other	58 (2.9)	52 (2.6)	110 (2.8)

*excluded patients from site 91009
**excluded patients from sites 91009, 3314, and 1008
Source: trial 205.372 CSR; tables 10.1:1 and 11.1:1; pg 76 and 79

Exposure
Overall 3917 patients were exposed to at least one dose of trial medications and were included in the TS. The mean treatment exposure was 308.5 days in the SR 5mcg group and 299.5 days in the placebo group. The median exposure time was 337 days in both groups.

Deaths
The Applicant analyzed death based on 4 different treatment intervals which were planned treatment (day 337), planned treatment+30day washout (day 367), actual treatment+1 day, and actual treatment+30 days. Deaths occurring during these intervals were similar, and in all intervals deaths were more frequent in SR 5mcg compared to placebo by 0.6-0.8%. Vital status data was available for 99% of the patients at day 337. At day 367, vital status was only available for 60% of patients. These results are summarized in Table 6.

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Table 6. Trial 205.372. Death

	SR 5mcg	Placebo
Number of patients treated	1952 (100.0)	1965 (100.0)
Deaths during planned treatment (Day 337)		
With death cut off[1]	52 (2.7)	38 (1.9)
Without death cut off[2]	54 (2.8)	42 (2.1)
Deaths during planned treatment +30 days washout (Day 367)		
With death cut off[1]	55 (2.8)	43 (2.2)
Without death cut off[2]	57 (2.9)	44 (2.2)

[1]Death counted if the onset was within interval and death occurred within interval
[2]Deatth counted if the onset was within interval
source: trial 205.372; table 12.3.1:1; pg 118

The difference in deaths between SR and placebo in patients on LABAs at randomization was slightly higher at 0.9-1.2%. These data are summarized in Table 7.

Table 7. Trial 205.372. Mortality by LABA use

	+LABA use		No LABA	
	SR 5mcg	Placebo	SR 5mcg	Placebo
Number of patients treated	1058	1033	894	932
Deaths during planned treatment (Day 337)				
With death cut off[1]	26 (2.5)	16 (1.5)	26 (2.9)	22 (2.4)
Without death cut off[2]	28 (2.6)	18 (1.7)	26 (2.9)	24 (2.6)
Deaths during planned treatment +30 days washout (Day 367)				
With death cut off[1]	29 (2.7)	17 (1.6)	26 (2.9)	26 (2.8)
Without death cut off[2]	31 (2.9)	18 (1.7)	26 (2.9)	26 (2.8)

[1]Death counted if the onset was within interval and death occurred within interval
[2]Deatth counted if the onset was within interval

During the planned randomized treatment period, small numerical differences favoring placebo were seen under the system organ classes (SOC) cardiac disorders; general disorders; and neoplasms benign, malignant, and unspecified. There was also a numerical imbalance in the Applicant designated respiratory, thoracic, and mediastinal SOC subset of 'other respiratory system disorders.' Causes of death at day 337 are summarized in Table 8. This interval was chosen given that vital status data was available for 99% of patients. Note that coding is based on MedDRA 11.1 and that the Applicant also grouped together certain MedDRA preferred terms under a single 'BI collapsed term.' An example of this is the BI collapsed term for 'myocardial infarction' which included the MedDRA preferred terms acute myocardial infarction, myocardial infarction, papillary muscle infarction, and silent myocardial infarction. The Applicant also subdivided the SOC respiratory, thoracic, and mediastinal disorders into 3 categories of respiratory system disorders (upper, lower, and other). Definitions for the collapsed terms used were reviewed and considered reasonable.

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Table 8. Trial 205.372. Cause of deaths at day 337 (adjudicated) by system organ class (SOC) and preferred term (PT)

SOC/PT	SR 5mcg n(%)	ID	Placebo n(%)	ID
Number of patients treated	1952 (100)		1965 (100)	
Total treated with all fatal AE events	52(2.7)	2.94	38(1.9)	2.13
Cardiac disorders	9(0.5)	0.51	4(0.2)	0.22
Acute coronary syndrome	1(0.1)	0.06	0(0.0)	0.00
Cardiac arrest	2(0.1)	0.11	0(0.0)	0.00
Cardiac failure	1(0.1)	0.06	1(0.1)	0.06
Cardiac failure congestive	2(0.1)	0.11	0(0.0)	0.00
Cardiopulmonary failure	0(0.0)	0.00	1(0.1)	0.06
Left ventricular failure	0(0.0)	0.00	1(0.1)	0.06
Myocardial infarction$	3(0.2)	0.17	2(0.1)	0.11
Gastrointestinal disorders	1(0.1)	0.06	1(0.1)	0.06
Duodenal ulcer hemorrhage	0(0.0)	0.00	1(0.1)	0.06
Intestinal ischemia	1(0.1)	0.06	0(0.0)	0.00
General disorders and administration site conditions	19(1.0)	1.07	12(0.6)	0.67
Death	10(0.5)	0.56	7(0.4)	0.39
Sudden death	9(0.5)	0.51	5(0.3)	0.28
Infections and infestations	3(0.2)	0.17	5(0.3)	0.28
Hemophilus sepsis	1(0.1)	0.06	0(0.0)	0.00
Sepsis	1(0.1)	0.06	2(0.1)	0.11
Septic shock	1(0.1)	0.06	3(0.2)	0.17
Neoplasms benign− malignant and unspecified (incl cysts and polyps)	4(0.2)	0.23	2(0.1)	0.11
Bone cancer metastatic	0(0.0)	0.00	1(0.1)	0.06
Brain neoplasm	1(0.1)	0.06	0(0.0)	0.00
Gastric cancer	1(0.1)	0.06	0(0.0)	0.00
Gastrointestinal carcinoma	0(0.0)	0.00	1(0.1)	0.06
Gastrointestinal stromal tumor	1(0.1)	0.06	0(0.0)	0.00
Hepatic neoplasm malignant	1(0.1)	0.06	0(0.0)	0.00
Pericardial effusion malignant	0(0.0)	0.00	1(0.1)	0.06
Nervous system disorders	1(0.1)	0.06	0(0.0)	0.00
Cerebral hemorrhage	1(0.1)	0.06	0(0.0)	0.00
Psychiatric disorders	0(0.0)	0.00	1(0.1)	0.06
Completed suicide	0(0.0)	0.00	1(0.1)	0.06
Renal and urinary disorders	1(0.1)	0.06	0(0.0)	0.00
Renal failure	1(0.1)	0.06	0(0.0)	0.00
Reproductive system and breast disorders	1(0.1)	0.06	0(0.0)	0.00
Prostatic hemorrhage	1(0.1)	0.06	0(0.0)	0.00
Respiratory system disorders**(Lower)	9(0.5)	0.51	16(0.8)	0.89
Acute respiratory failure	0(0.0)	0.00	1(0.1)	0.06
Aspiration	1(0.1)	0.06	0(0.0)	0.00
Bronchitis$	0(0.0)	0.00	1(0.1)	0.06
Bronchopulmonary aspergillosis	1(0.1)	0.06	0(0.0)	0.00
COPD exacerbation$	4(0.2)	0.23	6(0.3)	0.34
Emphysema	0(0.0)	0.00	1(0.1)	0.06

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Pneumonia aspiration	2 (0.1)	0.11	1 (0.1)	0.06
Pneumonia$	1 (0.1)	0.06	8 (0.4)	0.45
Respiratory arrest	1 (0.1)	0.06	0 (0.0)	0.00
Respiratory failure	0 (0.0)	0.00	2 (0.1)	0.11
Respiratory system disorders**(Other)	5 (0.3)	0.28	2 (0.1)	0.11
Lung cancer metastatic	0 (0.0)	0.00	1 (0.1)	0.06
Lung neoplasm malignant	4 (0.2)	0.23	0 (0.0)	0.00
Non−small cell lung cancer	1 (0.1)	0.06	0(0.0)	0.00
Pulmonary embolism	0 (0.0)	0.00	1 (0.1)	0.06
Respiratory system disorders**(Upper)	1 (0.1)	0.06	0 (0.0)	0.00
Epiglottitis	1 (0.1)	0.06	0 (0.0)	0.00

**All primary SOCs were defined by MedDRA except for respiratory, thoracic, and mediastinal which was divided into lower, upper, and other respiratory disorders
$BI respiratory collapsed PT includes multiple MedDRA PTs
ID=incidence density=100*total treated with event/at-risk patient years
Source: trial 205.372 CSR; table 15.3.2.2:2; pp 657-659

When comparing investigator assigned and adjudicated causes of death, in the majority cases, the cause of death matched (63%). Mismatch was most common in the SOC cardiac disorders.

Serious Adverse Events (SAE)
Six hundred seventy eight patients (678) experienced SAEs (placebo=17.1% and SR 5mcg=17.5%). SAEs most commonly occurred in the cardiac disorder (2.8%) and respiratory thoracic and mediastinal (RTM) (11.7%) SOCs. The Applicant subdivided the RTM SOC into lower respiratory tract disorders, upper respiratory tract disorders, and other respiratory disorders. Of the SAEs in the RTM SOC, the Applicant classified almost all as lower respiratory tract disorder. SAEs in the cardiac disorders SOC were more common in the SR 5mcg compared to placebo (3.1% versus 2.4%) and were fairly balanced in the RTM SOC. Numerical differences favoring placebo were also evident for the SOCs general disorders and administrative site conditions and neoplasms benign, malignant, and unspecified. SAEs by SOC are summarized in Table 9.

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Table 9. Trial 205.372. Serious adverse events by system organ class (SOC). The preferred term (PT) is included if occurred in ≥3 patients/group and was more common in SR 5mcg compared to placebo (on treatment +30days)

SOC/PT	SR 5mcg n (%)	Placebo n (%)	Total n (%)
Number of patients treated	1952 (100.0)	1965 (100.0)	3917 (100.0)
Patients with serious adverse events	342 (17.5)	336 (17.1)	678 (17.3)
Blood and lymphatic system disorders	2 (0.1)	2 (0.1)	4 (0.1)
Cardiac disorders	60 (3.1)	48 (2.4)	108 (2.8)
Acute coronary syndrome	3 (0.2)	2 (0.1)	5 (0.1)
Atrial fibrillation/flutter$	3 (0.2)	2 (0.1)	5 (0.1)
Cardio-respiratory arrest	4 (0.2)	1 (0.1)	5 (0.1)
Coronary artery disease	5 (0.3)	2 (0.1)	7 (0.2)
Myocardial ischemia	5 (0.3)	0	5 (0.1)
Ear and labyrinth disorders	2 (0.1)	1 (0.1)	3 (0.1)
Endocrine disorders	1 (0.1)	0 (0.0)	1 (0.0)
Eye disorders	1 (0.1)	1 (0.1)	2 (0.1)
Gastrointestinal disorders	30 (1.5)	31 (1.6)	61 (1.6)
General disorders and administrative site conditions	24 (1.2)	6 (0.3)	30 (0.8)
Chest pain	4 (0.2)	0	4 (0.1)
Death	5 (0.3)	1 (0.1)	6 (0.2)
Hepatobiliary disorders	2 (0.1)	7 (0.4)	9 (0.2)
Immune system disorders	0 (0.0)	1 (0.1)	1 (0.0)
Infections and infestations[1]	25 (1.3)	25 (1.3)	50 (1.3)
Sepsis	4 (0.2)	2 (0.1)	6 (0.2)
Urinary tract infection$	3 (0.2)	2 (0.1)	5 (0.1)
Injury, poisoning and procedural complications[1]	19 (1.0)	17 (0.9)	36 (0.9)
Fall	5 (0.3)	4 (0.2)	9 (0.2)
Road traffic accident	4 (0.2)	1 (0.1)	5 (0.1)
Investigations	4 (0.2)	2 (0.1)	6 (0.2)
Metabolism and nutrition disorders	8 (0.4)	8 (0.4)	16 (0.4)
Musculoskeletal and connective tissue disorders	9 (0.5)	9 (0.5)	18 (0.5)
Neoplasms benign, malignant and unspecified (incl. polyps and cysts)[1]	29 (1.5)	18 (0.9)	47 (1.2)
Brain neoplasm	3 (0.2)	0	3 (0.1)
Gastric cancer	3 (0.2)	1 (0.1)	4 (0.1)
Nervous system disorders	19 (1.0)	22 (1.1)	41 (1.0)
Cerebral infarction	3 (0.2)	2 (0.1)	5 (0.1)
Psychiatric disorders	3 (0.2)	7 (0.4)	10 (0.3)
Renal and urinary disorders	17 (0.9)	6 (0.3)	23 (0.6)
Renal failure	3 (0.2)	1 (0.1)	4 (0.1)
Renal failure acute	3 (0.2)	2 (0.1)	5 (0.3)
Urinary retention	5 (0.3)	1 (0.1)	6 (0.2)
Reproductive system and breast disorders	6 (0.3)	3 (0.2)	9 (0.2)
Benign prostatic hyperplasia	5 (0.3)	1 (0.1)	6 (0.2)
Lower respiratory system disorders[2]	191 (9.8)	211 (10.7)	402 (10.3)
Acute respiratory failure	4 (0.2)	3 (0.2)	7 (0.2)
Bronchitis$	7 (0.4)	6 (0.3)	13 (0.3)
Dyspnea$	11 (0.6)	4 (0.2)	15 (0.4)
Pulmonary edema	3 (0.2)	1 (0.1)	4 (0.1)
Other respiratory system disorders[2]	25 (1.3)	15 (0.8)	40 (1.0)
Bronchial carcinoma	3 (0.2)	2 (0.1)	5 (0.1)
Lung neoplasm malignant	10 (0.5)	2 (0.1)	12 (0.3)
Pulmonary embolism	3 (0.2)	2 (0.1)	5 (0.1)

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Upper respiratory system disorders[2]	8 (0.4)	7 (0.4)	15 (0.4)
Upper respiratory tract infection	5 (0.3)	3 (0.2)	8 (0.2)
Skin and subcutaneous tissue disorders	2 (0.1)	1 (0.1)	3 (0.1)
Social circumstances	1 (0.1)	0 (0.0)	1 (0.0)
Surgical and medical procedures	3 (0.2)	2 (0.1)	5 (0.1)
Vascular disorders	8 (0.4)	12 (0.6)	20 (0.5)

[1]PTs with secondary relationship to SOC RTM are not included
[2]All primary SOCs were defined by MedDRA except for RTM which was divided into lower, upper, and other respiratory disorders
$BI collapse preferred term included multiple MedDRA preferred terms
source: trial 205.372 CSR; tables 12.3.2:1 and 15.3.2.1:4; pg139 and 460-474

It should also be noted that for the BI collapsed term of myocardial infarction, the percentage of patients with events was similar between treatment groups (0.4-0.5%), and for the BI collapse terms COPD exacerbation and pneumonia there were fewer events in the SR 5mcg group compared to placebo (7.1% vs. 8.5% and 1.6 vs. 2.4%, respectively).

ECG and vital signs
ECGs were performed at the screening visit, week 4, and at end of study. Any significant findings were reported as adverse events. At screening, the percentage of patients with significant findings were similar between groups (SR 5mcg=10.8%, placebo=9.3%). At week 4 and at end of treatment, similar percentages of patients had no new/worsening of ECG findings between treatment groups.

Vital signs were taken at screening, weeks 0, 4, 24, and end of treatment. Mean baseline blood pressures and pulse rates were similar between treatment groups. No clinically significant differences between treatment groups were observed from baseline to the end of the treatment period.

Common adverse events
Common adverse events (≥3%) were generally similar between treatment groups or more frequent in the placebo group compared to SR 5mcg. However, events in the collapsed term dry mouth occurred more frequently in the SR 5mcg group compared to placebo. This is not surprising as this is a known anticholinergic effect. The AEs are typical of what would be expected in a COPD population. These are summarized in Table 10

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Table 10. Trial 205.372. Common adverse events (≥3%) by SOC and PT

	SR n(%)	Placebo n(%)	Total n(%)
Number of patients treated	1952 (100.0)	1965 (100.0)	3917 (100.0)
Patients with any AE	1369 (70.1)	1361 (69.3)	2730 (69.7)
Gastrointestinal disorders	278 (14.2)	238 (12.1)	516 (13.2)
Dry mouth[2]	60 (3.1)	27 (1.4)	87 (2.2)
Lower respiratory system disorders[1]	902 (46.2)	1013 (51.6)	1915 (48.9)
Bronchitis[2]	67 (3.4)	95 (4.8)	162 (4.1)
COPD exacerbation	641 (32.8)	759 (38.6)	1400 (35.7)
Cough	124 (6.4)	108 (5.5)	232 (5.9)
Dyspnea[2]	136 (7.0)	152 (7.7)	288 (7.4)
Pneumonia[2]	65 (3.3)	74 (3.8)	139 (3.5)
Productive cough	60 (3.1)	61 (3.1)	121 (3.1)
Upper respiratory system disorders[1]	459 (23.5)	439 (22.3)	898 (22.9)
Nasopharyngitis	157 (8.0)	151 (7.7)	308 (7.9)
Upper respiratory tract infection[2]	124 (6.4)	144 (7.3)	268 (6.8)

[1] All primary SOCs were defined by MedDRA except for RTM which was divided into lower, upper, and other respiratory disorders
[2]BI collapse preferred term included multiple MedDRA preferred terms
Source: trial 205.372 CSR; table 12.2.2.1:1; pg108

As with the exacerbation trials (205.254 and 205.255) submitted with the initial NDA, trial 205.372 also demonstrates a small numerical mortality difference favoring placebo. This difference did not appear to be driven by a single SOC or PT, also consistent with trials 205.254 and 205.255. These are later discussed in the context of the full development program (section 7 Review of Safety).

5.3.2 Large Safety Trial [205.452 (TIOSPIR)]

Administrative Information

- **Title**: A randomized, active-controlled, double-blind, double dummy, parallel group multicenter trial to compare efficacy and safety of treatment of tiotropium inhalation solution 2.5mcg and 5 mcg delivered by the Respimat inhaler with tiotropium inhalation capsules 18mcg delivered by the Handihaler in patients with chronic obstructive pulmonary disease (COPD)
- **Dates:** May 14, 2010 to May 23, 2013
- **Sites:** Multi-national (50 countries, 1280 sites)
- **Report date: September 23, 2013**

Objectives/Rationale

- To evaluate the safety and efficacy of SR 2.5 and 5mcg compared to SHH in patients with COPD

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Study Design and Conduct

Overview

This trial was a multicenter, multinational, randomized, double-blind, double dummy parallel group trial to compare the efficacy and safety of SR 2.5 mcg and 5 mcg compared with SHH 18 mcg in patients with COPD. This trial was event driven and designed to end after approximately 1,266 fatal adverse events which was predicted to occur within 3.5 years. All patients were followed until the end of the trial for vital status, regardless of if trial medication was discontinued.

This trial was projected to have 10-17 clinics visits depending on the length of time required to accrue 1266 fatal events. At the initial visit (visit 0), eligibility was determined and consent obtained. Eligible patients returned for visit 1, where eligibility was confirmed and patients were randomized to receive SR 2.5mcg, SR 5mcg or SHH. After the randomization visit, patients were seen at week 6 and 12, and then every 12-weeks thereafter until the end of the trial. In between visits, there was interim contact every 6 weeks. All patients also received salbutamol/albuterol MDI inhalers for rescue use and were permitted to use stable baseline respiratory medications other than anticholinergics (usual care). LABAs were allowed as background therapy.

This trial also included a PFT sub-study in which a randomized subset of patients received periodic PFTs (spirometry every 24 weeks until trial close-out). The sub-study was projected to included 1305 patients. Eligibility criteria were the same as the larger trial. Allowed medications were also similar, except that a 24-hour washout period for long-acting anticholinergic agents prior to PFTs was required. The trial and PFT sub-study assessment schedules are summarized in Table 11 and Table 12.

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Table 11. Trial 205.452 Assessment schedule

		Treatment Period						Follow up contact
Visit Number	0	1	2	3	Interim contact[6]	4 to *Last treatment visit determined by event-driven end of trial*	*End of treatment*	
Visit Time	Visits 0 and 1 may occur on the same day in some cases[1]	Week 0 (Maximum 4 weeks from Visit 0)	Week 6 (± 7 days)	Week 12 (± 7 days)	Week 18 (± 7 days) and 6 weeks after each treatment visit (Weeks 30, 42, 54, 66, 78, 90, 102, 114, 126, 138, 150, 162, 174)	Week 24 and every 12 weeks (± 14 days) thereafter (Weeks 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180)	*Variable depending on event driven end of trial*	(30 ± 5 days)
Informed consent	X							
Demographics		X						
Medical History including MMRC dyspnea scale		X						
Inclusion / exclusion criteria		X						
PFTs (FEV_1 / FVC)		X[2]						
Physical examination		X						
Pregnancy test for women of childbearing potential		X[3]					X[3]	
Vital signs (seated)		X						
12-lead ECG		X						
Training in use of study drugs		X	X	X		X		
Conclusion of screening		X						
Randomization (IVRS / IWRS)		X						
Dispense study drugs		X		X		X		
Inhalation of first dose of study medication		X[4]						
Collect study drugs				X		X	X	
Drug accountability			X	X		X	X	
Review smoking status		X	X	X		X	X	X
Review exacerbation status		X	X	X	X	X	X	X
Adverse Events[7]		X	X	X	X	X	X	X
Concomitant therapies		X	X	X	X	X	X	X
Dispense subject reminder card		X	X	X		X	X	
Collect subject reminder card			X	X	X[9]	X	X	X[9]
Trial ID card dispensed		X						
Termination of trial medication							X[5,8]	

1 The subject was required to sign informed consent prior to any study related activities. In some cases, subjects may have signed consent (Visit 0) and have been randomized (Visit 1) on the same day. This was acceptable if the subject had spirometry data documented at the site or the site had the facilities to perform spirometry after informed consent was provided. Subjects who needed to be referred to a separate site for spirometry testing, or who did not have the spirometry data documented at the site, were not to have been randomized until spirometry results were available at the site.

2 Pulmonary function tests were to be conducted after the inhalation of 400 µg salbutamol / albuterol (preferred). Testing with either 200 µg salbutamol/albuterol or a combination of salbutamol / albuterol with ipratropium bromide (2 to 4 actuations) was acceptable. Additionally, other short-acting beta agonists, such as terbutaline may have been used for the testing. The medication used for the testing was documented. Furthermore historical data from measurements within the past 6 months either at the site or at a referral site may have been used. If the measurements were not performed at the trial site, a referral letter and signed copies of the measurement printouts must have been provided to the trial site for source data verification. Subjects were not have been randomized to the study without the availability of spirometry data at the actual study site.

3 Urine test at site prior to randomization and at final treatment visit. If urine test was not acceptable to local authorities, a blood test could have been done at a local laboratory.

4 Subjects taking commercial tiotropium who took their daily tiotropium dose on the day of randomization were trained on the proper inhalation techniques by using the placebo training devices but were not to inhale the first dosage of study drug on that day (overdosing). The investigator / study nurse assembled the first Respimat® device with the cartridges together with the subject and the subject self-administered the first dosage the day after Visit 1 at home.

5 Termination of study medication was at final visit. The entire length of the treatment period was determined by the event driven defined end of the trial.

6 A personal contact (preferably telephone) took place between each treatment visit. The PI or designee contacted the subject and collected information regarding COPD exacerbation status, concomitant medication status, and adverse events (See footnote 8). For subjects who discontinued trial medication, a personal contact was made every 12 weeks.

7 Adverse event reporting included COPD exacerbations, pneumonia, MACE, SAEs, related AEs, and AEs leading to discontinuation.

8 Subjects who discontinued treatment prior to the declared end of the trial were contacted for the 30-day follow up contact (e.g., telephone call). Following this, the subject was followed for vital status information every 12 weeks until the end of the trial.

9 The reminder card information collected during the interim contacts and the follow-up contact was done verbally.

Source: Trial 205.452 CSR; table 9.5.8:1; pp65-67

Table 12. Trial 205.452. Assessment schedule PFT sub-study

		Treatment Period	
Visit Number	**0**	**1**	**Visit 4 to *Last treatment visit determined by event driven end of trial (Visits 4, 6, 8, 10, 12, 14)***
Visit Time		+1 day[1] (At least 1 day between Visits 0 and 1 with maximum 4 weeks from Visit 0)	Every 24 weeks (± 14 days) thereafter (Weeks 24, 48, 72, 96, 120, 144)
Informed Consent	X		
Qualifying pulmonary function testing (FEV_1/FVC)		X[2]	
Randomization (IVRS/IWRS)		X	
Pre-dose pulmonary function testing (FEV_1/FVC)			At each of these visits, subjects were to complete PFTs at a single time point in triplicate to record pre-dose measurement. The PFTs were to be done in the clinic prior to the investigational product daily dosing and approximately 24 hours after dosing on the previous day. Therefore, the clinic visit was to be between 7:00 am and 10:00 am. Subjects were required to washout of certain medications.

1 Subjects treated with tiotropium were required to washout of tiotropium for at least 24 hours prior to performing the baseline measurements for the trial. Those subjects not taking commercial tiotropium must have met the specified washout criteria and could have returned as soon as the day following signed informed consent to perform the baseline spirometry and post-bronchodilator inclusion spirometry.
2 Subjects needed to qualify for the trial at this visit. For subjects participating in the spirometry sub-study, historical data was not to be used for inclusion. These subjects needed to qualify in the clinic at Visit 1 after performing a baseline measurement. These subjects performed a pre-dose PFT (baseline) which was followed by the administration of 400 µg salbutamol / albuterol followed by a post-dose PFT for qualification. See Table 9.5.8: 1 for details.

Source: Trial 205.452 CSR; table 9.5.8:2; pg69

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Trial Population

The trial consisted of COPD patients randomized using an interactive voice response system (IVRS) interactive web based response system (IWRS).

Key Inclusion Criteria

1. Signed informed consent consistent with ICH GCP guidelines prior to participation in the trial, including medication washout and restrictions
2. Male or female patients 40 years of age or older
3. Current or ex-smoker with a smoking history of ≥10 pack years; patients who had never smoked cigarettes were to be excluded
4. Diagnosis of COPD; patients must have relatively stable airway obstruction with a post-bronchodilator FEV1 ≤70% predicted and FEV1 ≤70% of FVC. This criterion may be met using historical data from the past 6-months at either the

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trial site or from the referral site. If measurements are not performed at the trial site, a referral letter with copies of the measurement printouts must be provided to the trial site. However, prior to randomization, spirometry data must be available from the actual trial site.

5. Patients must have been able to use the Respimat inhaler and Handihaler correctly

Key Exclusion Criteria

1. Significant diseases other than COPD. A significant disease is defined as a disease or condition which, in the opinion of the investigator, may put the patient at risk because of participation in the study or may influence the patients' ability to participate in the study.
2. Patients with a recent history (i.e., six months or less) of myocardial infarction.
3. Patients with any unstable or life-threatening cardiac arrhythmia requiring intervention or change in drug therapy during the last year.
4. Hospitalization for cardiac failure (New York Heart Association (NYHA) Class III or IV) during the past year.
5. Known active tuberculosis.
6. Patients with a history of asthma, cystic fibrosis, bronchiectasis, interstitial lung disease, or pulmonary thromboembolic disease
7. A history of thoracotomy with pulmonary resection. Patients with a history of thoracotomy for other reasons should be evaluated as per Exclusion 1.
8. Patients planning to undergo lung transplant or lung volume reduction surgery.
9. Malignancy for which the patient has undergone resection, radiation, chemotherapy or biological treatments within the last five years. Patients with treated basal cell carcinoma are allowed.
10. A respiratory infection or exacerbation of COPD in the four weeks prior to screening.
11. Known hypersensitivity to anticholinergic drugs, lactose, benzalkonium chloride (BAC), ethylenediaminetetraacetic acid (EDTA) or any other components of the HandiHaler or Respimat inhalation solution delivery system.
12. Patients with known moderate to severe renal impairment (as judged by the investigator).
13. Patients with known narrow angle glaucoma.
14. Patients with significant symptomatic prostatic hyperplasia or bladder-neck obstruction. Patients whose symptoms are controlled on treatment may be included.
15. Use of systemic corticosteroid medication at unstable doses (i.e., less than six weeks on stable dose) or at doses in excess of the equivalent of 10 milligrams (mg) prednisolone per day
16. Pregnant or nursing women or women of childbearing potential not using a medically approved means of contraception (i.e., oral contraceptives, intrauterine devices, diaphragm or subdermal implants) for at least three months prior to and for the duration of the trial

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17. Significant alcohol or drug abuse within the past 12 months.
18. Patients requiring the use of supplemental oxygen therapy for >12 hours per day
19. Patients who have completed a pulmonary rehabilitation program in the six weeks prior to the screening visit or patients who are currently in a pulmonary rehabilitation program that will not be maintained throughout the duration of the study.
20. Patients who have taken an investigational drug within 30 days prior to Screening Visit.
21. Previous participation (receipt of randomized treatment) in this study.
22. Patients who are currently participating in an interventional study.

Patient Removal Criteria
All patients including those who discontinue trial medication early will be followed until the end of the trial. An individual patient must be discontinued from study treatment if any of the following criteria are met:

1. Intercurrent illness or an adverse event, which requires discontinuation of treatment per protocol
2. Persistent gross non-compliance with the protocol
3. Decision by the Applicant
4. Withdrawal of consent

This protocol was previously reviewed and agreed upon by the agency and the Applicant. The inclusion and exclusion criteria are also appropriate. It is worth noting that there are no specific ECG exclusion or stopping criteria. Lack of such criteria may result in a study population that is more representative of a “real world” COPD population.

Treatments
Treatment Groups
SR 2.5mcg qD (2 actuations of 1.25mcg/actuation)
SR 5mcg qD (2 actuations of 2.5mcg/actuation)
SHH 18mcg
Double-dummy placebos

Concomitant/Restricted Medications:
Medications taken by the patient within 2 months of the screening visit and throughout the trial were recorded in the electronic case report form (eCRF). All medications used during the trial were also recorded in the eCRF. Use of short acting bronchodilators (beta-2 agonists) was allowed as necessary. In the case of life threatening COPD exacerbations, any and all therapies were allowed. Use of systemic corticosteroids at unstable doses (i.e. <6 weeks on stable dose) or at doses >10mg prednisolone per day was prohibited. Short and long-acting anticholinergic drugs were prohibited during the treatment period.

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Primary Endpoints
The primary safety endpoint was time to all-cause mortality. The primary efficacy endpoint was time to first COPD exacerbation.

Patients who discontinued trial medication prematurely continued to be followed every 12-weeks for vital status information until the end of the trial.

COPD exacerbation was defined as a complex of respiratory events/symptoms with a duration of ≥3 days, requiring a change in treatment where a complex respiratory event/symptom was defined as with ≥ 2 of the following:

- Shortness of breath
- Sputum production (volume)
- Occurrence of purulent sputum
- Cough
- Wheezing
- Chest tightness

The change in/or requirement of treatment includes the following:

- Prescription of antibiotics and / or systemic corticosteroids
- And/or a newly prescribed maintenance respiratory medication (i.e. bronchodilators including theophylline).

The onset of an exacerbation was defined by the onset of the first recorded symptom. The end of the exacerbation was recorded as defined by the investigator.
Exacerbation severity was defined as follows:

- Mild: a new prescription of maintenance bronchodilator therapy
- Moderate: antibiotics or systemic steroids without hospitalization
- Severe: hospitalization

Secondary Endpoints
Efficacy:
Secondary efficacy endpoints were as follows:

- Number of COPD exacerbations
- Time to first COPD exacerbation associated with hospitalization
- Number of COPD exacerbations associated with hospitalization

Endpoints in PFT-sub-study

- Trough FEV1
- Trough FVC

Trough was defined as defined the measurement at the -10 minute point at the end of the 24 hours dose interval

Safety:

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Secondary safety endpoints included analysis of adverse events. Given the large size of this trial only the following adverse events were collected:

- All adverse events determined by the investigator to be related to study medication
- All adverse events leading to permanent discontinuation of study medication
- All fatal adverse events (FAEs) including follow-up of vital status from patients who prematurely discontinue treatment. All causes of death were adjudicated by an independent Mortality Adjudication Committee (MAC).
- All serious adverse events (SAEs)

The following AEs were also collects as protocol defined outcome events:

- All COPD exacerbations
- All pneumonias
- All myocardial infarctions (serious and non-serious)
- All strokes (serious and non-serious)
- All transient ischemic attacks (TIA)

These protocol defined outcome events were collected on outcome event forms and also on adverse event forms. The outcome events were centrally monitored to determine if recorded events met the pre-specified definition outlined in the protocol.

Secondary safety endpoints also included analyses of major adverse cardiovascular events (MACE). The MACE related safety endpoints were as follows:

- Time to onset 1st MACE
- Time to death from MACE

For definitions for MACE, stroke, TIA, and MI see section 7.1.2 Categorization of Adverse Events.

Compliance
At each visit, patients were given a patient reminder card. On this card, they were to record if they missed any medication doses. These were returned at the following visits. Compliance was calculated based on the doses used during the maximum possible treatment period. Compliance was also to be inferred from data from the PFT sub-study.

All used and unused medication was returned at each patient visit, however, it does not appear that this was used to calculated compliance.

Ethics:
This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol. No changes were made without the IRB's approval.

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Statistical Analysis

Sample size

Sample size calculations were based on all-cause mortality data at 2-years from the UPLIFT trial (5.6% for SHH) and the following assumptions:

- one-sided significance level of 2.5%
- 5.6% death rates at 2 years for SHH, 5 µg and 2.5 µg SR
- length of accrual of 1.5 years
- maximum length of follow-up of 3.5 years
- a lost to follow-up rate of 1% (based on an assumption of close to complete vital status follow of all patients)
- 90% power
- a non-inferiority delta of 1.25

Based on this the Applicant estimated that to determine non-inferiority with 90% power, the minimum number of fatal cases needed was 1,266 and the total number of patients was 16,800 (5,587 patients per group). The point estimate of the hazard ratio can be no larger than 1.09. Power calculations are summarized in Table 13.

Table 13. Trial 205.452. Power calculations

	Power= 80%		Power=85%		Power=90%	
Non-inferiority delta	N per group	Hazard ratio[1]	N per group	Hazard ratio[1]	N per group	Hazard ratio*
1.20	6251	1.06	7151	1.07	8369	1.08
1.25	4174	1.07	4774	1.08	5587	1.09
1.30	3019	1.08	3454	1.10	4052	1.11

*maximum hazard ratio that will retain non-inferiority
Source: Trial 205-452 protocol; table 7.6:1; pg52

Analysis populations

This trial had three analysis populations: death analysis set, treated set, and sub-study set. The death analysis set (DAS) included all patients excluding only those who were documented as not treated. The treated set (TS) consisted of all patients from the DAS excluding patients from sites 1280 (n=5) and 49157 (n=14). These sites were excluded due to data irregularities found on audit. These sites were excluded prior to database lock. During a BI audit of site 1280, it was determined that there may have been a lapse in primary investigator (PI) oversight when the site PI changed. Site 49157 reported to BI that a previous study coordinator had reported invalid vital status data for one patient 1.5 years after the patient died. BI then audited the site and confirmed that the validity of the site data was questionable with respect to retrospective preparation of source data, discrepant data between source data and CRF, back-dating of signatures, and lack of audit trail for electronic source data. Final vital status data was collected a new study nurse and found to be reliable. The sub-study set (SSS) population included all patients

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in the TS who received PFTs and had at least baseline and on on-treatment trough FEV1. The DAS was used for analysis of all mortality related endpoints. The TS was used for all other planned analyses. The SSS was used to analysis of spirometry.

Primary Analysis
To control for type 1 error, non-inferiority analysis of the primary endpoints was hierarchical. The initial comparison for time to all-cause mortality was between SHH and SR 5mcg, and then SHH and SR 2.5mcg. The non-inferiority delta was 1.25. If the upper bound of the 95% CI for the hazard ratio was <1.25, then the Applicant concluded that non-inferiority was achieved. This analysis was performed using the DAS. Patients who prematurely discontinued were followed until the end of trial for vital status assessment. Those who were lost to follow-up were censored at the last known vital status. After non-inferiority for time to all-cause mortality was evaluated, SR 5mcg was compared to SHH for superiority in terms of time to exacerbation. This analysis was performed in the TS.

Secondary Analysis
Secondary endpoints which were time to event were analyzed using Cox proportional hazards regression model. Note that protocol defined outcome events (i.e., myocardial infarction, stroke, COPD exacerbations, transient ischemic attacks, and pneumonia) were analyzed as time to event. No multiplicity adjustments were made for the secondary endpoints.

PFT sub-study analysis
Analyses of PFT sub-study was conducted regardless of the outcome of the primary testing. Non-inferiority comparisons were performed in a hierarchical manner first comparing SR 5mcg to SHH, and then SR 2.5mcg to SHH. The non-inferiority delta used in both comparisons was 50mL.

Protocol amendments
One protocol amendment was made on 9/10/10. The changes included addition of the modified medical council (MMRC) dyspnea scale to the medical history and clarification as to which AEs were not being collected.

Additionally, due to data irregularities that brought into question the data generated at sites 1280 (5 patients) and site 49157 (14 patients), prior to database lock, the Applicant decided to only include these patients in the analysis of mortality (DAS). These patients were not included in the TS and not used in the analysis of the other non-objective endpoints.

The propose non-inferiority margin was previously agreed upon when the protocol was reviewed. Note that while a non-inferiority margin was pre-defined for all-cause mortality, this was not the case with MACE and/or CV events. With regard to the data irregularities at sites 1280 and 49157, given that these sites only included 19 patients,

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that they were evenly distributed among the treatment groups, and given the total size of the trial; it is unlikely that exclusion of these patients from the analyses of the non-mortality related would affect data interpretation. Including these 19 patients in the mortality analysis is reasonable given that mortality is an objective endpoint.

3.3.1 Trials 205.127, 205.249, 205.250, 205.254, 205.255 (48-week exacerbation trials), 205.251, and 205.252 (12-week bronchodilation trials)

These trials were previously reviewed by the Agency at the time of the original NDA submission (see Dr. Theresa Michele's review dated 7/31/08 and Dr. Yun Xu's review dated 7/31/08). For trials 205.254, 205.255, 205.251 and 205.252, this section will only include a brief summary of the protocols. Safety and efficacy results are not summarized here, as results from these trials are incorporated into the discussion of safety and efficacy in Section 6 Review of Efficacy and Section 7 Review of Safety. For trials 205.127, 205.249, and 205.250 a brief summary of the protocol and results are included in this section as they are not discussed elsewhere in this document.

Trial 205.127: Dose Selection Trial

Trial 205.127 was a randomized, double-blind, placebo controlled parallel group dose-ranging trial in patients with COPD. Treatment arms included SR 1.25mcg, 2.5mcg, 5mcg, 10mcg, and 20mcg. In addition, there was also a SHH treatment arm, Handihaler placebo arm, and Respimat placebo arm. This trial included a 1-week screening period, a 3-week treatment period, and a 1-week follow-up period. The primary endpoint was trough FEV1 at the end of treatment. Secondary endpoints included other spirometric parameters, pharmacokinetic (PK) evaluations, and rescue medication use. Safety endpoints included adverse events, vital signs, laboratory evaluations, ECGs, and physical examinations. The trial included 202 moderate to severe COPD patients of which 191 completed. With regard to the primary endpoint, there was a numerical increase in trough FEV1 at week 3 for all SR groups relative to placebo, though there was no clear dose ordering. The difference from placebo was only statistically significant for SR 5mcg 20mcg. The SR 1.25 and 2.5mcg groups did not demonstrate a clinically important response and SR 20mcg did not appear to show a benefit above the lower doses. These results are summarized in Table 14.

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Table 14. Trial 205.127. Trough FEV1 dose response results

Treatment group	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**
Placebo Respimat qD	24	0.02	
Spiriva Handihaler 18 mcg qD	25	0.23	0.32**
Handihaler Placebo	23	-0.09	

*adjusted for baseline
**statistically significant
Source: CDTL memo of NDA 21936 dated 8/22/08; table 2; pg 9

Similar results were generally observed for the other spirometric endpoints. Rescue medication use was also decreased in SR groups compared to placebo. With regard to PK evaluations, urinary excretion of tiotropium was dose-dependent and increased with increasing doses across the SR groups. Dose dependency was also apparent for peak and trough values. Based on these results, the Applicant carried the SR 5 and 10mcg doses to phase 3. With regard to safety, no specific safety concerns were raised.

Trial 205.249 and 205.250: Serial Spirometry and Pharmacokinetic (PK) Trials
Design
Trials 205.249 and 205.250 were identical in design. They were 4-week treatment period, randomized, double-blind, double-dummy, placebo-controlled cross-over trials in COPD patients. Cross-over treatment arms included SR 5mcg, SR 10mcg, SHH, and placebo treatment arms. Treatment periods were 4-weeks and were separated by a 4-week washout period. Included patients had a diagnosis of COPD with an FEV1 ≤ 60% predicted and FEV1/FVC ratio of ≤70%. All were current of ex-smokers. Use of anticholinergic and LABA drugs was prohibited during the treatment period (except for trial medication). The primary endpoint was trough FEV1 at the end of each 4-week treatment period. Trough FEV1 was defined as in trial 205.372. Secondary endpoints included FEV1 AUC(0-12hrs) after 4-weeks of treatment. Blood and urine samples were also collected for PK evaluation. Safety evaluations included adverse events, physical exam, vital signs, ECG, and clinical labs.

Results 205.249
Trial 205.249 randomized 131 patients. Of the randomized patients, 38 patients discontinued prematurely, 5 during the SR 5mcg period, 8 during the SR 109 mcg period, 2 during the SHH period, 9 during the placebo period, and 14 during washout periods. The majority of patients were white (98%) males (64%) with a mean age of 64 years and mean FEV1 of 1.0 L and FEV1/FVC ratio of 45%.

Reference ID: 3618244

Compliance was assessed based on diary entries. Across treatment periods, compliance was approximately 99%. Results for the primary endpoint are summarized in Table 15. The treatment effect at week of treatment for SHH is numerically smaller than both SR doses.

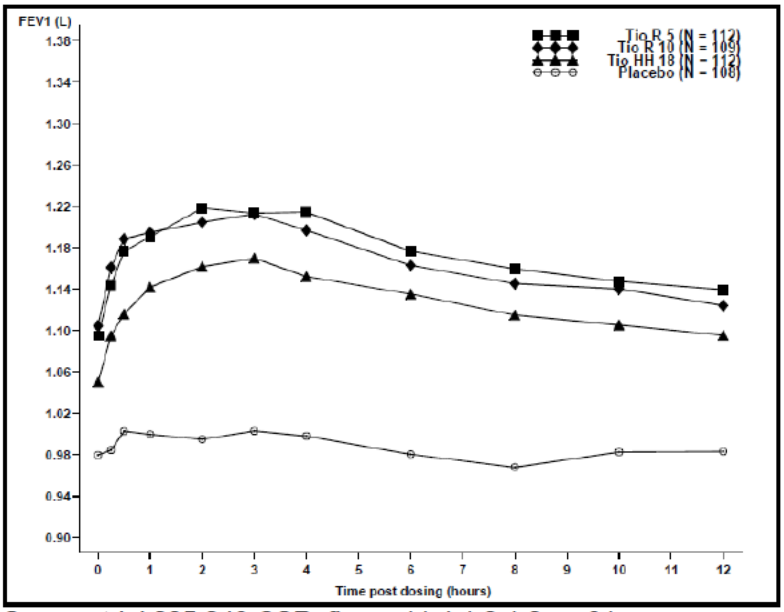
Table 15. Trial 205.249. Trough FEV1 difference from placebo

Treatment	Trough FEV1 Difference from placebo	95% confidence interval	p-value
SR 5mcg (n=112)	0.116	(0.083, 0.149)	<0.001
SR 10mcg (n=109)	0.125	(0.092, 0.158)	<0.001
SHH (n=112)	0.070	(0.037, 0.104)	<0.001
Placebo (n=108)	-	-	-

Source: trial 205.249 CSR; table 11.4.1.1:1; pg89

For FEV1 AUC (0-12hours), SR 5mcg, SR 10mcg, and SHH demonstrated statistically significant improvement versus placebo. Results for FEV1 AUC(0-12hrs) are summarized graphically in Figure 4.

Figure 4. Trial 205.249. Mean FEV1 (L) time response curve at week 4



Source: trial 205.249 CSR; figure 11.4.1.2.1:2; pg91

These data demonstrate that SR 5mcg, 10mcg, and SHH improve trough FEV1 compared to placebo. PK data from this trial is summarized in Figure 2

Mean exposures to SR 5mcg, SR 10mcg, SHH, and placebo during the cross-over treatment periods ranged from 28-30 days. There were two fatal events during this trial. One was a 66 year old male with COPD and a history of coronary artery disease, hypertension, 1st degree atrioventricular block, and bundle branch block. The fatal event occurred on day 2 of SR 5mcg treatment period and the cause of death was cardiac

arrest due to atherosclerotic coronary artery disease. The other fatal event occurred in a 68 year old male with COPD and recent history of thrombus in superior vena cava. The fatal event occurred on day 27 of placebo treatment and the cause of death was listed as sudden cardiac arrest secondary to atherosclerotic coronary artery disease. Given the patients' history and timing of the event it appears unlikely that these were related to SR exposure.

A total of 18 patients experienced a serious adverse event (SAE). SAEs were evenly distributed across treatment periods. The most common SAE was COPD exacerbation. During each treatment period, no SAE by preferred term occurred in >2 patients. Common AEs (>3% in any treatment period) were fairly similar between treatment periods (range: 29-33%). Common AEs included COPD exacerbation and upper-respiratory tract infection. The frequency of COPD exacerbations was similar between treatment periods. Upper respiratory tract infections were more frequent during the SR 5mcg treatment period (4.5%) compared to the other treatment periods (1.8-1.9%). Overall, the safety profile of SR seen in this trial is consistent with that seen in the larger pooled safety databases.

Results 205.250
Trial 205.250 randomized 76 patients. Of the randomized patients, 1 patient discontinued during the SR 5mcg period and 2 during the placebo period. The majority of patients were white (99%) males (63%) with a mean age of 65 years and mean FEV1 of 1.1 L and FEV1/FVC ratio of 37%.

Compliance was assessed based on diary entries. Across treatment periods, compliance was approximately 90-100%. Results for the primary endpoint are summarized in Table 15. The treatment effect at week of treatment for SHH is numerically smaller than both SR doses.

Table 16. Trial 205.249. Trough FEV1 difference from placebo

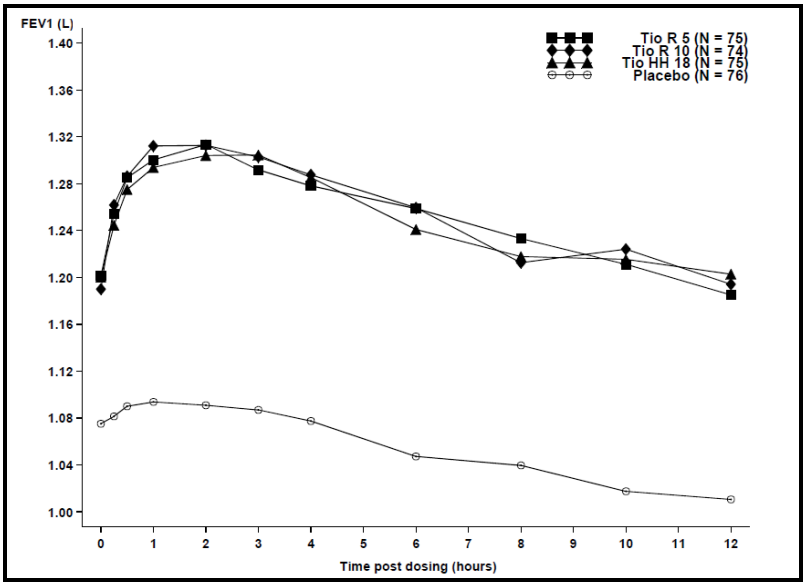
Treatment	Trough FEV1 Difference from placebo	95% confidence interval	p-value
SR 5mcg (n=75)	0.126	(0.086, 0.166)	<0.001
SR 10mcg (n=74)	0.115	(0.075, 0.155)	<0.001
SHH (n=75)	0.125	(0.085, 0.165)	<0.001
Placebo (n=76)	-	-	-

Source: trial 205.250 CSR; table 11.4.1.1:1; pg85

For FEV1 AUC (0-12hours), SR 5mcg, SR 10mcg, and SHH demonstrated statistically significant improvement versus placebo. Results for FEV1 AUC (0-12hrs) are summarized graphically in Figure 5.

Reference ID: 3618244

Figure 5. Trial 205.250. Mean FEV1 (L) time response curve at week 4



Source: trial 205.250 CSR; figure 11.4.1.2.1:2; pg88

These data demonstrate that SR 5mcg, 10mcg, and SHH improve trough FEV1 compared to placebo. Compared to trial 205.249, the treatment effect for SHH is larger in this trial. PK data from this trial is summarized in Figure 2

Mean exposures to SR 5mcg, SR 10mcg, SHH, and placebo during the cross-over treatment periods was 30 days. There were two fatal events during this trial. One was in a 57 year old female with COPD and a history right bundle branch block. The fatal event occurred during the SR 5mcg treatment period. This patient experienced a COPD exacerbation and was seen by her physician who recommended hospitalization. The patient refused hospitalization and was found dead two days later. The second fatal event occurred in a 60 year old male approximately 50 days after the end of his SHH treatment period and on day 47 of a hospitalization for a COPD exacerbation. Cause of death was a cerebrovascular accident. Based on the available information causality cannot be assessed.

A total of 8 patients experienced a serious adverse event (SAE). SAEs were evenly distributed across treatment periods. The most common SAE was COPD exacerbation. During each treatment period, no SAE by preferred term occurred in >2 patients. Common AEs (>3% in any treatment period) included COPD exacerbation, dyspnea, influenza, dry mouth, and nasopharyngitis. COPD exacerbations, dyspnea, and influenza were more frequent during the placebo treatment period (21%, 25%, and 4%, respectively) compared to the other treatment periods (ranges: 13-17%, 8-13%, 0-3%, respectively). Overall, the safety profile of SR seen in this trial is consistent with that seen in the larger pooled safety databases.

Trial 205.254 and 205.255: Exacerbation Trials
Trials 205.254 and 205.255 were 48-week, randomized, double-blind, placebo controlled, parallel group international efficacy and safety trials comparing treatment with two doses of SR (5 and 10 mcg) to placebo in patients with COPD. Included patients had a diagnosis of COPD with an FEV1 ≤ 60% predicted and FEV1/FVC ratio of ≤70%. All were current of ex-smokers. The inclusion/exclusion criteria were similar to the newly submitted exacerbation trial (205.372) as were restricted medications. However, in these trials patients were not allowed to use LABA during the randomized treatment period as compared to 205.372. Eligible patients were randomized to receive SR 5mcg, SR 10mcg, or placebo. The co-primary endpoints were trough FEV1 at week 48 and St. George's Respiratory Questionnaire (SGRQ) score after 48-weeks so of treatment. Additional endpoints included other spirometric parameters, Mahler Transition Dyspnea Index (TDI), COPD exacerbations, rescue medication use, COPD symptoms, global evaluations, and COPD hospitalizations. TDI and COPD exacerbations were also pre-specified as co-primary endpoints for combined data from Studies 205.254 and 205.255. Safety endpoints included adverse events, vital signs, laboratory evaluations, ECGs, Holter testing, and physical examinations.

Trials 205.251 and 205.252: Bronchodilation Trials
Trials 205.251 and 205.252 were replicate 12-week, randomized, double-blind, placebo controlled, parallel group international efficacy and safety trials comparing the bronchodilator effect of two doses of SR (5 and 10 mcg) to placebo in patients with COPD. Included patients had a diagnosis of COPD with an FEV1 ≤ 60% predicted and FEV1/FVC ratio of ≤70%. All patients were current of ex-smokers. As with exacerbation trials 205.254 and 205.255, LABA were not allowed during the treatment period. Eligible patients were randomized to receive SR 5mcg, SR 10mcg, or placebo. The primary endpoint was trough FEV1 response after 12-weeks of treatment. Additional endpoints included trough FEV1 response at various time-points during the treatment period, rescue medication use, and COPD symptoms scores. Safety endpoints included adverse events, vital signs, laboratory evaluations, ECGs, and physical examinations.

5.3.2 Trials from a different drug program that included Spiriva Respimat treatment arms (1205.14 and 1205.04)

These trials were part of another drug development program. However, they included SR 5mcg and placebo arms. Because of this, the Applicant included safety data from these trials in the two pooled safety database used to evaluate safety of SR 5mcg versus placebo. As these trials were not part of the TR program and were only used in pooled safety analyses, only brief review of the protocol and safety data will follow.

Trial 1205.14
Design

Reference ID: 3618244

This was a 24-week randomized double-blind placebo and active controlled safety and efficacy trial in patients with COPD. Treatment arms included 427 patients who received SR 5mcg, 429 patients who received placebo, and three other groups other patients who received a different bronchodilator under development. This trial was conducted in 11 countries at 72 sites. Included patients were >40 year of age with a diagnosis of COPD (FEV1<80% of normal with an FEV1/FVC ratio≤70%). Patients were also current smokers or had a smoking history of >10 pack-years. Patients were excluded if they had had an MI in the past 1-year, hospitalization for cardiac failure in the past 3 years, or had ever been hospitalized for an unstable/life threatening cardiac arrhythmia. Patients were seen in clinic at screening (week -2) to assess for eligibility. At week zero, the randomized treatment period began. Patients were seen in clinic thereafter at weeks 1, 2, 4, 8, 12, 18, and 24. A follow-up visit was performed at 3-weeks later. Use of anticholinergic drugs was prohibited during the treatment period (except for trial medication). Otherwise, patients were allowed their usual COPD care (e.g., LABA).

Results
This trial randomized 2080 patients; 429 patients in the placebo group, 427 in the TR 5mcg group, and 1224 across the three experimental drug dose groups. Of the randomized patients, approximately 90% did not discontinue prematurely. Discontinuations were more common in the placebo group compared to TR 5mcg. The most common reason for discontinuation was adverse events. Patient disposition data is summarized in Table 17.

Table 17. Trial 1205.14. Disposition

	Placebo n(%)	TR 5mcg n(%)
Entered/randomized	429 (100.00)	427 (100.00)
Treated	429 (100.00)	427 (100.00)
Not prematurely discontinued	365 (85.08)	390 (91.33)
Prematurely discontinued	64 (14.92)	37 (8.67)
Adverse event	32 (7.46)	18 (4.22)
AE study disease worse	18 (4.20)	4 (0.94)
AE other disease worse	1 (0.23)	1 (0.23)
AE other	13 (3.03)	13 (3.04)
Lack of efficacy	7 (1.63)	3 (0.70)
Non-compliance with protocol	1 (0.23)	2 (0.47)
Lost to follow-up	2 (0.47)	3 (0.70)
Refused to continue medication	16 (3.73)	6 (1.41)
Other	6 (1.40)	5 (1.17)

Data for experimental drug not included in this table.
Source: trial 1205.14 CSR; table 10.1:1; pg63

Patient demographics were similar between treatment groups and typical for a COPD trial. The majority of patients were white (89%) males (65%) with a mean age of 64

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years. Baseline spirometry was also similar between groups with a mean FEV1 of 43% predicted across groups.

Compliance was assessed based on diary entries and was similar between treatment groups. Approximately 92% of patients took trial medication 90-100% of the time. Efficacy results will not be discussed, as this trial was only used to evaluate safety.

Mean exposures to placebo and TR 5mcg were 153 days and 160 days, respectively. Median exposure in both groups was 169 days. The majority of patients were exposed for 85-175 days (86%). On treatment deaths (end of treatment +30days) were more common in the placebo group compared to TR 5mcg [5 (1.2%) versus 2 (0.5%)]. The causes of death in the TR 5mcg group were myocardial infarction and brain herniation. Deaths in the placebo group were due to septic shock, lung neoplasm malignant, cardiac arrest, cardiorespiratory failure, and respiratory failure. At vital status follow-up for those that discontinued prematurely, there were 4 additional deaths in the placebo group and 3 in the TR 5mcg group. With these deaths taken into account, the imbalance favoring TR 5mcg was still observed [placebo=9 (2.1%) and TR 5mcg=5 (1.2%)].

Serious adverse events were more common in the placebo group [n=43 (10%)] compared to TR 5mcg [n=35 (8.2%)]. The most common SAEs across all treatment groups fell into the following system organ classes (SOC): respiratory, thoracic, and mediastinal (3%); infections and infestations (2.2%); and cardiac disorders (1.5%). These are summarized in Table 18.

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Table 18. Serious adverse events by SOC. PT included if occurred in ≥2 patients/group and was more common in TR 5mcg compared to Placebo (on treatment +30days)

	Placebo n(%)	TR 5mcg n(%)
Number of patients	429 (100.00)	427 (100.00)
Total with SAEs	43 (10)	35 (8.2)
Infections and infestations	13 (3.0)	9 (2.1)
Bronchitis	0	2 (0.5)
Neoplasm benign, malignant, and unspecified	7 (1.6)	3 (0.7)
Blood and lymphatic disorders	2 (0.5)	1 (0.2)
Metabolism and nutrition	1 (0.2)	0
Psychiatric disorders	1 (0.2)	0
Nervous system disorders	2 (0.5)	2 (0.5)
Eye disorders	0	1 (0.2)
Cardiac disorders	5 (1.2)	7 (1.6)
Myocardial infarction	0	2 (0.5)
Acute myocardial infarction*	0	1 (0.2)
Myocardial ischemia*	0	1 (0.2)
Vascular disorders	1 (0.2)	1 (0.2)
Respiratory, thoracic, and mediastinal	18 (4.2)	10 (2.3)
Gastrointestinal disorder	5 (1.2)	2 (0.5)
Hepatobiliary disorders	1 (0.2)	0
Musculoskeletal and connective disorders	1 (0.2)	1 (0.2)
Renal and urinary disorders	1 (0.2)	0
General disorders and administration site conditions	5 (1.2)	2 (0.5)
Injury, poisoning, and procedural complications	4 (0.9)	4 (0.9)
Surgical and medical procedures	1 (0.2)	0

*included given its similarity to the preferred term myocardial infarction
Source: trial 1205.14 CSR; table 15.3.2:6; pp405-412

The observed serious adverse events are typical for a COPD trial. Only the cardiac disorders SOC demonstrated a numerical imbalance favoring placebo. This small imbalance appeared to be driven predominantly by imbalances in the PTs acute myocardial infarction, myocardial infarction, and myocardial ischemia. These imbalances are later discussed in the context of the full development program (7.3 Major Safety Results).

Common adverse events (≥2%) were balanced between treatment groups and are typical of what would be expected in a COPD population. These are summarized in Table 19.

Table 19. Trial 1205.14. Common adverse events by preferred term (≥2%)

	Placebo n(%)	TR 5mcg n(%)
Number of patients	429 (100.0)	427 (100.0)
Total with adverse events	261 (60.8)	254 (59.5)
COPD	85 (19.8)	68 (15.9)
Nasopharyngitis	38 (8.9)	27 (6.3)
Upper respiratory tract infection	20 (4.7)	19 (4.4)
Dyspnea	25 (5.8)	13 (3.0)
Cough	13 (3.0)	10 (2.3)
Bronchitis	10 (2.3)	12 (2.8)
Headache	7 (1.6)	16 (3.7)
Sinusitis	7 (1.6)	10 (2.3)

Source: trial 1205.14 CSR; table 12.2.2:1; pg91

Trial 1205.04

Design

This was a 4-week randomized double-blind, placebo and active controlled, parallel group dose-ranging trial in patients with COPD. This trial included 55 patients who received placebo and 53 who received SR 5mcg, as well as 5 treatment groups who received the other experimental drug. This trial was conducted in 2 countries at 35 sites. Included patients were >40 year of age with a diagnosis of COPD (FEV1≥30% and ≤80% of normal with an FEV1/FVC ratio≤70%) and demonstrate ≥12% increase in FEV1 following bronchodilation with ipratropium. Patients were also current smokers or had a smoking history of >10 pack-years. Patients were excluded if they had had an MI in the past 1-year, were hospitalized for an unstable or life-threatening arrhythmia in the past 1-year, or were hospitalized for cardiac failure in the past 3 years. Patients were seen in clinic at screening (week -2) to assess for eligibility. At week zero, the randomized treatment period began. Patients were seen in clinic thereafter at weeks 1, 2, and 4. A follow-up visit was performed 3-weeks later. Use of anticholinergic drugs and long-acting beta-adrenergic agents were prohibited during the treatment period.

The primary efficacy endpoint was change from baseline in trough FEV1 after 4 weeks of treatment. Secondary endpoints included change from baseline in various spirometric endpoints throughout the 4-week treatment period. Relevant to this submission, safety findings (deaths, SAE, AEs, etc.) are included as part of the clinical safety database.

Results

This trial randomized 389 patients. This included 55 placebo patients and 53 TR 5mcg patients. The remainder received experimental drug. Of the randomized patients, approximately 96% did not discontinue prematurely. There were no discontinuations in the TR 5mcg group and 2 (3.6%) in the placebo group. The two placebo patients discontinued due to adverse events. The mean exposure for the placebo and TR 5mcg groups was 29 days.

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One death was reported during this trial in the placebo group (malignant urinary tract neoplasm). No deaths were reported in the SR 5mcg group. Serious adverse events occurred in 2 (3.6%) placebo patients and 2 (3.8%) SR 5mcg patient. Except for the preferred term COPD no SAE occurred in more than 1 patient. The SAE COPD exacerbation was reported one placebo and one patient taking the experimental drug. Common adverse events are fairly typical for a COPD trial of this length. These are summarized in Table 20

Table 20. Trial 1205.04. Common adverse events by preferred term (≥2%)

	Placebo n(%)	TR 5mcg n(%)
Number of patients	55	53
Total with adverse events	26 (47.3)	20 (37.7)
Nasopharygitis	7 (12.7)	4 (7.5)
Influenza	1 (1.8)	2 (3.8)
Headache	2 (3.6)	3 (5.7)
Hypertension	1 (1.8)	4 (7.5)
COPD	6 (10.9)	2 (3.8)
Respiratory tract congestion	2 (3.6)	0
Dysphonia	0	2 (3.8)
Dry mouth	2 (3.6)	0
Diarrhea	1 (1.8)	2 (3.8)

Source: trial 1205.04 CSR; table 12.2.3.1:1; pg92

6 Review of Efficacy

Efficacy Summary

Support for efficacy is derived from two 12-week trials (205.251 and 205.252) that assessed lung function (bronchodilation) and three 48-week exacerbation trials (205.254, 205.255, and 205.372). All trials except the new exacerbation trial, 205.372, were submitted and reviewed with the initial NDA submission. At the conclusion of the first review cycle, a Complete Response action was taken primarily due to safety concerns. It was also noted in the response that there was a lack of replicate evidence for demonstration of an exacerbation reduction benefit. Trial 205.372 has been included in this resubmission to provide replicate evidence of exacerbation reduction and additional support for bronchodilation.

To support bronchodilation, all 5-trials included a primary spirometric endpoint of trough FEV1 response. In trials 205.251 and 205.252, trough FEV1 response was assessed after 12-weeks of treatment. In exacerbation trials 205.254, 205.255, and 205.372, trough FEV1 response was assessed after 48-weeks of treatment. To support exacerbation, trials 205.254 and 205.255 included a co-primary endpoint of rate of

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exacerbation and trial 205.372 included a co-primary endpoint of time to 1st exacerbation. All three exacerbation trials also included a variety of other exacerbation related secondary endpoints.

Efficacy for Bronchodilation
In all 5-trials, Spiriva Respimat (SR) 5mcg once daily demonstrated significant improvements in tough FEV1 response. The difference from placebo at the end of the treatment periods for trials 205.251, 205.252, 205.254, 205.255, and 205.372 were 0.11, 0.12, 0.14, 0.11, and 0.10L, respectively. All differences were statistically significant. In the trials that included a SR 10mcg treatment arm (205.251, 205.252, 205.254, and 205.255), the 10mcg dose also demonstrated a statistically significant response compared to placebo in terms of trough FEV1 response, however, there was little incremental benefit of the 10mcg dose over the 5mcg dose (Table 14). Efficacy was further supported by other spirometric secondary endpoints which included trough FEV1 at various times throughout the treatment period and forced vital capacity (FVC). Overall, spirometric data from these trials demonstrate that SR 5mcg has a significant effect on bronchodilation.

Efficacy for Exacerbation Reduction
Efficacy was assessed with respect to exacerbations in 48-week trials 205.254, 205.255, and 205.372. Trials 205.254 and 205.255 were replicate trials. Trial 205.372 was a standalone trial and larger compared to the replicate trials. Exacerbation definitions between the trials were similar. For the replicate trials, only 205.255 demonstrated a statistically significant difference when comparing SR 5mcg to placebo for the primary endpoint of exacerbation rate, although trial 205.254 demonstrated a similar numerical trend. Secondary exacerbation related endpoints were generally consistent with the primary analysis. In trial 205.372, for the primary endpoint of time to first exacerbation a statistically significant difference was demonstrated when comparing SR 5mcg to placebo. The same was true for the secondary endpoint of exacerbation rate. Overall, two of the three exacerbations trials demonstrated statistically significant improvements in SR 5mcg compared to placebo in terms of exacerbation. Overall, the exacerbation data demonstrate that SR 5mcg has a significant effect on exacerbations.

6.1 Indication

The proposed indication is for the maintenance treatment of COPD and reduction of exacerbations. In the initial NDA review cycle, the submitted efficacy data supported that a dose of SR 5mcg once daily was an effective bronchodilator in patients with COPD and that the higher 10mcg dose once daily dose did not demonstrate a significant incremental benefit over the 5mcg dose. This conclusion was based on trough FEV1 data from replicate 12-week bronchodilator trials (205.251 and 205.252) and pulmonary function data from replicate 48-week exacerbation trials (205.254 and

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205.255). These data demonstrated that at the end of the treatment period, both SR doses demonstrated a statistically significant improvement in trough FEV1 response compared to placebo. These data are summarized in Table 21.

Table 21. Mean trough FEV1 response at the end of treatment period

	SR 5mcg	SR 10mcg	Placebo
Trial 205.251			
Trough FEV1 @ week 12 [L]	1.34	1.41	1.23
Difference from placebo	0.11	0.18	
p-value	0.003	<0.0001	
Trial 205.252			
Trough FEV1 @ week 12 [L]	1.11	1.10	0.99
Difference from placebo	0.12	0.12	
p-value	<0.0001	<0.0001	
Trial 205.254			
Trough FEV1 @ week 48 [L]	1.17	1.19	1.03
Difference from placebo	0.14	0.16	
p-value	<0.0001	<0.0001	
Trial 205.255			
Trough FEV1 @ week 48 [L]	1.14	1.16	1.02
Difference from placebo	0.11	0.14	
p-value	<0.0001	<0.0001	

Source: CDTL review of NDA 21936 dated 8/22/08; table 3; pg12

However, for the proposed exacerbation reduction indication, replicate evidence of efficacy was not demonstrated. In the Applicant's initial NDA submission, the Applicant submitted the pooled analysis of two 48-week exacerbation trials (205.254 and 205.255) as support for the exacerbation claim and planned to reference SHH exacerbation data from trial 205.266 as evidence for replication. However, as SHH is a distinct product from SR, the Division concluded that trial 205.266 was not acceptable as replicate evidence. While the pooled analysis did demonstrate a statistically significant treatment effect in terms of exacerbation rate (Table 22), when analyzed as single trials, only one trial (205.255) demonstrated a statistically significant treatment effect. As such, there was no replication of reduction in exacerbation.

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Table 22. Exacerbation rate

	Trial 205.254			Trial 205.255			Pooled		
	SR 5mcg	SR 10mcg	Placebo	SR 5mcg	SR 10mcg	Placebo	SR 5mcg	SR 10mcg	Placebo
	n=332	n=332	n=319	n=338	n=335	n=334	n=670	n=667	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. placebo	0.2	0.07		0.003	0.004		0.002	0.0008	

*(number of exacerbations in subject/number of days of treatment received by subject) times 365.25 days per year; Wilcoxon Mann Whitney test
Source: CDTL review of NDA 21936 dated 8/22/08; table 5; pg14

Because of this, the following efficacy deficiency was conveyed to the Applicant.

> Deficiency (efficacy)
> The submitted data do not provide substantial evidence to support the proposed claim of reduction of COPD exacerbation….replication of the finding is necessary to support a labeling claim. Results of the two individual 48-week studies are not sufficient for replication because only one of the two studies showed a statistically significant difference from placebo.
>
> To resolve the deficiency and to support the proposed claim of reduction of COPD exacerbation, provide data from an adequate and well controlled clinical study that shows statistically significant reduction in COPD exacerbation with SR compared to placebo.

6.1.1 Methods

In order to address the deficiency, the Applicant submitted a third exacerbation trial (205.372) to demonstrate replicate evidence of efficacy in terms of exacerbation reduction. The design and conduct of this trial is outlined in detail in Section 5.3.1 New Exacerbation Trial (205.372). Briefly, it was a 48-week, randomized, double-blind placebo controlled, trial in moderate to severe COPD patients. The co-primary endpoints were trough FEV1 at week 48 (day 367) and time to first COPD exacerbation. As compared to trials 205.254 and 205.255, trial 205.372 was larger, did not include a SR 10mcg treatment arm, and allowed for concomitant LABA during the treatment period. Note that in trials 205.254 and 205.255, the primary exacerbation endpoint was number of COPD exacerbations occurring in a year, and time to first exacerbation was a secondary endpoint. Otherwise, the trials were largely similar in design. Overall trial 205.372 was adequately designed to assess for exacerbation reduction and provide replicate evidence for efficacy.

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6.1.2 Demographics

Overall, patient demographics of trial 205.372 were similar between treatment groups. Most patients were white males with a mean age of 65. The average pack year history was 45 years and most patients were ex-smokers. The average time since COPD diagnosis was 8.2 years. Across groups, 38% of patients were Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II and 46% were GOLD stage III. The average FEV1 was 40% predicted across groups. These data are summarized Table 23

Table 23. Trial 205.372. Demographics and baseline characteristics (treated set)

	SR 5mcg	Placebo	Total
Number of treated patients, n (%)	1952 (100.0)	1965 (100.0)	3917 (100.0)
Age, mean (±SD) [years]	64.8 (9.1)	64.8 (9.0)	64.8 (9.0)
Sex, n (%)			
Male	1524 (78.1)	1513 (77.0)	3037 (77.5)
Female	428 (21.9)	452 (23.0)	880 (22.5)
Race, n (%)			
White	1343 (68.8)	1346 (68.5)	2689 (68.6)
Black	29 (1.5)	38 (1.9)	67 (1.7)
Asian	580 (29.7)	581 (29.6)	1161 (29.6)
Smoking status, n (%)			
Never smoked	1 (0.1)	0 (0.0)	1 (0.0)
Ex-smoker	1254 (64.2)	1260 (64.1)	2514 (64.2)
Current smoker	697 (35.7)	705 (35.9)	1402 (35.8)
Smoking history, mean (±SD) [pack years]	46.01 (26.14)	44.98 (26.50)	45.49 (26.32)
Duration of COPD, mean (±SD) [years]	8.34 (7.00)	8.11 (6.52)	8.22 (6.76)
FEV1 % predicted (±SD)	39.9 (12.0)	39.8 (12.0)	39.8 (12.0)
FEV1/FVC (±SD)	47.2 (10.8)	16.7 (10.7)	47.0 (10.8)
FEV% change after albuterol (±SD)	14.8 (16.7)	15.1 (17.0)	15.0 (16.9)
LABA use at baseline [n(%)]	1060 (52.6)	1022 (52.0)	2082 (53.2)

source: Trial 205.372 CSR; tables 11.2:1, 11.2:2, 15.1.4:5; pp80, 82, 265

The patients' demographics and baseline characteristics were balanced across groups and are typical for a COPD trial. They were also generally similar to that seen in trials 205.254 and 205.255. However, in trials 205.254 and 205.255 approximately 30% of patients were on baseline LABA as compared to 52% in this trial.

6.1.3 Subject Disposition

Three thousand nine hundred ninety one (3991) patients were randomized and received at least one dose of trial medication, however due to concerns regarding trial conduct, 74 patients were excluded from the treated set, leaving 3917 patients in the treated set (TS). Because of concerns with trial conduct at two additional sites (3314, and 1008) 25 additional patients were excluded from the full analysis set (FAS). This left 3892 patients in the FAS. The FAS was used for analysis of efficacy. Of these, 3300 completed the trial. Six hundred ninety-one (691) patients discontinued from the trial

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medication prematurely. The most common reason for discontinuations were AEs (7.5%), lack of efficacy (2.4%), and other (2.8%). Discontinuations were less common in SR 5mcg compared to placebo. 'Lack of efficacy' as a reason for withdrawal was more common in placebo patients. Patient disposition and analysis populations are summarized in Table 24.

Table 24. Trial 205.372. Patient disposition

	SR 5mcg n(%)	Placebo n(%)	Total n(%)
Randomized Set	1989	2002	3991
Treated Set*	1952 (98.1)	1965 (98.2)	3917 (98.1)
Full Analysis Set**	1939 (97.5)	1953 (97.6)	3892 (97.5)
Not prematurely discontinued trial medication	1671 (84.0)	1629 (81.4)	3300 (82.7)
Prematurely discontinued trial medication	318 (16.0)	373 (18.6)	691 (17.3)
Adverse events	143 (7.2)	156 (7.8)	299 (7.5)
Worsening of disease under study	46 (2.3)	77 (3.8)	123 (3.1)
Worsening of other pre-existing disease	14 (0.7)	7 (0.3)	21 (0.5)
Other AE	83 (4.2)	72 (3.6)	155 (3.9)
Lack of efficacy	28 (1.4)	67 (3.3)	95 (2.4)
Non-compliant with protocol	47 (2.4)	35 (1.7)	82 (2.1)
Lost to follow-up	22 (1.1)	28 (1.4)	50 (1.3)
Consent withdrawn	20 (1.0)	35 (1.7)	55 (1.4)
Other	58 (2.9)	52 (2.6)	110 (2.8)

*excluded patients from site 91009
**excluded patients from sites 91009, 3314, and 1008
source: Trial 205.372 CSR; tables 10.1:1, 11.1:1; pp 76 &79

More patients in the placebo group withdrew due to 'worsening of disease under study' and 'lack of efficacy' compared to the SR group. This implies a beneficial treatment effect for the SR 5mcg dose. The line listings for patients who withdrew due to 'other' were reviewed. Based on that review, it appears that the majority of withdrawals were due to external factors (e.g. relocation, lack of time (job pressure), changes in social situation, etc.) or the patient changing their mind about participation. The 'other' withdrawals, in general, did not appear to be related to safety or efficacy.

6.1.4 Analysis of Primary Endpoint(s)

Co-primary endpoints
The two co-primary endpoints for trial 205.372 were trough FEV1 response at day 337 and time to first COPD exacerbation. Trough FEV1 was defined as the pre-treatment (trough) FEV1 (10 minutes prior to trial medication). Response was defined as change from baseline and was assessed at day 337 (week 48). COPD Exacerbation was defined as a complex of respiratory events/symptoms with a duration of ≥3 days with ≥ 2 of the following (increase of symptoms or new onset):

- Shortness of breath / dyspnea / shallow, rapid breathing

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- Sputum production (volume)
- Occurrence of purulent sputum
- Cough
- Wheezing
- Chest tightness

The change in/or requirement of treatment includes the following:

- Prescription of antibiotics and / or systemic corticosteroids
- And/or a significant change of the prescribed respiratory medication (bronchodilators including theophylline).

Both co-primary endpoints are appropriate for the desired indications and commonly used in COPD trials. The exacerbation definition is consistent with that used in the original 48-week exacerbations trials submitted with the initial NDA (trials 205.254 and 205.255).

The co-primary endpoints were tested sequentially, with time to first COPD exacerbation only being analyzed after a statistically significant difference for trough FEV1 response was demonstrated. For SR 5mcg, the trough FEV1 response was 119mL and 18mL for placebo. The difference from placebo for SR 5mcg was statistically significant ($p<0.0001$).

As with the first co-primary lung function endpoint, SR 5mcg also demonstrated a statistically significant difference from placebo for the second co-primary endpoint. The Cox proportional hazard ratio (HR) of SR 5mcg versus placebo for time to first exacerbation was 0.69 (95 % CI 0.63, 0.77) with a $p<0.0001$. The spirometric and exacerbation data are summarized in Table 25. In Figure 6, the time to first exacerbation data is presented graphically as a Kaplan-Meier plot of the probability of no COPD exacerbation during the treatment period. The Kaplan-Meier plot demonstrates clear separation between the two treatment groups.

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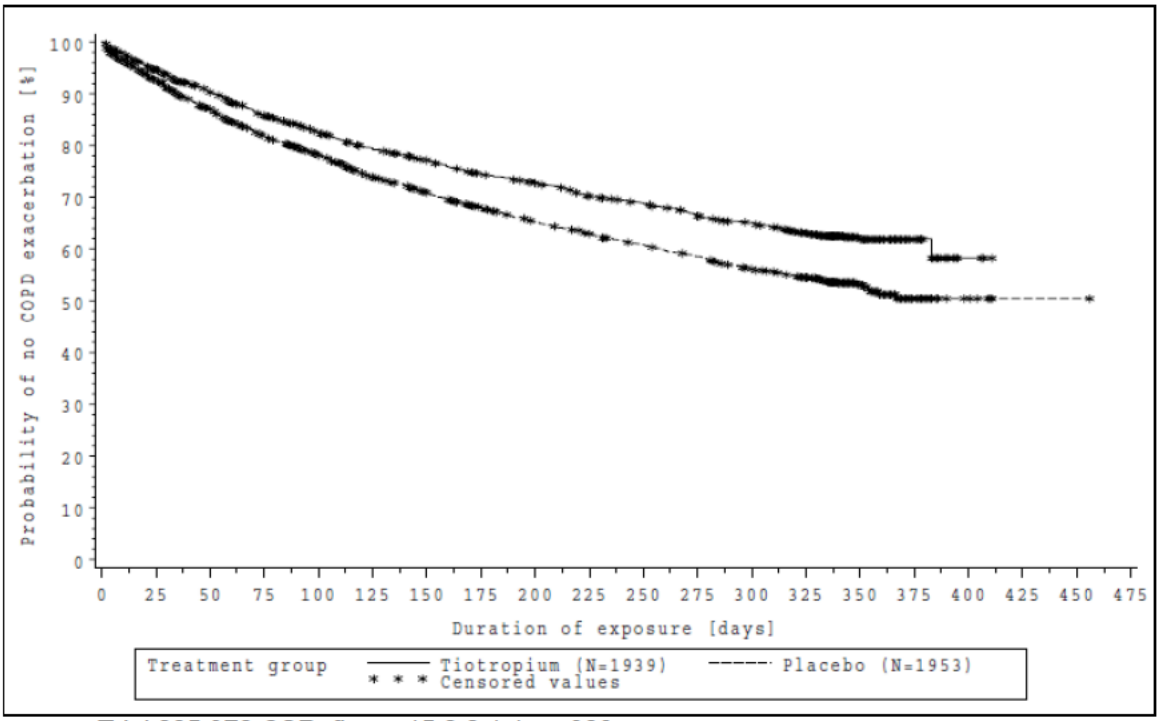
Table 25. Trial 205.372. Co-primary endpoints (FAS)

	SR 5mcg (n=1939)	Placebo (n=1953)
Trough FEV1		
Baseline trough FEV1 mean	1.11	1.106
Day 337 trough FEV1 adjusted mean	1.23	1.13
Δ from baseline, adjusted mean	0.12	0.02
Difference from placebo		
Adjusted mean	0.10	
95% CI	0.09, 0.12	
p-value	<0.0001	
Time to first exacerbation (on treatment)*		
Number of patients with at least one exacerbation [n(%)]	685 (35)	842 (43)
Number of censored patients [n(%)]	1254 (65)	1111 (57)
Hazard ratio v. placebo (95% CI)	0.69	
95% CI	(0.63, 0.77)	
p-value	<0.0001	

*exacerbations counted if they occurred between date of first dose and date of last dose +1 day
source: Trial 205.372 CSR; tables 11.4.1.1.1:1 and 11.4.1.1.2:1; pp 86 and 88

Figure 6. Trial 205.372. Probability of no COPD exacerbation during the randomized treatment period.



source: Trial 205.372 CSR; figure 15.2.2.1:1; pg308

While the treatment difference in terms of FEV1 between SR 5mcg and placebo was statistically significant, it was lower in magnitude than that seen in the similarly design 48-week trials (205.254 and 205.255) submitted with the initial NDA submission, where the difference from placebo ranged from 0.113-0.142L (average 0.127L). This discrepancy may be related to the fact that in trial 205.372, patients were allowed to be on LABA during the treatment period as compared to trials 205.254 and 205.255. However, as this is a cross-trial comparison, the ability to make conclusions is limited. The treatment effect with regard to COPD exacerbation rate was evaluated in trial 205.372 and similar to trials 205.254 and 205.255, the SR 5mcg group had a lower rate of exacerbations (Table 27).

The Applicant also performed sensitivity analysis for both co-primary endpoints including sites 3314, 1008, 91009. The results were similar. The Applicant also analyzed time to first COPD exacerbation looking at the time period from first dose of randomized treatment to planned randomized treatment stop day (day 337). Results were similar demonstrating a slightly larger treatment effect (HR 0.72, p<0.0001). Subgroup analysis was also performed based on LABA use. Fewer non-LABA users had at least one exacerbation compared to LABA users (41.5% vs. 47.3%). The HR time to first exacerbation for the SR 5mcg group versus placebo for non-LABA users was 0.63 (95% CI 0.53, 0.76) compared to 0.76 (95% CI 0.66, 0.87) for LABA users. For both the p-values were <0.0001. This numerical difference is not necessarily surprising as patients on LABA likely are more symptomatic and/or have more severe disease compared to those not on LABA. Similar subgroup analysis was performed for trough FEV1. The differences in FEV1 response were minimal.

6.1.5 Analysis of Secondary Endpoints(s)

Spirometric
This trial included two spirometric secondary endpoints which where trough FEV1 response at weeks 4 (day 29) and 24 (days 169) and trough FVC response at weeks 4, 24, and 48. For trough FEV1 response at weeks 4 and 24, SR 5mcg had a difference from placebo of 93mL and 103mL (p<0.0001), respectively.

Trough FVC data demonstrated similar results as trough FEV1 data. At weeks 4, 24, and 48 SR 5mcg demonstrated a statistically significant difference from placebo with respect to trough FVC response. The differences from placebo were 0.151, 0.160, and 0.168L at weeks 4, 24, and 48, respectively (p<0.0001). Note that while p-values are given, they were not corrected for multiplicity.

Exacerbations
This trial included multiple exacerbation related secondary endpoints. The endpoints included time to first hospitalization for COPD exacerbation, time to first moderate or severe exacerbation, number of COPD exacerbations, number of moderate to severe exacerbations, number of hospitalizations for COPD exacerbations, number of patients

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with at least one COPD exacerbation, and number of patients with at least one hospitalization for COPD exacerbation. The results for these endpoints were consistent with the co-primary exacerbation endpoint.

The percentage of patients with hospitalizations due to COPD exacerbations was higher in the placebo group compared to SR 5mcg (10.1% vs. 8.3%). Additionally, the hazard ratio (SR 5mcg vs. placebo) for time to first hospitalization for COPD exacerbation was 0.73 (Table 26). Similar results were seen with the time to first moderate or severe COPD exacerbation. These results are consistent with the results from trials 205.254 and 205.255 when a similar analysis was performed.

Table 26. Time to first COPD exacerbation leading to hospitalization and time to first moderate to severe COPD exacerbation (Cox proportional hazards analysis)

	SR 5mcg (n=1939)	Placebo (n=1953)
Patients with at least 1 COPD exacerbation leading to hospitalization [n(%)]	161 (8.3)	198 (10.1)
Number of censored patients n (%)	1778 (91.7)	1755 (89.9)
Hazard ratio vs. placebo	0.73	
95% CI	(0.59, 0.90)	
p-value	0.0034	
Patients with at least 1 moderate or severe COPD exacerbation [n(%)]	538 (27.7)	666 (34.1)
Number of censored patients n (%)	1401 (72.3)	1287 (65.9)
Hazard ratio vs. placebo	0.70	
95% CI	(0.62, 0.79)	
p-value	<0.0001	

source: trial 205.372 CSR; tables 11.4.1.2.2:1 and 15.2.2.1:17; pp91 and 333

For exacerbation endpoints related to numbers of exacerbation, SR 5mcg patients had a lower exacerbation rate/patient year compared to placebo. The rate of all exacerbations, moderate/severe exacerbations, and exacerbations leading to hospitalization were all lower in the SR 5mcg group compared to placebo. There were also fewer patients in the SR 5mcg group who experienced an exacerbation, a moderate/severe exacerbation, or an exacerbation leading to hospitalization compared to placebo. These data are summarized in Table 27.

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Table 27. Trial 205.372. Other secondary exacerbation endpoints

	SR 5mcg (n=1939)	Placebo (n=1953)
Patient years at risk*	1645.3	1607.8
Numbers of COPD exacerbations		
Number of COPD exacerbations	1168	1434
Mean rate/patient year (95% CI)	0.69 (0.64, 0.74)	0.87 (0.82, 0.93)
Relative Rate vs. placebo (95% CI)	0.79 (0.72, 0.87)	
p-value	<0.0001	
Number of hospitalizations related to COPD exacerbations	210	253
Mean rate/patient year (95% CI)	0.12 (0.11, 0.14)	0.15 (0.14, 0.17)
Relative rate vs. placebo (95% CI)	0.81 (0.70, 0.93)	
p-value	0.0036	
Number of moderate or severe COPD exacerbations	851	1055
Mean rate/ patient year (95% CI)	0.5 (0.46, 0.54)	0.64 (0.60, 0.69)
Relative rate vs. placebo (95% CI)	0.78 (0.71, 0.87)	
p-value	<0.0001	
Patients with COPD exacerbation		
Number of patients with at least one COPD exacerbation, n(%)	685 (35.3)	842 (43.1)
Odds ratio vs. placebo (95% CI)	0.70 (0.62, 0.80)	
p-value	<0.0001	
Number of patients with at least one hospitalization due to COPD, n (%)	161 (8.3)	198 (10.1)
Odds ratio vs. placebo (95% CI)	0.82 (0.66, 1.02)	
p-value	0.0728	
Number of patients with at least one moderate of severe COPD exacerbation, n (%)	538 (27.7)	666 (34.1)
Odds ratio vs. placebo (95% CI)	0.73 (0.63, 0.82)	
p-value	<0.0001	

*Period of risk defined as start of randomized treatment to the last dose +1 day.
Poisson distribution correcting for overdispersion for analysis of rates
source: trial 205.372 CSR; tables 11.4.1.2.2:2, 11.4.1.2.2:3, 15.2.2.2:2, 15.2.2.2:10, 15.2.2.2:18; pp94, 96, 352, 362, 372

Across the primary and secondary exacerbation related endpoints, SR 5mcg consistently demonstrated a beneficial effect compared to placebo. These results are consistent with the findings from exacerbation trials 205.254 and 205.255. Overall, these findings are supportive of a reduction of exacerbation claim for SR 5mcg.

SGRQ

In trials 205.254 and 205.255, SGRQ was assessed and while there were statistically significant improvements in SGRQ score, for both trials, the improvements were less than the minimal clinically important difference (MCID = 4) for the SR 5mcg dose (-3.3

and -3.7 in trials 205.254 and 205.255, respectively). Similar results were seen in this trial, where SGRQ total and domain scores were analyzed at day 169 and 337. While SGRQ total scores were significantly lower in the SR 5mcg group compared to placebo at both time points, the difference for total scores at days 169 and 337 were less than the MCID, -2.2 and -2.9, respectively. These results are consistent with trials 205.254 and 205.255 where, while there were statistically significant improvements in SGRQ scores, the improvements did not meet the MCID. These results do not support an improvement in the quality of life claim.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

In the original NDA submission, multiple subgroup analyses were performed in trials 205.254 and 205.255. These included intrinsic factors of gender, age, race, and disease severity. Extrinsic factors of steroid use at baseline, xanthine use at baseline, and smoking status were also assessed. Efficacy measurements of spirometry, TDI, SGRQ, and COPD exacerbations were evaluated. No significant effects were seen. In the new exacerbation trial (205.372), subgroup analysis was performed based on use of LABA use (previously discussed). Differences were small between LABA users and non-users in terms of trough FEV1.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose selection was determined from trial 205.127 which was submitted during the first review cycle. Based on the results of that trial (Table 14), both 5 and 10 mcg doses were assessed in trials 205.251, 205.252, 205.254 and 205.255, again submitted previously. Based on review of those studies, which demonstrated that the 5 mcg dose produced significant bronchodilation (Table 21) and that I the 10mcg did not offer an incremental benefit over the 5mcg dose, the 5 mcg dose alone was studied in trial 205.372.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Spirometry was performed at day 1, 29, 169, and 337. The trough FEV1 response compared to placebo was maintained at similar levels at all time-points measured. Pairwise comparisons to placebo were also statistically significant ($p<0.0001$) at all time-points. This is consistent with trials 205.254 and 205.255. These results suggest that tolerance to SR did not occur during the 48-week treatment period.

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6.1.10 Additional Efficacy Issues/Analyses

Although trial 205.452 was primarily meant to address SR safety concerns, the trial also included multiple exacerbation related endpoints. The primary efficacy endpoint was time to first exacerbation, where exacerbation was defined as in trial 205.372. Secondary efficacy endpoints included the following:

- Number of COPD exacerbations
- Time to first COPD exacerbation associated with hospitalization
- Number of COPD exacerbations associated with hospitalization
- Time to first moderate to severe COPD exacerbation

All comparisons were made to the active control SHH. All of these analyses were performed in the treated set (TS). Results are as follows:

Primary Efficacy Endpoint:
Time to first COPD exacerbation was similar when comparing SR treatment groups to SHH based on hazard ratios. Additionally similar numbers of patients in each treatment group experienced a COPD exacerbation and median time to event was similar between groups for patients in the lowest quartile. There were no statistically significant differences between treatment groups. These data are summarized in Table 28.

Table 28. Trial 205.452 (TIOSPIR). Time to first COPD exacerbation.

	SR 2.5 mcg	SR 5mcg	SHH
Number of patients	5724	5705	5687
Patients with COPD exacerbations [n (%)]	2827 (49.4)	2733 (47.9)	2782 (48.9)
Hazard ratio (SR vs. SHH)	1.016	0.978	
95% CI	(0.964,1.070)	(0.928, 1.032)	
p-value	0.5593	0.4194	

Source: trial 205.452 CSR; table 11.4.1.1.2:1; pg105

These data indicate that neither SR dose is superior to SHH in terms of time to first exacerbation. Results of the secondary efficacy endpoints assessed in trial 205.452 are consistent with the primary efficacy endpoint in that SR 5mcg and SHH demonstrated similar results.

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Secondary Efficacy Endpoints
These results are summarized in Table 29 and Table 30.

Table 29. Trial 205.452 (TIOSPIR). Time to first hospitalization due to COPD exacerbation and time to first moderate to severe COPD exacerbation

	SR 2.5mcg	SR 5mcg	SHH
Number of patients	5724	5705	5687
Patients with hospitalizations due to COPD [n (%)]	869 (15.2)	826 (14.5)	811 (14.3)
Comparison vs. SHH			
Hazard ratio	1.068	1.024	
95 % Confidence interval	(0.971, 1.176)	(0.929, 1.128)	
p-value	0.1762	0.6348	
Patients with moderate to severe COPD exacerbations [N (%)]	2769 (48.4)	2694 (47.2)	2732 (48.0)
Comparison vs. SHH			
Hazard ratio	1.011	0.983	
95 % Confidence interval	(0.959, 1.066)	(0.932, 1.037)	
p-value	0.6823	0.5377	

Source: trial 205.452 CSR; tables 11.4.2.2:1 and 11.4.1.2.4:1;pg109 and 111

Table 30. Trial 205.452 (TIOSPIR). Exacerbation rates

	SR 2.5mcg	SR 5mcg	SHH
Number of treated patients	5724	5705	5687
Total exposure (patient-years)	11420	11358	11352
Total number of COPD exacerbations	6565	6425	6504
Observed number of events (per patient-year)	0.57	0.57	0.57
Adjusted rate of events (per patient-year)			
Mean	0.59	0.59	0.59
95% CI	(0.57, 0.62)	(0.56, 0.61)	(0.57, 0.61)
Rate ratio of events versus SHH			
Mean	1.01	0.99	
95% CI	(0.95, 1.06)	(0.94, 1.05)	
p-value	0.8330	0.8047	
Total number of hospitalizations due to COPD exacerbations	1316	1284	1216
Observed number of events (per patient-year)	0.12	0.11	0.11
Adjusted rate of events (per patient-year)			
Mean	0.12	0.12	0.11
95% CI	(0.11, 0.13)	(0.11, 0.13)	(0.10, 0.12)
Rate ratio of events versus SHH			
Mean	1.09	1.06	
95% CI	(0.98, 1.22)	(0.94, 1.18)	
p-value	0.1255	0.3441	

Negative binomial adjusted for exposure
Source: trial 205.452 CSR; table 11.4.2.1:1 and 11.4.1.2.3:1; pg 108 and 110

Across multiple endpoints, neither SR group demonstrated superiority to SHH in terms of exacerbation. This is not necessarily surprising as SR consists of the same active ingredient as SHH, and SHH carries an exacerbation reduction claim. While SR is not superior to SHH in terms of exacerbation, it cannot be concluded that the two are equivalent as statistical testing only assessed for superiority.

7 Review of Safety

Safety Summary

In the initial NDA review cycle, this application was given a Complete Response (CR) due to a mortality differences observed in both 48-week exacerbation trials (205.254 and 205.255) and a potential mortality and stroke risk suggested by a pooled analysis of trials from the SR and SHH development programs. In order to address the mortality concern, during the initial review cycle, the Applicant submitted preliminary data from a 4-year, approximately 6000 patient, placebo controlled trial titled Understanding Potential Long-term Impacts of Function with Tiotropium (UPLIFT). This trial included prospective vital status follow-up, a pre-specified mortality endpoint, and all deaths were adjudicated by an independent mortality adjudication committee. Treatment arms were SHH and placebo. While this placebo-controlled trial did not include a SR 5mcg

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treatment arm, as the both SHH and SR contain the same active pharmaceutical ingredient, mortality data from UPLIFT were thought to be potentially applicable to the SR program, provided that SR 5mcg had similar/lower systemic exposure. However, as the UPLIFT data was preliminary at the time of action, it was insufficient to address the mortality concerns and the NDA was given a complete response. Once the final report was available, it was reviewed by the Agency. UPLIFT demonstrated that there was no increased mortality risk when comparing SHH to placebo. The rate ratio for all-cause mortality (SHH: placebo) at day 1470 was 0.89 [95% CI (0.79, 1.01)]. For fatal COPD exacerbations, fatal myocardial infarction, and fatal stroke the rate ratios were 0.79 [95%CI (0.62, 1.01)], 1.00 [95% CI (0.43, 2.30)], and 0.82 [95% CI 0.40, 1.66)], respectively. The rate ratio for deaths falling under the cardiac disorders system organ class (SOC) was 0.81 [95% CI (0.48, 1.36)]. For serious adverse events (on-treatment +30days), the rate ratios for MI, and stroke were 0.71 [95% CI (0.52, 0.99)] and 0.92 [95% CI(0.55, 1.56)]. The rate ratio for SAEs in the cardiac disorders SOC was 0.84 [95% CI (0.73, 0.98)].[9] In addition to the UPLIFT data, the Applicant also submitted data from a third 48-week exacerbation trial (205.372). As with the previous two 48-week exacerbation trials, trial 205.372 again demonstrated a numerical mortality imbalance favoring placebo. Data from these trials were discussed at a Pulmonary Allergy Drug Advisory Committee (PADAC) held on 11/19/2009. While the PADAC concluded that SHH carried no increased mortality risk compared to placebo based on UPLIFT there were still concerns regarding the persistent mortality imbalances observed in the SR exacerbation trials (205.254, 205.255, and 205.372). Given the continued mortality concerns for SR, at the PADAC, the Applicant decided to perform a large safety trial (205.452) to definitively address the mortality concern for SR.

Trial 205.452, titled Tiotropium Safety and Performance in Respimat (TIOSPIR) was a multicenter, multinational, randomized, double-blind, double dummy parallel group trial to compare the efficacy and safety of SR 2.5 mcg and 5 mcg with SHH 18 mcg (SHH) in patients with COPD. This trial was designed to end after approximately 1,266 fatal adverse events and included approximately 17,000 patients. All patients were followed until the end of the trial for vital status, regardless of whether trial medication was discontinued. The total patient year exposure to SR 5mcg was 11,343 years. The primary endpoint was all-cause mortality with an agreed to non-inferiority margin of 1.25. Results demonstrated a hazard ratio of 0.957 [95 % CI (0.837, 1.094)]. As such, non-inferiority of SR 5mcg to SHH was clearly demonstrated in terms of all-cause mortality. While the trial met its primary mortality endpoint, sub-analyses showed that deaths due to myocardial infarction (MI) were more frequent in SR 5mcg patients [n=11 (0.2%)] compared to SHH [n=3 (0.1%)] with a rate ratio of 3.64 [95% CI (1.02, 13.06)]. However, the observation was noted only for mortality due to MI and was not supported by results for MI-related serious adverse events or MACE and stroke related deaths and SAEs which were similar between SR and SHH groups.

9 NDA 21395; trial 205.235 (UPLIFT) CSR; tables 15.3.2.2.1.1:2 and 15.3.2.1.1.2:3; pp1031-1035 and 735-761

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In addition to the large safety trial (TIOSPIR), the Applicant also included analyses of two placebo controlled databases as additional support for safety. These were termed the vital status database and clinical safety database. The vital status database was used for mortality analysis and consisted of randomized, double-blind, placebo controlled trials that were ≥24 weeks in length, included a SR 5mcg treatment arm, and had vital status follow-up at the end of the planned treatment period for all patients (including those who had prematurely discontinued). This included the three 48-week exacerbation trials (205.254, 205.255, and 205.372) and a 24-week trial from a different drug development program (1205.14). This database included 6096 patients and represented 2395 patient years of exposure to SR 5mcg. Trials included in the vital status database are summarized in Table 31.

The clinical safety database was used for analysis of serious adverse events and common adverse events. It consisted of randomized, double-blind, placebo controlled trials that were ≥4-weeks in length and included a SR 5mcg treatment arm. Seven trials were included in this pool. This included the four trials from the vital status database, two 12-week bronchodilator trials (205.251 and 205.252), and one 4-week dose-ranging trial from a different drug development program (trial 1205.04). This database included 6565 patients and represented 2440 patient years of exposure to SR 5mcg. This database was used for analysis of SAEs and AEs. Trials included in the vital status database are also summarized in Table 31.

Table 31. Placebo controlled safety databases

Database name	Types of trials included	Trials	SR 5mcg N	Placebo N	Safety Endpoints
Vital Status	R, DB, PG, PC, ≥24 weeks, vital status available (EOT)	205.254, 205.255, 205.372, 1205.14	3049	3047	Mortality (EOT); adjudication only in 205.372
Clinical Safety	R, DB, PG, PC, ≥4 weeks	Same as vital status + 205.251, 205.252, 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

In the pooled mortality analysis (vital status database), a numerical difference was observed when comparing SR 5mcg [n=68 (2.2%)] to placebo [n=51 (1.7%)] with a hazard ratio of 1.33 [95% CI (0.93, 1.92)]. This is not surprising as numerical differences in mortality had been previously identified in three of the four trials in the vital status database. A numerical difference was also observed in terms of MI related deaths with a SR 5mcg: placebo rate ratio of 4.49 [95% CI (0.96, 20.96)]. Fatal MACE also occurred in more SR 5mcg patients compared to placebo with SR 5mcg: placebo rate ratio of 2 [95% CI (1.03, 2.89]. This was driven by the already mentioned MI related death imbalance. In the analysis of the clinical safety database for all MACE and MI related

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SAEs, no differences were noted between treatment groups. No differences in stroke deaths and overall stroke events were observed when comparing SR 5mcg to placebo.

The mortality data when comparing trial 205.452 (TIOSPIR) and the vital status database are not entirely consistent. The TIOSPIR data demonstrate that SR 5mcg is non-inferior to SHH in terms of all-cause mortality, which given the UPLIFT data would imply that SR 5mcg should not carry an increased mortality risk compared to placebo. However, a numerical mortality difference favoring placebo was noted in the vital status database. While this was observed, it should be noted that TIOSPIR was specifically designed to address the observed mortality imbalance in three of the four trials in the vital status database. Additionally, TIOSPIR represented a 5-fold larger exposure compared to the vital status database. As such, one may argue that the TIOSPIR data outweighs that of the pooled analysis. With regard to specific causes of death, in both TIOSPIR and the vital status database, differences were noted in deaths related to MI. However, this was not observed for SAEs related to MI. Additionally, the overall number of events was small and these observed differences may have been related to chance and multiple comparisons.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Primary evidence for safety is derived from trial 205.452 (TIOSPIR) with additional evidence from two placebo controlled databases (Table 31). However, to put these into context, pertinent background regarding SR safety concerns and the previous Complete Response action will be first reviewed.

In the initial NDA review cycle two safety concerns lead to the CR action. These were mortality imbalances observed in the two 48-exacerbation trials (205.254 and 205.255) submitted with the initial NDA and a potential stroke risk identified in the Applicant's combined analysis of SHH and SR trials. The observed mortality imbalances are summarized in Table 32. While this mortality imbalance was observed, the imbalance was not driven by a single cause of death. Also note that in the original SR program, no safety signal related to stroke was identified.

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Table 32. Trials 205.254 and 205.255. All-cause mortality data

Number Fatal Adverse Events (%)*	SR 5 mcg	SR 10 mcg	Placebo	Relative Risk vs. Placebo (95% CI)**	
				SR 5 mcg	SR 10 mcg
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 Retro F/U‡	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 Retro F/U‡	7 (1.8%)	10 (2.8%)	2 (0.6%)	3.4 (0.7, 16.5)	5.0 (1.1, 22.9)
Studies 254 & 255 (n)	670	667	653		
Within Study	12 (1.9%)	16 (2.5%)	5 (0.9%)	2.1 (0.7, 5.9)	2.9 (1.1, 8.0)
With Retro F/U‡	15 (2.1%)	18 (2.5%)	9 (1.4%)	1.6 (0.7, 3.6)	1.9 (0.9, 4.3)

*Kaplan Meier estimates at 48 weeks
**Estimated by Cox proportional hazards regression with treatment as independent variable, stratified by study for pooled analysis
‡Vital status follow-up was obtained retrospectively
Source: CDTL review of NDA 21936 dated 8/22/08; table 6; pg16

In an attempt to address these concerns, the Applicant submitted preliminary data from trial 205.235 [Understanding Potential Long-term Impacts of Function with Tiotropium, UPLIFT (UPLIFT)], a long-term safety/efficacy trial is patients with moderate to severe COPD treated with either placebo or SHH. As the submitted data was only preliminary, it could not address the Agency's safety concerns. As such, at the end of the review cycle, the following safety-related deficiency was conveyed to the Applicant in the Complete Response letter:

> Safety Deficiency:
> Increased frequencies of death were observed in patients treated with Spiriva Respimat (SR) compared to placebo in the two 48-week studies submitted with this application and increased frequencies of stroke were observed in patients treated with tiotropium bromide compared to placebo in a pooled analysis of clinical study data with SHH and SR.
>
> To resolve the deficiency, the Applicant was asked to provide additional data from an adequate and well-controlled study to address the concerns of death and stroke and that if study 205.235 (The UPLIFT study) is used to address these safety concerns, the Applicant should provide justification for use of safety data from SHH to support the safety of SR.

Rather than rely completely on the results of the UPLIFT study, trial 205.452 (TIOSPIR) was conducted to address the deficiency stated in the Complete Response letter. Trial 205.452 (TIOSPIR) was a multicenter, multinational, randomized, double-blind, double

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dummy parallel group trial to compare the efficacy and safety of SR 2.5 mcg and 5 mcg with SHH 18 mcg in patients with COPD. This trial was event driven and designed to end after approximately 1,266 fatal adverse events which was predicted to occur within 3.5 years. All patients were followed until the end of the trial for vital status, regardless of if trial medication was discontinued. The primary safety endpoint was all-cause mortality. All deaths were adjudicated by an independent adjudication committee. Given the size of the trial (approximately 17,000 patients) adverse event data was only specifically collected for deaths, serious adverse events (SAE), and adverse events (AE) of interest [COPD exacerbations, myocardial infarction (MI), stroke, transient ischemic attack (TIA), and pneumonia]. In addition to evaluating COPD exacerbation, stroke, TIA, and MI based on investigator assignment, the Applicant also included in the protocol pre-specified definitions for these events which were monitored centrally.

This trial used SHH as an active comparator based on the safety findings of the UPLIFT trial (205.235). UPLIFT was previously reviewed by the Agency and discussed at the Pulmonary Allergy Drugs Advisory Committee (PADAC) held on 11/19/09. It was a 4-year, placebo controlled, parallel group trial enrolling approximately 6000 patients with moderate to severe COPD. The trial included a pre-specified mortality endpoint, prospective vital status collection for patients who discontinued from the trial early, and an independent adjudication committee to assess primary cause of death. Vital status information was known for 98% of SHH treated patients and 97% of placebo treated patients including discontinued patients out to at least 45 months post-randomization. The results showed a rate ratio for all-cause mortality (SHH: placebo) at day 1470 was 0.89 [95% CI (0.79, 1.01)]. For fatal COPD exacerbations, fatal myocardial infarction, and fatal stroke the rate ratios were 0.79 [95%CI (0.62, 1.01)], 1.00 [95% CI (0.43, 2.30)], and 0.82 [95% CI 0.40, 1.66)], respectively. The rate ratio for deaths falling under the cardiac disorders system organ class (SOC) was 0.81 [95% CI (0.48, 1.36)]. For serious adverse events (on-treatment +30days), the rate ratios for MI, and stroke were 0.71 [95% CI (0.52, 0.99)] and 0.92 [95% CI(0.55, 1.56)]. The rate ratio for SAEs in the cardiac disorders SOC was 0.84 [95% CI (0.73, 0.98)].[10] After Agency review and following PADAC discussion, there was consensus that SHH had a generally beneficial effect on mortality and no imbalances were identified when assessing specific causes of death or adverse events (e.g. stroke, myocardial infarction, cardiovascular events/death, etc.). Based on these findings, it was felt that a large safety trial (205.452, TIOSPIR) designed to compare all-cause mortality in patients with COPD treated with SHH versus that of patients treated with SR would be adequate to address any continued safety concerns with the SR product .Were SR 5mcg to demonstrate non-inferiority in terms of all-cause mortality to SHH and show a similar safety profile as SHH, than safety concerns from the initial NDA review cycle regarding cardiovascular events and mortality would be alleviated.

10 NDA 21395; trial 205.235 (UPLIFT) CSR; tables 15.3.2.2.1.1:2 and 15.3.2.1.1.2:3; pp1031-1035 and 735-761

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Additional evidence for safety is derived from the analyses of two databases consisting of pooled safety data from placebo-controlled trials that included a SR 5mcg arm (Table 31). Table 2 in Section 5 Sources of Clinical Data includes the trials used in these placebo controlled databases. The two placebo controlled databases were designated the vital status database and clinical safety database. The vital status database included randomized, double-blind, placebo controlled trials that were ≥24-weeks in length, included a SR 5mcg treatment arm, and had vital status (mortality) follow-up at the end of the planned treatment period for all patients (including those who had prematurely discontinued). This database was meant provide placebo controlled mortality data and to add context to the mortality data from trial 205.452. This database included the three 48-week exacerbation trials (205.254, 205.255 and 205.372) and one 24-week bronchodilator trial that had a SR 5mcg treatment arm, but was from another drug development program that (1205.14). The 48-week exacerbation trials were generally similar in design however, in contrast to trial 205.372, in trials 205.254 and 205.255 deaths were not adjudicated nor were LABA allowed during the treatment period. Additionally, vital status at the end of the planned treatment period was collected retrospectively in trials 205.254 and 205.255. Trial 1205.14 differed from the other 3-trials in that it was 24-weeks in length, and its exclusion criteria were more stringent in terms of myocardial infarction, heart failure, and cardiac arrhythmia. For example, patients with were excluded if they had had an MI in the past 12 months (compared to 6 months), were hospitalized for heart failure in the past 3-years (compared to 1-year), and had ever been hospitalized for arrhythmia (compared to in the past year).

The Applicant's second placebo-controlled database, designated the clinical safety database, included patients from the vital status database plus patients enrolled in shorter (≥4-weeks), double-blind, placebo-controlled trials that included a SR 5mcg treatment arm. Seven trials were included in this pool. This included the four trials from the vital status database, the two 12-week bronchodilator trials used to support the bronchodilator claim (205.251 and 205.252), and one 4-week dose-ranging trial from a different drug development program (1205.04). The clinical safety database added an additional 233 SR 5mcg exposed patients to the vital status database (45 patient years), albeit for a relatively short period of time. Safety data from this database was used to evaluate the overall safety of SR 5mcg compared to placebo in terms of serious and common adverse events. While this strategy does pool together trials of different lengths, this is acceptable as the safety analysis included exposure adjustment. Additionally, the pooled safety data from the 3 exacerbation trials was also analyzed with regard to S/AEs. The same was done for the pooled data from the 12-week bronchodilator trials.

Safety analyses for both trial 205.452 and the placebo controlled databases were based on one of two observation intervals:

- Vital status: This interval began at randomization and lasted until the planned end of treatment (EOT) for trials in the vital status database. For trial 205.452,

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this interval started from randomization and lasted until the last patient out date. This interval was used for mortality analyses.

- On treatment: This interval began at randomization and lasted until 30 days after individual treatment discontinuation (EOT+30-days). This interval was used in the analysis of all serious adverse events and adverse events.

As trial 205.452 (TIOSPIR) was specifically designed to address the safety concerns raised in the initial review cycle and because it represents an exposure approximately 5-fold higher than that in the placebo controlled safety databases, trial 205.452 (TIOSPIR) will be the focus of this review. Deaths, SAEs, and exposure data from the vital status database and clinical safety database will be presented to provide additional context and insight into trial 205.452 (TIOSPIR) results. For common adverse events, data from the clinical safety database will be presented as trial 205.452 (TIOSPIR) only collected SAEs and select AEs.

7.1.2 Categorization of Adverse Events

Trial 205.452 (TIOSPIR)
Given the size, scope, and primary objective of trial 205.452, all AEs were not collected. The AE reporting strategy and protocol defined outcome events (MI, stroke, TIA, and COPD exacerbation) for trial 205.452 (described below) were previously agreed upon between BI and the Agency prior to trial initiation. The following AE data was collected and reported using the MedDRA 16.0 dictionary:

- All adverse events determined by the investigator to be related to study medication
- All adverse events leading to permanent discontinuation of study medication
- All fatal adverse events (FAEs) including follow-up of vital status from patients who prematurely discontinue treatment
    - All FAEs were adjudicated by an independent blinded adjudication committee.
- All serious adverse events (SAEs)

The following AEs were also collected as protocol defined outcome events:
- All COPD exacerbations
- All pneumonias
- All myocardial infarctions (MI) (serious and non-serious)
- All strokes (serious and non-serious)
- All transient ischemic attacks (TIA)

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These protocol defined outcome events were collected on outcome event forms and also on adverse event forms. The outcome events were centrally monitored to determine if recorded events met the pre-specified definition outlined in the protocol.

Stroke, TIA, and MI were defined as follows:

Stroke was defined as an acute onset of focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death. Additionally, an event lasting <24 hours was considered as a stroke if this was due to 1) therapeutic intervention by pharmacological or non-pharmacological means (i.e., thrombolytics, intracranial angioplasty), or 2) brain imaging available early clearly documents a new hemorrhage or infarct. The stroke was categorized as ischemic or hemorrhagic (based on computerized tomography (CT), multi-task (MT) scanning or autopsy) or type unknown. Fatal stroke was defined as death from any cause within 30 days of stroke.

A TIA was defined as a rapid onset of a focal neurological deficit that resolves spontaneously without evidence of residual symptoms at 24 hours.

With regard to myocardial infarction (MI), any one of the following criteria would meet the diagnosis for MI

i. Detection of elevated values of cardiac biomarkers (preferably troponin T or I) above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
    - Ischemic symptoms;
    - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block (LBBB));
    - Development of pathological Q waves in the ECG;
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

ii. Sudden unexpected cardiac death, including cardiac arrest, with symptoms suggestive of myocardial ischemia, accompanied by new ST elevation, or new LBBB, or definite new thrombus by coronary angiography but dying before blood samples could be obtained, or in the lag phase of cardiac biomarkers in the blood.

iii. For percutaneous coronary intervention (PCI) in patients with normal baseline values, elevations of cardiac biomarkers above 99th percentile of the URL are indicative of per-procedural myocardial necrosis.

iv. For coronary artery bypass graft (CABG) in patients with normal baseline values, elevations of cardiac biomarkers above the 99th percentile of the URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile of the URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging

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evidence of new loss of viable myocardium have been designated as defining CABG-related MI.

v. Pathological findings post-mortem of an acute MI.

Major adverse cardiac event (MACE) analysis was also performed, where MACE was defined as follows:

- Fatal events in system organ classes cardiac and vascular disorders
- Events coding to sudden death, cardiac death, or sudden cardiac death
- Outcome event of myocardial infarction (serious and non-serious)
- Outcome event of stroke (serious and non-serious)
- Outcome event of TIA (serious and non-serious)

MACE analysis was performed using adverse event reporting where MACE was defined as follows:

- Fatal event in system organ classes (SOC) cardiac and vascular disorders
- Events coding to sudden death, cardiac death, or sudden cardiac death
- Events in the SMQ ischemic heart disease sub-SMQ myocardial infarction
- Events in the stroke pharmacovigilance endpoint (see below)

The Applicant also analyzed AEs by grouping together preferred terms based on Standardized MedDRA Queries (SMQ)(MedDRA 16.0) and Applicant defined pharmacovigilance endpoints (PVE). The objective of collapsing multiple preferred terms (PT) into a single group, whether by SMQ or PVE, was to identify potential safety signals that may otherwise be missed due to the granularity of individual PTs and potential over-inclusiveness of system organs classes (SOC)/high level grouping terms (HLGT). The BI defined PVE were created by collapsing multiple MedDRA PTs by similar concept that did not necessarily correspond to an SOC or a high level group term (HLGT). The Applicant had used a similar strategy of collapsing multiple MedDRA preferred terms into a single BI defined term in the initial NDA submission. The PTs included in the SMQs and PVEs were reviewed and were felt to be reasonable. Definitions for PVE are available in the SCS supplement [table 2.13.1].

<u>Placebo controlled databases</u>
In the placebo controlled databases, adverse events were reported based on MedDRA 16.0. Adverse events were also analyzed using collapsed terms. MACE analysis based on adverse events (as defined above) was also performed for the pooled placebo-controlled databases.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

See 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Trial 205.452 (TIOSPIR) was submitted as primary support of safety. This trial increased the safety database above the initial NDA submission by approximately 5-fold, with 11,343 years of patient exposure to SR 5mcg. A total of 17,183 COPD patients were included in this trial, of these 11,441 were treated with either SR 2.5mcg or 5mcg. Patient disposition and exposure for TIOSPIR is summarized in this section.

Safety data from the placebo controlled databases (vital status and clinical safety database) were submitted as additional support of safety. The vital status database and clinical safety databases included totals of 6,096 and 6,565 patients treated with SR 5mcg, respectively. This equated to 2,395 and 2,440 patient years of exposure, respectively. Pooled patient disposition and exposure data for the placebo controlled databases is also summarized in this section.

Disposition
Patient disposition for trial 205.452 (TIOSPIR) is summarized in Table 33. Overall 20,313 patients were enrolled and 17,183 were randomized. Forty-eight patients did not receive trial medication, leaving 17,135 who were eligible for vital status follow-up and inclusion in the death analysis set (DAS). Nineteen patients from the DAS were not included in the treated set (TS) due to data irregularities at two sites (see section 5.3.2 Large Safety Trial [205.452 (TIOSPIR)]). These 19 patients were evenly distributed across treatment groups. Of the TS, approximately 23% of patients discontinued prematurely. Discontinuations were distributed evenly across treatment groups. The two most common reasons for discontinuations were AEs and refusal to continue trial medication. Discontinuations due to AEs are discussed in section 7.3.3 Dropouts and/or Discontinuations.

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Table 33. Trial 205.452 (TIOSPIR). Patient Disposition

	SR 2.5mcg n (%)	SR 5mcg n (%)	SHH n (%)	Total n (%)
Entered/randomized	5741	5729	5713	17183
Not treated	11	18	19	48
Eligible for vital status follow up (DAS)	5730	5711	5694	17135
Patients at sites with data irregularities/fraud	6	6	7	19
Treated (TS)	5724 (100.0)	5705 (100.0)	5687 (100.0)	17116 (100.0)
Prematurely discontinued	1324 (23.1)	1306 (22.9)	1287 (22.6)	3917 (22.9)
Adverse event	602 (10.5)	606 (10.6)	635 (11.2)	1843 (10.8)
AE study disease worse	170 (3.0)	171 (3.0)	185 (3.3)	526 (3.1)
AE other disease worse	47 (0.8)	45 (0.8)	58 (1.0)	150 (0.9)
AE other	385 (6.7)	390 (6.8)	392 (6.9)	1167 (6.8)
Lack of efficacy	65 (1.1)	60 (1.1)	59 (1.0)	184 (1.1)
Non-compliance protocol	64 (1.1)	66 (1.2)	41 (0.7)	171 (1.0)
Lost to follow-up	52 (0.9)	63 (1.1)	55 (1.0)	170 (1.0)
Refused cont. medicine	331 (5.8)	335 (5.9)	319 (5.6)	985 (5.8)
Other	210 (3.7)	176 (3.1)	178 (3.1)	564 (3.3)

Deaths that caused discontinuation from trial medication are included in adverse events leading to discontinuation in contrast to Table 46
Source: trial 205.452 CSR; table 15.1.1:1; pg179

Patient disposition for the placebo controlled databases is summarized in Table 34. The vital status database and clinical safety database consisted of a total of 6096 and 6565 patients, respectively. Discontinuations were more common in placebo patients compared to SR 5mcg patients. The most common reason for discontinuation was adverse events which occurred more commonly in placebo patients compared to SR 5mcg.

Table 34. Placebo controlled databases. Patient Disposition.

	Vital status database		Clinical safety database	
	SR 5mcg n(%)	Placebo n(%)	SR 5mcg n(%)	Placebo n(%)
Number of patients treated	3049 (100)	3047 (100)	3282 (100)	3283 (100)
Prematurely discontinued	468 (15.3)	641 (21.0)	484 (14.7)	665 (20.3)
Adverse event	228 (7.5)	310 (10.2)	241 (7.3)	327 (10.0)
AE study disease worse	81 (2.7)	187 (6.1)	87 (2.7)	199 (6.1)
AE other disease worse	18 (0.6)	14 (0.5)	20 (0.6)	14 (0.4)
AE other	129 (4.2)	109 (3.6)	134 (4.1)	114 (3.5)
Lack of efficacy	31 (1.0)	74 (2.4)	31 (0.9)	74 (2.3)
Non-compliance protocol	57 (1.9)	50 (1.6)	57 (1.7)	50 (1.5)
Lost to follow-up	34 (1.1)	45 (1.5)	36 (1.1)	46 (1.4)
Refused cont. medicine	45 (1.5)	89 (2.9)	45 (1.4)	93 (2.8)
Other	73 (2.4)	73 (2.4)	74 (2.3)	75 (2.3)

Source: SCS supplement; tables 1.2.1, 1.2.2; pg 26, 27

As compared to trials from the placebo controlled databases (vital status and clinical safety databases), discontinuations were more balanced when comparing SR to the active control group in trial 205.452. This is not surprising as the control in 205.452 was SHH as opposed to placebo in the placebo controlled databases. In both placebo controlled databases, approximately 15% of SR 5mcg patients discontinued prematurely, as opposed to 20% of the placebo patients. While there was a disparity in discontinuations in the placebo controlled databases, it was relatively small and would likely represent a lack of efficacy in patients treated with placebo.

Exposure
A summary of the exposure data for trial 205.452 is provided in Table 35. Mean exposure in each treatment group ranged from 726-728 days. Total exposure time for SR 5mcg was 11343 years. The majority of patients were exposed for 24-36 months (~76.8%).

Table 35. Trial 205.452 (TIOSPIR). Overall exposure (Treated set)

	SR 2.5mcg		SR 5mcg		SHH		Total	
	n	%	n	%	n	%	n	%
Total treated	5724	(100.0)	5705	(100.0)	5687	(100.0)	17116	(100.0)
Time on treatment (days)								
Mean	727.8		726.2		728.1		727.4	
SD	256.1		258.7		255.0		256.6	
Min	1		1		1		1	
Median	835.0		835.0		835.0		835.0	
Max	1022		1027		1023		1027	
Total time on treatment [years]	11405.0		11343.1		11336.7		34084.8	
<1 month (0 - 30 days)	147	(2.6)	156	(2.7)	149	(2.6)	452	(2.6)
1 - 3 months (31 - 90 days)	180	(3.1)	201	(3.5)	169	(3.0)	550	(3.2)
3 - 6 months (91 - 180 days)	162	(2.8)	152	(2.7)	173	(3.0)	487	(2.8)
6 - 12 months (181 - 365 days)	260	(4.5)	259	(4.5)	239	(4.2)	758	(4.4)
12 - 18 months (366 - 547 days)	259	(4.5)	233	(4.1)	254	(4.5)	746	(4.4)
18 - 24 months (548 - 730 days)	322	(5.6)	308	(5.4)	345	(6.1)	975	(5.7)
24 - 30 months (731 - 912 days)	3098	(54.1)	3142	(55.1)	3112	(54.7)	9352	(54.6)
30-36 months (913-1095 days)	1296	(22.6)	1254	(22.0)	1246	(21.9)	3796	(22.2)

Source: trial 205.452 CSR; table 12.1:1; pg123

Exposure data for the placebo controlled databases are summarized in Table 36.

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Table 36. Placebo controlled databases. Overall Exposure

	Vital status database		Clinical safety database	
	SR 5mcg	Placebo	SR 5mcg	Placebo
Total treated (n)	3049	3047	3282	3283
Total time on treatment [years]	2395	2266	2440	2310
Exposure [n(%)]				
≥ 1 months	2961 (97.1)	2865 (93.9)	3139 (95.6)	3040 (92.6)
≥ 3 months	2844 (93.3)	2696 (88.5)	2868 (87.4)	2720 (82.9)
≥6 months	2349 (77.0)	2186 (71.7)	2349 (71.6)	2186 (66.6)
≥12 months	93 (3.1)	114 (3.7)	93 (2.8)	114 (3.5)

Source: SCS supplement; tables 1.1.1, 1.1.2, 1.1.5, 1.1.6; pg19, 20, 23, 24

The SR 5mcg exposure in the vital status and clinical safety databases (2,395 and 2,440 patient years exposure to SR 5mcg, respectively) is approximately 1/5 that of trial 205.452 (11,343 patient years exposure). Additionally for both placebo controlled databases, the mean exposure time per patient was much shorter compared to trial 205.452, as the longest trial in the placebo controlled databases was only 12 months. Because of this, safety findings from trial 205.452 are likely more robust compared to that from the placebo controlled databases.

Compliance
Compliance was based on doses used during the maximum possible treatment period, compared to doses missed as recorded on patient reminder cards. The patient reminder card included a section where patients were asked to record the dates when they missed study medications since the last study visit. Based on this, the majority of patients were between 80-120% compliant (approximately 90% across treatment groups).

Baseline characteristics
The majority of patients were male (71.5%) and white (81.6%) with a mean age of 65 years. The average percent predicted FEV1 was 48% and the majority of patients were GOLD II-III. Baseline patient characteristics were similar across treatment groups and fairly typical for a COPD trial. These data are summarized in Table 37.

Table 37. Trial 205.452 (TIOSPIR). Baseline characteristics (Treated Set)

	SR 2.5mcg	SR 5mcg	SHH	Total
Number of patients (TS)	5724	5705	5687	17116
Gender [N(%)]				
Male	4068 (71.1)	4134 (72.5)	4035 (71.0)	12237 (71.5)
Female	1656 (28.9)	1571 (27.5)	1652 (29.0)	4879 (28.5)
Race [N(%)]				
White	4683 (81.8)	4650 (81.5)	4630 (81.4)	13963 (81.6)
Black	77 (1.3)	94 (1.6)	85 (1.5)	256 (1.5)
Asian	810 (14.2)	802 (14.1)	816 (14.3)	2428 (14.2)

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Missing	154 (2.7)	159 (2.8)	156 (2.7)	469 (2.7)
Age [years]				
Mean	65.1	64.9	65.0	65.0
SD	9.1	9.1	9.0	9.1
BMI [kg/m2]				
Mean	26.2	26.2	26.2	26.2
SD	5.7	5.7	5.7	5.7
Duration of COPD [years]				
Mean	7.4	7.4	7.5	7.4
SD	6.1	6.2	6.2	6.2
Smoking History [N(%)]				
Never smoked	1	1	1	3
Ex-smoker	3556 (62.1)	3496 (61.3)	3542 (62.3)	10594 (61.9)
Currently smokes	2167 (37.9)	2208 (38.7)	2144 (37.7)	6519 (38.1)
Smoking history [pack years]				
Mean	43.6	44.1	43.7	43.8
SD	24.6	25.0	24.7	24.8
Post-bronchodilator				
%predicted FEV1 (%)				
Mean	48	48.5	48.4	48.3
SD	13.9	13.8	13.9	13.9
FEV1/FVC				
Mean	0.50	0.50	0.50	0.50
SD	0.12	0.11	0.11	0.11
GOLD stage [N (%)]				
$FEV_1/FVC \geq 70\%$	69 (1.2)	62 (1.1)	62 (1.1)	193 (1.1)
I	9 (0.2)	19 (0.3)	12 (0.2)	40 (0.2)
II	2679 (46.8)	2745 (48.1)	2728 (48.0)	8152 (47.6)
III	2302 (40.2)	2287 (40.1)	2257 (39.7)	6846 (40.0)
IV	650 (11.4)	573 (10.0)	619 (10.9)	1842 (10.8)

Source: trial 205.452 CSR; table 11.2.1:1 and 11.2.4:1; pp91-92 and 98

Baseline characteristics of patients in the placebo controlled databases are summarized in Table 38. They are generally similar to that seen in trial 205.452 (TIOSPIR).

Table 38. Placebo controlled databases. Baseline characteristics

	Vital status database		Clinical safety database	
	SR 5mcg	Placebo	SR 5mcg	Placebo
Number of patients	3049	3047	3282	3283
Gender [N(%)]				
Male	2296 (75.3)	2274 (74.6)	2451 (74.7)	2429 (74)
Female	753 (24.7)	773 (25.4)	831 (25.3)	854 (26)
Race [N(%)]				
White	2336 (76.6)	2324 (76.3)	2561 (78)	2552 (77.7)
Black	47 (1.5)	59 (1.9)	54 (1.6)	67 (2.0)
Asian	620 (20.3)	616 (20.2)	621 (18.9)	616 (18.8)
Mean age [years]	64.7	64.8	64.6	64.7
Mean BMI [kg/m2]	25.6	25.6	25.7	25.7
Mean Duration of COPD [years]	8.4	8.5	8.5	8.5
Smoking History [N(%)]				
Never smoked	1	0	1	0
Ex-smoker	1907 (62.5)	1912 (62.8)	2048 (62.4)	2045 (62.3)
Currently smokes	1141 (37.4)	1135 (37.2)	1233 (37.6)	1238 (37.7)
Mean smoking history [pack years]	46	46	47	46
Mean %predicted FEV1 (%)	46	46	46	46
Mean FEV1/FVC	0.47	0.47	0.47	0.47
GOLD stage [N (%)]				
$FEV_1/FVC \geq 70\%$	70 (2.3)	58 (1.9)	79 (2.4)	72 (2.2)
I	8 (0.3)	7 (0.2)	10 (0.3)	7 (0.2)
II	1132 (37.1)	1152 (37.8)	1230 (37.5)	1268 (38.6)
III	1388 (45.5)	1397 (45.8)	1490 (45.4)	1485 (45.2)
IV	426 (14)	417 (13.7)	448 (13.7)	434 (13.2)

Source: SCS supplement; table 1.3.1, 1.3.2, 1.3.3; pp 29-30, 31, 32-33

In trial 205.452 (TIOSPIR), patients cardiac, stroke, and COPD exacerbation history were specifically collected using a checklist with specific queries regarding MI, TIA, stroke, cardiac arrhythmia (and sub-types), heart failure (classes I-IV), and COPD exacerbations in the past year (0-5). Data regarding cardiac and stroke histories are summarized in Table 39. Cardiac and stroke histories across all treatment groups were similar and balanced. Approximately 2.3%, 1.4%, and 6.0% of trial 205.452 patients had histories of stroke, TIA, and myocardial infarction, respectively. Approximately 10.7% of patients had a history of cardiac arrhythmias and approximately 8% had a history of heart failure. The most common arrhythmia was atrial fibrillation/flutter and occurred in 3.9-4.1% of patients across treatment groups.

Reference ID: 3618244

Table 39. Trial 205.452 (TIOSPIR). Baseline cardiac and stroke history (Treated Set)

	SR 2.5 mcg	SR 5 mcg	SHH
Total treated	5724	5705	5687
Stroke and/or TIA	190 (3.3)	225 (3.9)	193 (3.4)
Stroke	124 (2.2)	139 (2.4)	125 (2.2)
TIA	74 (1.3)	98 (1.7)	74 (1.3)
Myocardial infarction	340 (5.9)	339 (5.9)	347 (6.1)
Ischemic heart disease/ coronary artery diseases	846 (14.8)	855 (15.0)	893 (15.7)
Cardiac arrhythmia	604(10.6)	614 (10.8)	607 (10.7)
Atrial fibrillation or flutter	222 (3.9)	232 (4.1)	222 (3.9)
Ventricular fibrillation	11(0.2)	9 (0.2)	9 (0.2)
Supraventricular tachycardia	57 (1.0)	51 (0.9)	58 (1.0)
Ventricular tachycardia	19 (0.3)	25 (0.4)	27 (0.5)
Bradycardia	55 (1.0)	62 (1.1)	74 (1.3)
Atrioventricular (AV) block	48 (0.8)	32 (0.6)	48 (0.8)
Bundle branch (BB) block	139 (2.4)	145 (2.5)	137 (2.4)
Other conduction disorder	121 (2.1)	125 (2.2)	117 (2.1)
Heart failure class			
None	5256 (91.8)	5259 (92.2)	5251 (92.3)
Class I	187 (3.3)	184 (3.2)	153 (2.7)
Class II	226 (3.9)	226 (4.0)	246 (4.3)
Class III	46 (0.8)	31 (0.5)	32 (0.6)
Class IV	2 (0.0)	2 (0.0)	3 (0.1)
Missing	7 (0.1)	3 (0.1)	2(0.0)

Source: trial 205.452 CSR; table 11.2.2:1; pg93

In the vital status database, baseline medical history was not collected using a standardized checklist as in trial 205.452, but rather through verbatim terms coded to MedDRA preferred terms. Because of this, it is difficult to directly compare the baseline cardiac and stroke history for patients in the vital status database compared to TIOSPIR however, the baseline cardiac and stroke history from the vital status database (Table 40) is generally comparable to that in TIOSPIR.

Table 40. Vital status database. Baseline cardiac and stroke history

	Vital status database	
	SR 5mcg	Placebo
Total treated	3049	3047
Stroke$	174 (5.7)	165 (5.4)
Myocardial infarction#	98 (3.2)	102 (3.3)
Ischemic heart disease/ coronary artery diseases#	420 (13.8)	439 (14.4)
Cardiac arrhythmia	405 (13.3)	321 (10.5)
Atrial fibrillation or flutter$	104 (3.4)	83 (2.7)

Ventricular fibrillation	0	0
Supraventricular tachycardia$	0	0
Ventricular tachycardia	3 (0.1)	0
Bradycardia	12 (0.4)	10 (0.3)
Conduction disorder	144 (4.7)	99 (3.2)
Heart failure class		
None	2940 (96.4)	2953 (96.9)
Class I-IV#	108 (3.5)	94 (3.1)

$BI collapse preferred term included multiple MedDRA preferred terms
#MedDRA SMQ including multiple preferred terms
Source: SCS; table 1.3.5:1; pg34

Pulmonary therapies at baseline in trial 205.452 were similar between treatment groups and were what would be expected in a COPD population. The use of baseline inhaled long-acting anticholinergics was more frequent in trial 205.452 (47%) compared to the vital status database (10%).Otherwise, the use of baseline pulmonary medications was similar in 205.452 and the vital status database.

Baseline cardiac medications were also similar between treatment groups in trial 205.452. Use of beta-blockers in trial 205.452 (14%) was higher compared to the vital status database (9%). Otherwise baseline cardiac medications were generally similar between trial 205.452 and the vital status database.

7.2.2 Explorations for Dose Response

Trial 205.452 included two doses of SR (2.5 and 5mcg), allowing for exploration of dose dependency of for recorded AEs.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Not applicable

7.2.5 Metabolic, Clearance, and Interaction Workup

Not performed

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Trial 205.452 (TIOPSIR) was specifically designed to address concerns related to mortality, and cardiovascular safety raised in the initial review cycle. In addition, due to known pharmacologic effects of tiotropium, adverse event data were specifically

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analyzed for anticholinergic events, such as ocular effects, urinary retention, and intestinal obstruction.

7.3 Major Safety Results

For the evaluation of safety, mortality data from trial 205.452 (TIOSPIR) is presented followed by data from the placebo-controlled vital status database. The placebo-controlled clinical safety database was not used for analysis of deaths as not all trials in this database included vital status follow-up information (as in the vital status database), and this database also included shorter trials (<24weeks). For the analysis of SAEs, data from trial 205.452 (TIOSPIR) and the placebo controlled clinical safety database are presented. SAE data from the vital status database was not separately analyzed as, all trials in the vital status database were included in the clinical safety database. Refer to Table 31 for the trials included in the placebo-controlled databases.

7.3.1 Deaths

Trial 205.452 (TIOSPIR)
The primary endpoint of trial 205.452 was all-cause mortality. Analysis of fatal events was based on the death analysis set (DAS), which consisted of 17,135 patients and included vital status follow-up at trial close-out. Vital status information was obtained in 99.7% of patients. There were a total of 1,302 deaths. There were similar numbers of events between treatment groups. When comparing hazard ratios (HR) for the SR groups versus SHH, point estimates were 0.957 and 0.996 for SR 5mcg and 2.5mcg, respectively. For both SR doses, the upper limit of the 95% confidence intervals were <1.25 and within the pre-specified non-inferiority-margin. These results are summarized in Table 41 and graphically in Figure 7.

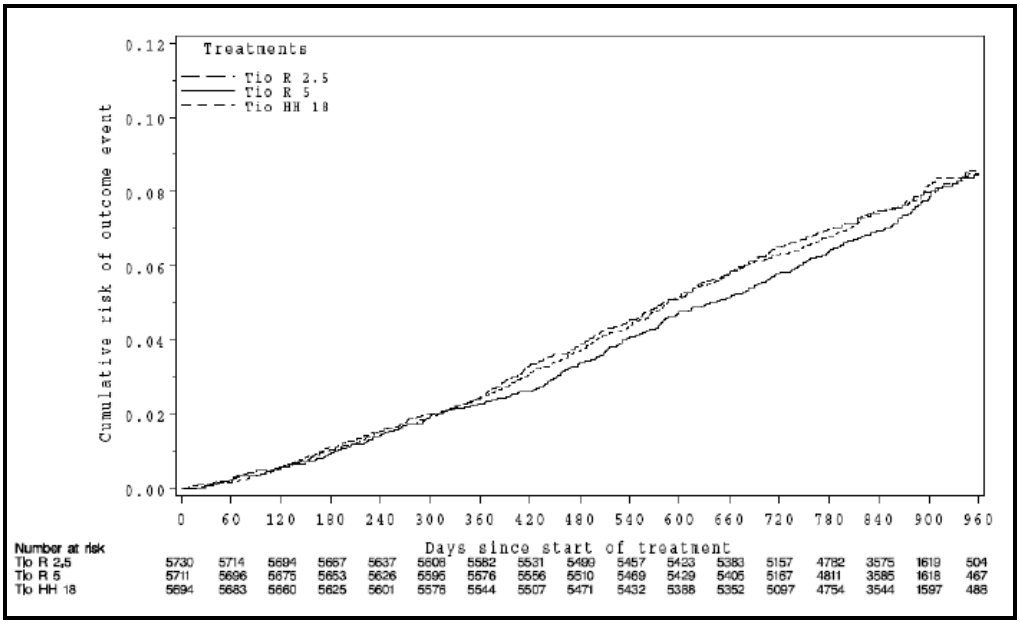
Table 41. Trial 205.452 (TIOSPIR). All-cause mortality (Death Analysis Set)

	SR 2.5mcg	SR 5mcg	SHH
Number of patients (DAS)	5730	5711	5694
Deaths [n(%)]	440 (7.7)	423 (7.4)	439 (7.7)
Comparison vs. SHH			
HR	0.996	0.957	
95% CI	(0.872, 1.136)	(0.837, 1.094)	

Source: trial 205.452 CSR; table 11.4.1.1.1:1; pg102

Reference ID: 3618244

Figure 7. Trial 205.452. Kaplan-Meier plot of time to death by treatment



Source: SCS; figure 2.1.2.1:1; pg46

A sensitivity analysis was also performed looking at only on treatment deaths (within 30 days of last treatment). The results for the sensitivity analyses were consistent with the primary analysis. Hazard ratio point estimates for the SR doses versus SHH were 0.913 and 1.001 for the 2.5mcg and 5mcg doses, respectively. For both HRs, the upper limit of the 95% confidence interval was 1.159 and 1.060 for the 2.5 and 5mcg doses, respectively).

All causes of death were adjudicated. At vital status follow-up, the most common causes of death were in the following system organ classes (SOC): respiratory, thoracic, and mediastinal; general disorders and administration site conditions; and neoplasms benign, malignant, and unspecified. Given the patient population, this is not surprising. In general, deaths were similar between treatment groups based on percentage and rate. However, for the cardiac disorder SOC, there was a small numerical difference when comparing SR groups to SHH. The rate ratios (RR) for SR 2.5mcg and SR 5mcg to SHH were 1.29 (95% CI 0.68, 2.42) and 1.58 (95% CI 0.86, 2.89), respectively. Based on RR, this was the largest difference observed when comparing SR 5mcg to SHH. Within the cardiac disorder SOC, there was also small difference in myocardial infarction when comparing SR groups to placebo. However, there was no evidence of dose response, which may imply that this is not drug related, but rather due to chance. Cardiovascular safety will be further discussed in 7.3.5 Submission Specific Primary Safety Concerns.

By preferred term (PT), the most common adjudicated causes of death were COPD (2%), sudden death (0.8%), lung neoplasm malignant (0.6%), death (0.6%), and sudden

cardiac death (0.5%). These were evenly distributed across the treatment groups. The adjudicated mortality data are summarized in Table 42.

Table 42. Trial 205.452 (TIOSPIR). Adjudicated causes of death at vital status follow-up by system organ class (SOC). Preferred terms (PT) were listed if ≥0.1% in any treatment group (Death Analysis Set)

SOC/PT	SR 2.5mcg		SR 5mcg		SHH	
	n (%)	rate/100 pt yrs	n (%)	rate/100 pt yrs	n (%)	rate/100 pt yrs
Number of patients	5730		5711		5694	
Total with primary cause of death determined by adjudication	440 (7.7)	3.3	423 (7.4)	3.2	439 (7.7)	3.4
Respiratory, thoracic and mediastinal disorders	116 (2.0)	0.9	123 (2.2)	0.9	130 (2.3)	1.0
COPD	110 (1.9)	0.8	115 (2.0)	0.9	117 (2.1)	0.9
Respiratory failure	2 (0.0)	0	2 (0.0)	0	6 (0.1)	0
General disorders and administration site conditions	117 (2.0)	0.9	96 (1.7)	0.7	107 (1.9)	0.9
Sudden death	45 (0.8)	0.3	38 (0.7)	0.3	46 (0.8)	0.4
Death	35 (0.6)	0.3	27 (0.5)	0.2	37 (0.6)	0.3
Sudden cardiac death	37 (0.6)	0.3	29 (0.5)	0.3	22 (0.4)	0.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	110 (1.9)	0.8	100 (1.8)	0.8	95 (1.7)	0.7
Lung neoplasm malignant	40 (0.7)	0.3	36 (0.6)	0.3	29 (0.5)	0.2
Colon cancer	4 (0.1)	0	2 (0.0)	0	3 (0.1)	0
Gastric cancer	3 (0.1)	0	1 (0.0)	0	5 (0.1)	0
Lung adenocarcinoma	5 (0.1)	0	3 (0.1)	0	5 (0.1)	0
Lung cancer metastatic	3 (0.1)	0	6 (0.1)	0	4 (0.1)	0
Pancreatic carcinoma	6 (0.1)	0	3 (0.1)	0	6 (0.1)	0
Small cell lung cancer	3 (0.1)	0	2 (0.0)	0	4 (0.1)	0
Infections and infestations	34 (0.6)	0.3	34 (0.6)	0.3	34 (0.6)	0.3
Pneumonia	23(0.4)	0.2	24 (0.6)	0.2	24 (0.4)	0.2
Sepsis	2 (0.0)	0	4 (0.1)	0	3 (0.1)	0
Cardiac disorders	22 (0.4)	0.2	27 (0.5)	0.2	17 (0.3)	0.1
Cardiac failure	1 (0.0)	0	5 (0.1)	0	3 (0.1)	0
Cardiac failure congestive	5 (0.1)	0	3 (0.1)	0	4 (0.1)	0
Myocardial infarction	9 (0.2)	0.1	6 (0.1)	0	2 (0.0)	0
Gastrointestinal disorders	6 (0.1)	0	10 (0.2)	0.1	16 (0.3)	0.1
Injury, poisoning and procedural complications	11 (0.2)	0.1	11 (0.2)	0.1	16 (0.3)	0.1
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
Vascular disorders	5 (0.1)	0	3 (0.1)	0	5 (0.1)	0
Hepatobiliary disorders	3 (0.1)	0	1 (0.0)	0	2 (0.0)	0
Musculoskeletal and connective tissue disorders	1 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Psychiatric disorders	1 (0.0)	0	2 (0.0)	0	4 (0.1)	0
Renal and urinary disorders	1 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Source: trial 205.452 CSR; tables 15.3.2.2:1 and 15.3.2.2:4; pp327-335 and 348-354

Placebo-controlled vital status database

Causes of death in the placebo controlled vital status database are summarized in Table 43. Vital status information was obtained in approximately 98% of patients in the vital status database. Consistent with the safety data available at the time of the original NDA submission, deaths were numerically more common in the SR 5mcg group compared to placebo based on rate and percentage. The hazard ratio (SR 5mcg:placebo) was 1.33 [95% CI of (0.93, 1.92)]. A small numerical difference favoring placebo was also observed for the cardiac disorder SOC in the vital status database. Within the cardiac SOC, deaths under the preferred term myocardial infarction were also more common in the SR 5mcg group compared to placebo based on rate (0.08 vs. 0.27 rate/100 patient years). This is consistent with the findings in trial 205.452 when comparing SR 5mcg to SHH. However, it should be noted that the overall numbers are small for deaths in the cardiac disorder SOC and MI PT. There were also more deaths in the neoplasm SOC when comparing placebo to SR 5mcg groups in the vital status database. The most commonly reported neoplasm was lung neoplasm malignant which was more common in SR 5mcg than placebo (0 vs. 0.16 rate/100-patient years). As with events cardiac deaths, the actual numbers were small.

Reference ID: 3618244

Table 43. Vital status database. Deaths by system organ class (SOC). Preferred terms (PT) listed if occurred in ≥2 patients/treatment group.

SOC/PT	SR 5mcg		Placebo	
	n(%)	rate/ 100 pt-yrs	n(%)	rate/ 100 pt-yrs
Total patients	3049		3047	
Total with fatal adverse events	68 (2.2)	2.64	51 (1.7)	1.98
Cardiac disorders	16 (0.5)	0.62	7 (0.2)	0.27
Cardiac arrest	2 (0.1)	0.08	2 (0.1)	0.08
Cardiac failure	2 (0.1)	0.08	1 (0.0)	0.04
Cardiac failure congestive	2 (0.1)	0.08	0	0
Cardiopulmonary failure	0	0	2 (0.1)	0.0
Myocardial infarction	7 (0.2)	0.27	2 (0.1)	0.08
Gastrointestinal disorders	1 (0.0)	0.04	3 (0.1)	0.12
General disorders and administration site conditions	19 (0.6)	0.74	15 (0.5)	0.58
Death	10 (0.3)	0.39	9 (0.3)	0.35
Sudden death	9 (0.3)	0.35	5 (0.2)	0.19
Infections and infestations	6 (0.2)	0.23	12 (0.4)	0.47
Pneumonia	1 (0.0)	0.04	7 (0.2)	0.27
Septic shock	1 (0.0)	0.04	2 (0.1)	0.08
Injury, poisoning and procedural complications	1 (0.0)	0.04	0	0.00
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (0.3)	0.39	3 (0.1)	0.12
Gastrointestinal carcinoma	0	0	2 (0.1)	0.08
Lung neoplasm malignant	4 (0.1)	0.16	0	0
Nervous system disorders	1 (0.0)	0.04	2 (0.1)	0.08
Psychiatric disorders	1 (0.0)	0.04	1 (0.0)	0.04
Renal and urinary disorders	2 (0.1)	0.08	0 (0.0)	0.00
Reproductive system and breast disorders	1 (0.0)	0.04	0	0.00
Respiratory, thoracic and mediastinal disorders	12 (0.4)	0.47	14 (0.5)	0.54
COPD	7 (0.2)	0.27	8 (0.3)	0.31
Pneumonia aspiration	2 (0.1)	0.08	1 (0.0)	0.04
Respiratory failure	2 (0.1)	0.08	3 (0.1)	0.12

Source: SCS supplement; table 2.3.5; pp245-254

As trial 1205.14 was shorter in duration compared to the other three trials (48-week exacerbation trials 205.254, 205.255, and 205.372) in the vital status database, deaths were also analyzed from the pooled exacerbation trials only. The results of this analysis demonstrated that the percentage of patients dead at vital status follow-up in the pooled 48-week exacerbations trials (SR 5mcg=2.5%, placebo=1.8%) were similar to the vital status database. The hazard ratio (SR 5mcg:placebo) was also similar [1.40, 95% CI(0.97, 2.04)].

Due to concerns raised in the initial NDA review cycle, further analyses of deaths were performed. These are discussed in 7.3.5 Submission Specific Primary Safety Concerns.

7.3.2 Serious Adverse Events

Trial 205.452 (TIOSPIR)
Analysis of serious adverse events in trial 205.452 was performed in the treated set (TS) (Table 44). This analysis population included 17,116 patients and as previously mentioned differed from the death analysis set (DAS) as the TS excluded patients from 2 clinical sites (n=19) where trial conduct and data capture were suspect. In the TS a total of 5625 patients (32.9%) experienced an SAE. Based on SOC, SAEs were balanced across treatment groups when comparing percentages and rates. As expected from a COPD population, SAEs were most commonly reported in respiratory, thoracic, and mediastinal (17.2%); infections and infestations (8.7%); and cardiac disorders (4.9%) SOCs. SAEs within the cardiac disorder SOC were similar between treatment groups based on rate and percentage. Based on preferred term (PT), the three most common SAEs were COPD (15.3%), pneumonia (6%), and lung neoplasm malignant (0.9%). By PT, based on rate and percentage, SAEs were generally similar between treatment groups.

Reference ID: 3618244

Table 44. Trial 205.452 (TIOSPIR). Serious adverse events by system organ class (SOC). Preferred terms (PT) listed if it occurred in >10 patients/group (Treated Set)

SOC/PT	SR 2.5mcg		SR 5 mcg		SHH	
	n (%)	rate/100 pt yrs	n (%)	rate/100 pt yrs	n (%)	rate/100 pt yrs
Number of patients (TS)	5724		5705		5687	
Total treated with SAE events	1937 (33.84)	19.7	1846 (32.36)	18.8	1842 (32.39)	18.6
Blood and lymphatic system disorders	22 (0.38)	0.2	16 (0.28)	0.1	29 (0.51)	0.2
Anemia	10 (0.17)	0.1	10 (0.18)	0.1	13 (0.23)	0.1
Cardiac disorders	293 (5.12)	2.5	273 (4.79)	2.4	270 (4.75)	2.3
Acute myocardial infarction	21 (0.37)	0.2	21 (0.37)	0.2	13 (0.23)	0.1
Angina pectoris	20 (0.35)	0.2	28 (0.49)	0.2	22 (0.39)	0.2
Angina unstable	10 (0.17)	0.1	19 (0.33)	0.2	10 (0.18)	0.1
Atrial fibrillation	41 (0.72)	0.3	37 (0.65)	0.3	32 (0.56)	0.3
Atrial flutter	10 (0.17)	0.1	6 (0.11)	0.1	4 (0.07)	0.0
Cardiac arrest	12 (0.21)	0.1	7 (0.12)	0.1	9 (0.16)	0.1
Cardiac failure	30 (0.52)	0.3	23 (0.4)	0.2	24 (0.42)	0.2
Cardiac failure congestive	26 (0.45)	0.2	22 (0.39)	0.2	29 (0.51)	0.2
Cardiopulmonary failure	9 (0.16)	0.1	11 (0.19)	0.1	9 (0.16)	0.1
Coronary artery disease	18 (0.31)	0.2	25 (0.44)	0.2	23 (0.4)	0.2
Myocardial infarction	53 (0.93)	0.4	45 (0.79)	0.4	39 (0.69)	0.3
Myocardial ischemia	7 (0.12)	0.1	7 (0.12)	0.1	11 (0.19)	0.1
Eye disorders	16 (0.28)	0.1	21 (0.37)	0.2	19 (0.33)	0.2
Cataract	13 (0.23)	0.1	10 (0.18)	0.1	14 (0.25)	0.1
Gastrointestinal disorders	152 (2.66)	1.3	148 (2.59)	1.3	140 (2.46)	1.2
Gastrointestinal hemorrhage	11 (0.19)	0.1	12 (0.21)	0.1	8 (0.14)	0.1
Inguinal hernia	10 (0.17)	0.1	16 (0.28)	0.1	15 (0.26)	0.1
General disorders and administration site conditions	108 (1.89)	0.9	99 (1.74)	0.8	111 (1.95)	0.9
Death	28 (0.49)	0.2	21 (0.37)	0.2	13 (0.23)	0.1
Non−cardiac chest pain	19 (0.33)	0.2	23 (0.4)	0.2	22 (0.39)	0.2
Sudden death	27 (0.47)	0.2	13 (0.23)	0.1	18 (0.32)	0.2
Hepatobiliary disorders	48 (0.84)	0.4	28 (0.49)	0.2	26 (0.46)	0.2
Cholecystitis	11 (0.19)	0.1	7 (0.12)	0.1	6 (0.11)	0.1
Cholelithiasis	12 (0.21)	0.1	12 (0.21)	0.1	4 (0.07)	0.0
Infections and infestations	497 (8.68)	4.4	502 (8.8)	4.4	495 (8.7)	4.4
Bronchitis	16 (0.28)	0.1	9 (0.16)	0.1	11 (0.19)	0.1
Cellulitis	6 (0.1)	0.1	14 (0.25)	0.1	14 (0.25)	0.1
Gastroenteritis	11 (0.19)	0.1	5 (0.09)	0.0	8 (0.14)	0.1
Infective exacerbation of chronic	16 (0.28)	0.1	8 (0.14)	0.1	8 (0.14)	0.1
Lobar pneumonia	16 (0.28)	0.1	15 (0.26)	0.1	12 (0.21)	0.1
Pneumonia	339 (5.92)	2.9	344 (6.03)	3.0	340 (5.98)	3.0
Sepsis	18 (0.31)	0.2	22 (0.39)	0.2	16 (0.28)	0.1
Septic shock	6 (0.1)	0.1	6 (0.11)	0.1	12 (0.21)	0.1
Injury, poisoning and procedural complications	116 (2.03)	1.0	93 (1.63)	0.8	97 (1.71)	0.8

Fall	8 (0.14)	0.1	19 (0.33)	0.2	4 (0.07)	0.0
Hip fracture	11 (0.19)	0.1	5 (0.09)	0.0	11 (0.19)	0.1
Metabolism and nutrition disorders	33 (0.58)	0.3	40 (0.7)	0.3	31 (0.55)	0.3
Musculoskeletal and connective tissue disorders	80 (1.4)	0.7	63 (1.1)	0.5	82 (1.44)	0.7
Back pain	11 (0.19)	0.1	3 (0.05)	0.0	6 (0.11)	0.1
Osteoarthritis	10 (0.17)	0.1	12 (0.21)	0.1	23 (0.4)	0.2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	279 (4.87)	2.4	274 (4.8)	2.4	250 (4.4)	2.2
Basal cell carcinoma	17 (0.3)	0.1	26 (0.46)	0.2	15 (0.26)	0.1
Bladder cancer	13 (0.23)	0.1	10 (0.18)	0.1	4 (0.07)	0.0
Colon cancer	13 (0.23)	0.1	4 (0.07)	0.0	10 (0.18)	0.1
Lung neoplasm malignant	52 (0.91)	0.4	60 (1.05)	0.5	48 (0.84)	0.4
Prostate cancer	17 (0.3)	0.1	17 (0.3)	0.1	14 (0.25)	0.1
Squamous cell carcinoma	9 (0.16)	0.1	12 (0.21)	0.1	19 (0.33)	0.2
Nervous system disorders	136 (2.38)	1.2	138 (2.42)	1.2	121 (2.13)	1.0
Cerebrovascular accident	35 (0.61)	0.3	38 (0.67)	0.3	35 (0.62)	0.3
Syncope	14 (0.24)	0.1	17 (0.3)	0.1	15 (0.26)	0.1
Transient ischemic attack	18 (0.31)	0.2	23 (0.4)	0.2	14 (0.25)	0.1
Psychiatric disorders	20 (0.35)	0.2	31 (0.54)	0.3	21 (0.37)	0.2
Renal and urinary disorders	48 (0.84)	0.4	65 (1.14)	0.6	59 (1.04)	0.5
Renal failure acute	17 (0.3)	0.1	14 (0.25)	0.1	24 (0.42)	0.2
Reproductive system and breast disorders	20 (0.35)	0.2	17 (0.3)	0.1	14 (0.25)	0.1
Benign prostatic hyperplasia	8 (0.14)	0.1	14 (0.25)	0.1	4 (0.07)	0.0
Respiratory, thoracic and mediastinal disorders	1017 (17.77)	9.4	957 (16.77)	8.9	964 (16.95)	8.9
Acute respiratory failure	30 (0.52)	0.3	32 (0.56)	0.3	28 (0.49)	0.2
Chronic obstructive pulmonary disease	895 (15.64)	8.2	868 (15.21)	8.0	851 (14.96)	7.8
Dyspnea	24 (0.42)	0.2	17 (0.3)	0.1	21 (0.37)	0.2
Hemoptysis	10 (0.17)	0.1	8 (0.14)	0.1	13 (0.23)	0.1
Pneumothorax	25 (0.44)	0.2	25 (0.44)	0.2	21 (0.37)	0.2
Pulmonary embolism	28 (0.49)	0.2	28 (0.49)	0.2	24 (0.42)	0.2
Respiratory failure	42 (0.73)	0.4	40 (0.7)	0.3	35 (0.62)	0.3
Surgical and medical procedures	49 (0.86)	0.4	47 (0.82)	0.4	48 (0.84)	0.4
Vascular disorders	91 (1.59)	0.8	92 (1.61)	0.8	91 (1.6)	0.8
Aortic aneurysm	8 (0.14)	0.1	15 (0.26)	0.1	12 (0.21)	0.1
Deep vein thrombosis	5 (0.09)	0.0	11 (0.19)	0.1	6 (0.11)	0.1
Hypertension	8 (0.14)	0.1	8 (0.14)	0.1	12 (0.21)	0.1

Source: trial 205.452 CSR; table 15.3.2.3:3; pp380-385

Placebo-Controlled Clinical Safety Database

SAE data for patients in the clinical safety database are summarized in Table 45. As expected from a COPD population and similar to trial 205.452 (TIOSPIR), SAEs were most commonly reported in respiratory, thoracic, and mediastinal; infections and infestations; and cardiac disorders SOCs. Compared to trial 205.452, there were more

numerical differences based on SOC in the clinical safety database when comparing SR 5mcg and placebo treatment groups.

Table 45. Clinical safety database. Serious adverse events by system organ class (SOC). Preferred term (PT) listed if ≥5 patients/treatment group

SOC/PT	SR 5mcg		Placebo	
	n(%)	rate/ 100 pt-yrs	n(%)	rate/ 100 pt-yrs
Total patients	3282		3283	
Total with serious adverse events	491 (15.0)	19.47	496 (15.1)	20.81
Blood and lymphatic system disorders	3 (0.1)	0.11	5 (0.2)	0.19
Cardiac disorders	84 (2.6)	3.13	69 (2.1)	2.70
Acute myocardial infarction	3 (0.1)	0.11	5 (0.2)	0.19
Angina pectoris	7 (0.2)	0.26	4 (0.1)	0.16
Angina unstable	2 (0.1)	0.07	5 (0.2)	0.19
Atrial fibrillation	8 (0.2)	0.3	5 (0.2)	0.19
Cardiac failure	12 (0.4)	0.44	13 (0.4)	0.51
Cardiac failure congestive	8 (0.2)	0.3	5 (0.2)	0.19
Coronary artery disease	7 (0.2)	0.26	3 (0.1)	0.12
Myocardial infarction	9 (0.3)	0.33	10 (0.3)	0.39
Myocardial ischemia	6 (0.2)	0.22	1 (0.0)	0.04
Ear and labyrinth disorders	2 (0.1)	0.07	2 (0.1)	0.08
Endocrine disorders	1 (0.0)	0.04	0	0.00
Eye disorders	3 (0.1)	0.11	1 (0.0)	0.04
Gastrointestinal disorders	45 (1.4)	1.67	43 (1.3)	1.68
Abdominal pain	6 (0.2)	0.22	2 (0.1)	0.08
Diarrhea	0	0	5 (0.2)	0.19
Inguinal hernia	7 (0.2)	0.26	6 (0.2)	0.23
General disorders and administration site conditions	32 (1.0)	1.19	17 (0.5)	0.66
Chest pain	10 (0.3)	0.37	2 (0.1)	0.08
Death	5 (0.2)	0.18	3 (0.1)	0.12
Hepatobiliary disorders	6 (0.2)	0.22	11 (0.3)	0.43
Cholelithiasis	0	0	5 (0.2)	0.19
Immune system disorders	0	0.00	2 (0.1)	0.08
Infections and infestations	100 (3.0)	3.75	132 (4.0)	5.23
Bronchitis	9 (0.3)	0.33	9 (0.3)	0.35
Gastroenteritis	3 (0.1)	0.11	8 (0.2)	0.31
Infective exacerbation of COPD	9 (0.3)	0.33	18 (0.5)	0.7
Lobar pneumonia	3 (0.1)	0.11	10 (0.3)	0.39
Lower respiratory tract infection	2 (0.1)	0.07	6 (0.2)	0.23
Pneumonia	47 (1.4)	1.75	50 (1.5)	1.95
Injury, poisoning and procedural complications	32 (1.0)	1.19	28 (0.9)	1.09
Fall	7 (0.2)	0.26	7 (0.2)	0.27
Road traffic accident	5 (0.2)	0.18	1 (0.0)	0.04
Investigations	6 (0.2)	0.22	2 (0.1)	0.08
Metabolism and nutrition disorders	6 (0.2)	0.22	11 (0.3)	0.43
Musculoskeletal and connective tissue	12 (0.4)	0.44	12 (0.4)	0.47

disorders				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	66 (2.0)	2.46	44 (1.3)	1.72
Bronchial carcinoma	6 (0.2)	0.22	4 (0.1)	0.16
Lung neoplasm malignant	13 (0.4)	0.48	7 (0.2)	0.27
Prostate cancer	5 (0.2)	0.18	5 (0.2)	0.2
Nervous system disorders	27 (0.8)	1.00	29 (0.9)	1.13
Psychiatric disorders	9 (0.3)	0.33	9 (0.3)	0.35
Renal and urinary disorders	19 (0.6)	0.70	11 (0.3)	0.43
Reproductive system and breast disorders	6 (0.2)	0.22	4 (0.1)	0.16
Benign prostatic hyperplasia	6 (0.2)	0.22	4 (0.1)	0.16
Respiratory, thoracic and mediastinal disorders	223 (6.8)	8.49	245 (7.5)	9.85
COPD	172 (5.2)	6.51	207 (6.3)	8.28
Dyspnea	13 (0.4)	0.48	7 (0.2)	0.27
Hemoptysis	4 (0.1)	0.15	7 (0.2)	0.27
Pneumothorax	9 (0.3)	0.33	8 (0.2)	0.31
Pulmonary embolus	6 (0.2)	0.22	4 (0.1)	0.16
Respiratory failure	12 (0.4)	0.44	15 (0.5)	0.58
Skin and subcutaneous tissue disorders	6 (0.2)	0.22	2 (0.1)	0.08
Social circumstances	1 (0.0)	0.04	0	0.00
Surgical and medical procedures	3 (0.1)	0.11	5 (0.2)	0.19
Vascular disorders	10 (0.3)	0.37	17 (0.5)	0.66

Source: SCS supplement; table 2.5.3; pp325-380

Analysis of SAEs was also performed on the pooled safety data from the three 48-week exacerbation trials (205.254, 205.255, and 205.372). Compared to the clinical safety database, the pooled exacerbation trials had 1325 fewer patients (660 for SR 5mcg and 665 for placebo) and 91 fewer SAEs (41 for SR 5mcg and 50 for placebo). Differences between percent of patients who experienced an SAE by SOC and PT were minimal when comparing the two pools. Analysis did not reveal any new concerns that were not seen in the clinical safety database. Overall, the SAE data for the pooled exacerbation trials were consistent with the SAE data for the clinical safety database.

The incidence rate/100-patient years of exposure for SAEs in the SR 5mcg group was similar between trial 205.452 and the clinical safety database. The types of SAEs when comparing trial 205.452 and the placebo controlled clinical safety database were also generally similar.

Due to submission specific safety concerns further analyses of SAEs were performed. These are discussed in 7.3.5 Submission Specific Primary Safety Concerns.

7.3.3 Dropouts and/or Discontinuations

Trial 205.452 (TIOSPIR)

Reference ID: 3618244

Of the 17,135 patients who received study drug (DAS), 17,116 were included in the TS. Of these, 3917 patients were discontinued from the trial. Discontinuations were evenly distributed between treatment groups (see 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations, Table 33). The most common reason for discontinuation was an adverse event (1414). Note that this number only included those who reported an event and then discontinued. Patients that discontinued due to death were not included. Discontinuations due to adverse events were slightly higher in the SHH group (8.8%) compared to the SR 5mcg and 2.5mcg groups (8.2% and 7.8%, respectively). The three most common SOCs with AEs leading to discontinuation were respiratory, thoracic, and mediastinal (RTM); neoplasms, benign, malignant and unspecified; and infections and infestations. Discontinuations due to RTM AEs were more frequent in the SHH group compared to the SR groups, but otherwise, discontinuations by SOC were generally balanced. The slight difference observed in the RTM SOC was not driven by a single PT or any grouping of similar PTs. By PT, the most common AEs cited as reasons for discontinuation were COPD (1.8%) and pneumonia (0.6%). Discontinuations by PT were also generally balanced. Discontinuations by SOC are summarized in Table 46.

Table 46. Trial 205.452 (TIOSPIR). Adverse events leading to discontinuation by system organ class (Treated Set)

System organ class	SR 2.5 n(%)	SR 5 n(%)	SHH n (%)
Number of subjects	5724 (100.0)	5705 (100.0)	5687 (100.0)
Total with AEs leading to permanent discontinuation	448 (7.8)	468 (8.2)	498 (8.8)
Infections and infestations	46 (0.8)	53 (0.9)	51 (0.9)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	88 (1.5)	65 (1.1)	79 (1.4)
Blood and lymphatic system	1 (0.0)	0 (0.0)	1 (0.0)
Immune system disorders	2 (0.0)	3 (0.1)	1 (0.0)
Metabolism and nutrition disorders	0 (0.0)	3 (0.1)	3 (0.1)
Psychiatric disorders	5 (0.1)	10 (0.2)	6 (0.1)
Nervous system disorders	34 (0.6)	35 (0.6)	24 (0.4)
Eye disorders	3 (0.1)	3 (0.1)	7 (0.1)
Ear and labyrinth disorders	1 (0.0)	2 (0.0)	1 (0.0)
Cardiac disorders	42 (0.7)	40 (0.7)	40 (0.7)
Vascular disorders	6 (0.1)	7 (0.1)	7 (0.1)
Respiratory, thoracic and mediastinal disorders	163 (2.8)	175 (3.1)	198 (3.5)
Gastrointestinal disorders	39 (0.7)	39 (0.7)	31 (0.5)
Hepatobiliary disorders	4 (0.1)	0 (0.0)	1 (0.0)
Skin and subcutaneous tissue disorders	7 (0.1)	11 (0.2)	16 (0.3)
Musculoskeletal and connective tissue disorders	5 (0.1)	5 (0.1)	7 (0.1)
Renal and urinary disorders	13 (0.2)	9 (0.2)	12 (0.2)
Reproductive system and breast disorders	1 (0.0)	5 (0.1)	4 (0.1)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	1 (0.0)
General disorders and administration site conditions	12 (0.2)	21 (0.4)	27 (0.5)

Reference ID: 3618244

Investigations	2 (0.0)	2 (0.0)	1 (0.0)
Injury, poisoning and procedural complications	5 (0.1)	6 (0.1)	13 (0.2)
Surgical and medical procedures	0 (0.0)	2 (0.0)	1 (0.0)

Source: trial 205.452 CSR; table 12.2.2.4:1; pg129

In the clinical safety database, discontinuations due to AEs based on SOC were also generally similar in frequency between placebo and SR 5mcg groups.

7.3.4 Significant Adverse Events

See 7.3.5 Submission Specific Primary Safety Concerns

7.3.5 Submission Specific Primary Safety Concerns

Due to safety concerns with this product, additional safety analyses of data from trial 205.452 (TIOSPIR) and the placebo controlled databases (vital status and clinical safety database) were performed. As in the safety analyses in sections 7.3.1 Deaths and 7.3.2 Serious Adverse Events, in this section mortality data was analyzed from trials 205.452 (TIOSPIR) and the placebo-controlled vital status database. For the analysis of SAEs, data from trial 205.452 (TIOSPIR) and the placebo controlled clinical safety database were analyzed. Refer to Table 31 for the trials included in the placebo-controlled databases.

The additional safety analyses included analyses of cardiovascular and respiratory safety using MedDRA defined standard MedDRA Queries (SMQs) and Applicant defined pharmacovigilance endpoints (PVE). A similar approach was also used to assess safety with respect to neoplasm and anticholinergic class effects. MACE analysis was also performed. In addition, in trial 205.452 (TIOSPIR), the Applicant included analysis of stroke, transient ischemic attack (TIA), and myocardial infarction (MI) which used pre-specified definitions delineated in the protocol. These were termed outcome events and were centrally monitored.

Cardiovascular Safety
The Applicant analyzed cardiovascular events based on a number of cardiovascular related SMQs which included cardiac arrhythmias (including sub-SMQs), cardiac failure (narrow), and ischemic heart disease (including sub-SMQs). PVEs included cardiac arrest, cardiac arrest/sudden death.

Ischemic heart disease—Fatal events
Trial 205.452 (TIOSPIR)
Based on SMQ analysis, imbalances were noted in adjudicated deaths attributed to preferred terms (PT) within ischemic heart disease related SMQs. While the numerical imbalances were small based on percentage and rate, when comparing rates using rate

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ratios, the differences were magnified. The rate ratio (RR) for the ischemic heart disease related SMQs ranged from 2.0-3.6 when comparing SR treatment groups to SHH. These data are summarized in Table 47. All preferred terms for the sub-SMQs overlap with the larger SMQ ischemic heart disease. As such, PTs are not list for the sub-SMQs.

Table 47. Trial 205.452 (TIOSPIR). Adjudicated deaths by ischemic heart disease related SMQs (Death Analysis Set)

	SR 2.5 mcg		SR 5 mcg		SHH		Rate Ratio	
	n (%)	rate/ 100 pt yrs	n(%)	rate/ 100 pt yrs	n (%)	rate/ 100 pt yrs	SR 2.5mcg vs. SHH (95% CI)	SR 5mcg vs. SHH (95% CI)
Number of patients (DAS)	5730		5711		5694			
Total deaths	440		423		439			
SMQ Ischemic heart disease	12 (0.2)	0.1	14 (0.2)	0.1	4 (0.1)	0.0	2.98 (0.96, 9.24)	3.48 (1.14,10.56)
Acute coronary syndrome	0	0.0	2	0.0	0	0.0		
Acute myocardial infarction	1 (0.0)	0.0	3 (0.1)	0.0	1 (0.0)	0.0	0.99 (0.06,15.88)	2.98 0.31,28.66)
Coronary artery disease	0	0.0	1 (0.0)	0.0	1 (0.0)	0.0		0.99 (0.06,15.89)
Coronary artery insufficiency	0	0.0	2 (0.0)	0.0	0	0.0		
Ischemic cardiomyopathy	1 (0.0)	0.0	0	0.0	0	0.0		
Myocardial infarction	9 (0.2)	0.1	6 (0.1)	0.0	2 (0.0)	0.0	4.47 (0.97, 20.69)	2.98 (0.60,14.77)
Myocardial ischemia	1 (0.0)	0.0	0	0.0	0	0.0		
SMQ Ischemic heart disease sub-SMQ myocardial infarction	10 (0.2)	0.1	11 (0.2)	0.1	3 (0.1)	0.0	3.31 (0.91, 12.03)	3.64 (1.02, 13.06)
SMQ Ischemic heart disease sub-SMQ other ischemic heart disease	2 (0.0)	0.0	3(0.1)	0.0	1 (0.0)	0.0	1.99 (0.18, 21.91)	2.98 (0.31, 28.66)

Source: trial 205.452 CSR; tables 15.3.2.2:5: and 15.3.2.2:6; pp355-363 and 364-370

For the SMQs, the rate ratios are greater for the SR 5mcg to SHH comparison versus the 2.5 mcg to SHH comparison. Additionally, for the 5mcg dose, for two of the three SMQs, the 95% confidence interval excluded 1. This imbalance in these SMQs appears to be driven by the PT myocardial infarction.

Placebo-controlled vital status database

When examining the vital status database, there was also a numerical imbalance in deaths falling under the SMQ ischemic heart disease [RR 4.49 95% CI (0.96, 20.96)] when comparing SR 5mcg to placebo. This was driven almost entirely by imbalances in the preferred term myocardial infarction. The point estimate is consistent with the mortality data from trial 205.452. Data from the vital status database are summarized in Table 48. Note that there were no causes of death falling under the SMQ Ischemic heart disease sub-SMQ other ischemic heart disease.

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Table 48. Vital status database. Deaths by ischemic heart disease related SMQs

	SR 5mcg		Placebo		Rate Ratio
	n (%)	rate/100 pt yrs	n (%)	rate/100 pt yrs	SR 5mcg vs. SHH (95% CI)
Number of patients	3049		3047		
Total deaths	68		51		
SMQ Ischemic heart disease	9 (0.3)	0.35	2 (0.1)	0.08	4.49 (0.96, 20.96)
Acute coronary syndrome	1 (0.0)	0.04	0 (0.0)	0.0	
Acute myocardial infarction	1 (0.0)	0.04	0 (0.0)	0.0	
Myocardial infarction	7 (0.2)	0.27	2 (0.1)	0.08	3.48 (0.71, 16.94)
SMQ Ischemic heart disease sub-SMQ myocardial infarction	9 (0.3)	0.35	2 (0.1)	0.08	4.49 (0.96, 20.96)

Source: SCS supplement study report; tables 2.3.7 and 2.3.8; pp265-275 and 276-286

Overall, the mortality data from trial 205.452 and the vital status database, may suggest that SR 5mcg exposure increases the risk of mortality due to ischemic heart disease compared to both SHH and placebo, and that this is driven by the PT myocardial infarction.

Ischemic heart disease—adverse events
Trial 205.452 (TIOSPIR)
Serious adverse events in trial 205.452 and the clinical safety database were analyzed in a similar fashion to deaths. Results for trial 205.452 were not consistent with the death analysis, as no imbalances in SAEs were seen in ischemic heart disease related SMQs or the constituent PTs. These results are summarized in Table 49. The Applicant also performed similar analysis of all AEs, which was consistent with the SAE analysis.

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Table 49. Trial 205.452 (TIOSPIR). Serious adverse events by cardiovascular SMQs (Treated Set)

	SR 2.5 mcg		SR 5mcg		SHH		Rate Ratio	
	n (%)	rate/ 100 pt yrs	n(%)	rate/ 100 pt yrs	n (%)	rate/ 100 pt yrs	SR 2.5mcg vs. SHH (95% CI)	SR 5mcg vs. SHH (95% CI)
Number of patients (TS)	5724		5705		5687			
Patients with SAE	1937	19.7	1846	18.8	1842	18.6	1.06 (0.99, 1.13)	1.01 (0.95, 1.08
SMQ Ischemic heart disease	143 (2.5)	1.2	143 (2.5)	1.2	124 (2.2)	1.1	1.15 (0.90, 1.46)	1.15 (0.91, 1.47)
SMQ Ischemic heart disease sub-SMQ myocardial infarction (broad)	79 (1.4)	0.7	70 (1.2)	0.6	64 (1.1)	0.5	1.23 (0.88, 1.71)	1.09 (0.78,1.53)
SMQ Ischemic heart disease sub-SMQ other ischemic heart disease (broad)	68 (1.2)	0.6	81 (1.4)	0.7	73 (1.3)	0.6	0.93 (0.67, 1.29)	1.11 (0.81, 1.52)

Source: trial 205.452 CSR; tables 12.3.2.2.2:1 and 15.3.2.3:6; pp146 and 423-448

In trial 205.452, in addition to analyzing ischemic heart disease based on SMQs, MI was also evaluated as an outcome event. Note that for the MI outcome event, data was collected on all AEs and not just SAEs. As the MI outcome events were pre-defined and centrally evaluated, these results may be more accurate as compared to the investigator assigned AEs. Not surprisingly there were fewer MI outcome events compared to MI adverse events. The MI outcome event was marginally more frequent in SR groups compared to SHH. These results are summarized in Table 50.

Table 50. Trial 205.452 (TIOSPIR). Analysis of time to first outcome event of MI (Treated Set)

	SR 2.5 mcg	SR 5 mcg	SHH
Number of patients (TS)	5724	5705	5687
Patients with MI [n(%)]	70 (1.2)	73 (1.3)	52 (0.9)
Comparison versus SHH			
Hazard ratio	1.34	1.41	
95% confidence interval	(0.96, 1.92)	(0.98, 2.00)	
p-value	0.1105	0.0612	

Source: trial 205.452 CSR; table 12.3.3.2.2:1; pg152

These data do not demonstrate a clear imbalance when comparing either SR dose to SHH, however, the point estimate trends in the same direction as the mortality data.

Placebo controlled clinical safety database
The analysis of serious adverse events in the clinical safety database using ischemic heart disease related SMQs was consistent with trial 205.452 results. No imbalances were seen when comparing SR 5mcg to placebo for SAEs falling under ischemic heart

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disease related SMQs. The same was true for the constituent PTs. Results from the analysis of all AEs was also generally similar, though, for the SMQ ischemic heart disease sub-SMQ other ischemic heart disease, a numerical imbalance was noted [RR SR 5mcg v. placebo 1.61 95% CI (1.01, 2.49)]. This appeared to be driven by the PT angina pectoris and coronary artery disease.

The data regarding ischemic heart disease related events is mixed. While the mortality data from both trial 205.452 and the vital status database suggest that SR 5 mcg exposure increases the risk of death related to ischemic heart disease, the SAE/AE data do not; while the MI outcome event data is somewhat ambiguous. Were there a large safety signal, one may expect that the findings would be consistent between deaths, SAEs, AEs, and MI outcome event data. The lack of concordance suggests that the mortality finding may be a chance occurrence potentially related to a relatively small number of events and multiple comparisons. However, because all causes of death from trial 205.452 were adjudicated by an independent committee rather than assigned by various investigators, as with the SAE and AE data, the mortality data from trial 205.452 may demonstrate less variability compared the S/AE data. Additionally, while the MI outcome event data from trial 205.452 do not clearly demonstrate an imbalance, the data trends in the same direction as the mortality data, and the MI outcome event was based on a pre-specified definition in the protocol making it less susceptible to variations in investigator reporting. Further, while not all the causes of death in the vital status database were adjudicated (only in trial 205.372), the results trended in the same direction as trial 205.452 (i.e., an imbalance in ischemic heart disease related deaths not favoring SR 5mcg). As such, it is difficult to dismiss the imbalance in ischemic heart disease related deaths as a chance occurrence.

However, it should be noted that in trial 205.452 for all-cause mortality SR 5mcg was non-inferior to SHH. Thus, if the ischemic heart disease mortality imbalance is real, then the excess ischemic heart disease related deaths would have to have been offset by other causes favoring SR 5mcg.

Stroke—Fatal events
Trial 205.452 (TIOSPIR)
To evaluate for stroke, the Applicant analyzed deaths and SAEs using several SMQs and PVEs. This analysis included the SMQs hemorrhagic cerebrovascular conditions, ischemic cerebrovascular conditions and the PVE stroke. These results did not reveal imbalances when comparing SR doses to SHH based on SMQ/PVE or their constituent PTs. Mortality data from trial 205.452 (TIOSPIR) is summarized in Table 51.

Reference ID: 3618244

Table 51. Trial 205.452 (TIOSPIR). Adjudicated deaths by stroke related SMQ/PVE (Death Analysis Set)

	SR 2.5 mcg		SR 5 mcg		SHH		Rate Ratio	
	n (%)	rate/ 100 pt yrs	n (%)	rate/ 100 pt yrs	n (%)	rate/ 100 pt yrs	SR 2.5mcg vs. SHH (95% CI)	SR 5mcg vs. SHH (95% CI)
Number of patients (DAS)	5730		5711		5694			
Total deaths	440		423		439			
SMQ hemorrhagic cerebrovascular conditions	11 (0.2)	0.1	14 (0.2)	0.1	12 (0.2)	0.1	0.91 (0.4, 2.06)	1.16 (0.54, 2.51)
SMQ ischemic cerebrovascular conditions	6 (0.1)	0.0	10 (0.2)	0.1	9 (0.2)	0.1	0.66 (0.24, 1.86)	1.1 (0.45, 2.72)
Stroke PVE	10 (0.2)	0.1	14 (0.2)	0.1	11 (0.2)	0.1	0.9 (0.38, 2.13)	1.26 (0.57, 2.79)

Source: trial 205.452; table 15.3.2.2:6; pp364-370

Placebo controlled vital status database
As in trial 205.452 (TIOSPIR), fatal stroke events in the vital status database were analyzed using SMQs and PVEs. These results did not imbalances when comparing SR 5mcg to placebo groups.

Stroke—Adverse events
Trial 205.452 (TIOSPIR)
Serious adverse events were analyzed in a similar fashion to deaths. Results for trial 205.452 were consistent with the death analysis, as no imbalances in SAEs were seen in the stroke related SMQs/PVE or their constituent PTs.

In addition to using SMQ/PVE, in trial 205.452 the Applicant also used the pre-defined outcome events of stroke and TIA to assess for stroke risk. As these events were pre-defined and centrally monitored, these results may more accurately reflect the potential stroke risk for SR versus SHH as compared to using investigator assigned terms. Hazard ratios for these outcome events when comparing SR 5mcg to SHH were near 1. These results are summarized in Table 52.

Reference ID: 3618244

Table 52. Trial 205.452 (TIOSPIR). Time to first outcome event of stroke (fatal and non-fatal)(Treated Set)

	SR 2.5 mcg	SR 5mcg	SHH
Number of patients (TS)	5724	5705	5687
Patients with stroke [n(%)]	56 (1)	52 (0.9)	57 (1)
Ischemic	30	39	36
Hemorrhagic	15	5	11
Uncertain	11	8	13
Comparison versus SHH			
Hazard ratio	0.98	0.91	
95% confidence interval	(0.68, 1.41)	(0.63, 1.33)	
p-value	0.90	0.63	
Patients with TIA [n(%)]	25 (0.4)	30 (0.5)	20 (0.4)
Comparison versus SHH			
Hazard ratio	1.24	1.50	
95% confidence interval	(0.69, 2.24)	(0.85, 2.64)	
p-value	0.47	0.16	

Source: Trial 205.452 CSR; table 12.3.3.2.1:1 and 12.3.3.2.3:1; pp 151 and 152

Compared to SHH, SR 5mcg exposure does not appear to increase the risk of the outcome events of stroke or TIA. These results are consistent with the analysis of death and adverse events.

Placebo controlled clinical safety database.
Serious adverse events were analyzed in a similar fashion to deaths. As with the analysis of deaths, analysis stroke relates SAEs did not reveal imbalances when comparing SR 5mg to placebo groups. The same was true when examining all adverse events. This is not necessarily surprising as no stroke signal specific to the SR product was identified in the initial NDA review cycle.

Overall the analyses of stroke in trial 205.452 (TIOSPIR) and both placebo controlled databases in consistent. The observed consistency across multiple measures of stroke suggests that SR 5mcg exposure does not increase stroke risk compared to either placebo or SHH.

MACE—Fatal events
Trial 205.452 (TIOSPIR)
Given the cardiovascular safety concerns for anticholinergic agents, the Applicant also performed a MACE analysis of deaths. Fatal MACE events were fairly balanced between treatment groups based on percentage and rate. For the individual components of MACE, the largest difference between groups was seen for SMQ ischemic heart disease sub-SMQ MI (see previous discussion regarding ischemic heart disease). A *post-hoc* analysis was also performed including the PT death in the MACE definition. The results were consistent with the pre-specified analysis. These data are summarized in Table 53.

Reference ID: 3618244

Table 53. Trial 205.452 (TIOSPIR). Fatal (adjudicated) MACE including vital status follow-up (Death Analysis Set)

	SR 2.5 mcg		SR 5 mcg		SHH		Rate ratio	
	n (%)	rate/ 100 pt yrs	n (%)	rate/ 100 pt yrs	n (%)	rate/ 100 pt yrs	SR 2.5mcg vs. SHH (95% CI)	SR 5mcg vs. SHH (95% CI)
Patients	5730		5711		5694			
Fatal MACE	119 (2.1)	0.91	113 (2.0)	0.86	101 (1.8)	0.77	1.17 (0.9, 1.53)	1.11 (0.85, 1.45)
Cardiac Death PT (fatal)	0	0	2 (0.0)	0.02	0	0		
Cardiac Disorders SOC (fatal)	22 (0.4)	0.17	27 (0.5)	0.21	17 (0.3)	0.13	1.29 (0.68, 2.42)	1.58 (0.86, 2.89)
SMQ ischemic heart disease sub –SMQ MI (broad) (fatal)	10 (0.2)	0.08	11 (0.2)	0.08	3 (0.1)	0.02	3.31 (0.91, 12.03)	3.64 (1.02, 13.06)
Stroke PVE (fatal)	10 (0.2)	0.08	14 (0.2)	0.11	11 (0.2)	0.08	0.9 (0.38, 2.13)	1.26 (0.57, 2.79)
Sudden cardiac death PT	37 (0.6)	0.28	29 (0.5)	0.22	22 (0.4)	0.17	1.67 (0.99, 2.83)	1.31 (0.75, 2.28)
Sudden death PT	45 (0.8)	0.34	38 (0.7)	0.29	46 (0.8)	0.35	0.97 (0.64, 1.47)	0.82 (0.53, 1.26)
Vascular disorder SOC (fatal)	5 (0.1)	0.04	3 (0.1)	0.02	5 (0.1)	0.04	0.99 (0.29, 3.43)	0.6 (0.14, 2.49)
Fatal MACE including PT death	154 (2.7)	1.17	140 (2.5)	1.07	138 (2.4)	1.06	1.11 (0.88, 1.40)	1.01 (0.80, 1.28)

Source: SCS-supplement; table 2.9.3; pg899

Placebo controlled vital status database

A similar analysis of fatal MACE was performed in the vital status database. These results showed that fatal MACE occurred more commonly in SR 5mcg patients compared to placebo. The rate ratio was 2 [95% CI (1.03, 3.88)] when comparing SR5 to placebo. As with the fatal MACE data from trial 205.452, the MACE component with the largest imbalance was the SMQ ischemic heart disease sub-SMQ MI, which drove the imbalance. This imbalance has already been discussed (see discussion of SMQ ischemic heart disease). These data are summarized in Table 54.

Table 54. Vital status database. Fatal MACE

	SR 5mcg		Placebo		Rate ratio
	n(%)	rate/100 pt yrs	n(%)	rate/100 pt yrs	SR 5mcg vs. SHH (95% CI)
Patients	3049		3047		
Fatal MACE	26 (0.9)	1.01	13 (0.4)	0.51	2 (1.03, 3.89)
Cardiac Death PT (fatal)	0		0		
Cardiac Disorders SOC	16 (0.5)	0.62	7 (0.2)	0.27	2.28 (0.94, 5.55)
SMQ ischemic heart disease sub –SMQ MI (broad) (fatal)	9 (0.3)	0.35	2 (0.1)	0.08	4.49 (0.96, 20.96)
Stroke PVE (fatal)	1 (0.0)	0.04	1 (0.0)	0.04	0.98 (0.06, 15.09)
Sudden cardiac death PT	0		0		
Sudden death PT	9 (0.3)	0.35	5 (0.2)	0.19	1.82 (0.61, 5.42)
Vascular disorder SOC (fatal)	0		0		
Fatal MACE including PT death	36 (1.2)	1.4	22 (0.7)	0.86	1.64, 0.96, 2.78

Source: SCS-supplement; table 2.3.9 and 2.3.10; pg287 and 289

MACE—adverse events
Trial 205.452 (TIOSPIR)
Analysis of all MACE events was also performed in a manner similar to fatal MACE. As with the analysis of fatal MACE, all MACE were fairly well balanced between SR 5mcg and SHH treatment groups.

In addition to the analysis using adverse event data, in trial 205.452 (TIOSPIR) the Applicant also analyzed all MACE using the pre-defined outcome events of stroke, TIA, and MI outcome events. These results are summarized in Table 55. Based on percentages, rate, and rate ratios, MACE appears similar between groups.

Table 55. Trial 205.452 (TIOSPIR). On treatment MACE (fatal and non-fatal) by components using outcome events (Treated Set)

	SR 2.5 mcg		SR 5mcg		SHH		Rate Ratio	
	n(%)	rate/ 100 pt yrs	n(%)	rate/ 100 pt yrs	N(%)	rate/ 100 pt yrs	SR 2.5mcg vs. SHH (95% CI)	SR 5mcg vs. SHH (95% CI)
# of patients	5724		5705		5687			
MACE	224 (3.9)	1.91	222 (3.9)	1.91	202 (3.6)	1.73	1.1 (0.91, 1.34)	1.1 (0.91, 1.33)
Stroke*	56 (1.0)	0.47	52 (0.9)	0.44	57 (1.0)	0.49	0.98 (0.68, 1.41)	0.91 (0.63, 1.33)
MI*	70 (1.2)	0.59	73 (1.3)	0.62	52 (0.9)	0.44	1.34 (0.94, 1.92)	1.40 (0.98, 2.00)
TIA*	25 (0.4)	0.21	30 (0.5)	0.26	20 (0.4)	0.17	1.24 (0.69, 2.24)	1.50 (0.85, 2.64)
CV death**	102 (1.8)	0.86	97 (1.7)	0.82	95 (1.7)	0.81	1.07 (0.81, 1.41)	1.02 (0.77, 1.35)

*outcome event
**As determined by adjudication
Source: response to IR dated 5/9/14; table 3.3.1; pg68

Placebo controlled clinical safety database

Analysis of all MACE events (non-fatal and fatal) was also performed in the clinical safety database. In contrast to fatal MACE events, events were fairly balanced whether examining the composite measure or its individual components.

Based on the overall and fatal MACE data from trial 205.452, SR 5mcg use does not appear to increase risk of MACE compared to SHH. This is not entirely consistent with MACE data from the vital status database, which suggest that SR 5mcg may increase risk of fatal MACE compared to placebo. Given the results of UPLIFT, where no cardiovascular safety signals were identified when comparing SHH to placebo, one would expect that results from trial 205.452 and the placebo controlled databases would be consistent with each other. The reason for this discrepancy is not clear.

Arrhythmia, heart failure, and cardiac arrest/death
Trial 205.452 (TIOSPIR)
Deaths and SAEs from trial 205.452 were also analyzed using SMQs and PVEs to assess for imbalances in cardiac arrhythmia, heart failure, and cardiac arrest/death. While there were some numerical imbalances, they were generally small. Mortality findings are summarized in Table 56. Note that the tables only include SMQs/PVEs in which deaths were reported. Multiple other SMQs/PVEs were evaluated. These included SMQ cardiac arrhythmia sub-SMQs tachyarrhythmias and ventricular tachyarrhythmias, as well as PVEs for cardiac arrest, atrial fibrillation/flutter, supraventricular tachycardia, and ventricular tachycardia/fibrillation. A similar analysis was performed on SAEs with similar results.

Table 56. Trial 205.452 (TIOSPIR). Adjudicated deaths by SMQ/PVE (Death Analysis Set)

	SR 2.5mcg		SR 5mcg		SHH		Rate Ratio	
	n (%)	rate/ 100 pt yrs	n (%)	rate/ 100 pt yrs	n (%)	rate/ 100 pt yrs	SR 2.5mcg vs. SHH (95% CI)	SR 5mcg vs. SHH (95% CI)
Number of patients (DAS)	5730		5711		5694			
Total deaths	440		423		439			
Cardiac arrest/sudden death PVE	84 (1.5)	0.6	70 (1.2)	0.5	69 (1.2)	0.5	1.21 (0.88, 1.66)	1.01 (0.72, 1.41)
Death/sudden death PVE	80 (1.4)	0.6	65 (1.1)	0.5	83 (1.5)	0.6	0.96 (0.7, 1.3)	0.78 (0.56, 1.08)
Cardiac failure-LV PVE	0	0.0	0	0.0	1 (0.02)	0.0		
Cardiac failure-RV PVE	1 (0.02)	0.0	1 (0.02)	0.0	1 (0.02)	0.0	0.99 (0.6, 15.88)	0.99 (0.6, 15.89)
SMQ cardiac failure	7 (0.12)	0.1	11 (0.2)	0.1	10 (0.2)	0.1	0.7 (0.26, 1.83)	1.09 (0.46, 2.57)
SMQ cardiac arrhythmias	84 (1.5)	0.6	70 (1.2)	0.5	69 (1.2)	0.5	1.21 (0.88, 1.66)	1.01 (0.72, 1.41)

Source: trial 205.452 CSR; table 15.3.2.2:6; pp364-370

Reference ID: 3618244

Placebo controlled databases
Similar analyses of deaths in the vital status database and SAEs in the clinical safety database were also performed. While there were some numerical differences when comparing SR 5mcg to placebo, these were generally small. These analyses did not reveal safety concerns.

Based on the analysis of trial 205.452 and the placebo controlled safety databases, no clear safety signal with regard to cardiac arrhythmia, cardiac failure, or cardiac arrest/death has been demonstrated when comparing SR 5mcg to SHH or placebo.

Adverse events following initial cardiac event
Safety analysis was also performed on patients in trial 205.452 who experienced an on treatment cardiac event and remained in the trial. The on treatment events were divided into cardiac arrhythmia, MI, and cardiac failure and were defined using the following SMQs: SMQ cardiac arrhythmias sub-SMQ cardiac arrhythmia terms, SMQ ischemic heart disease sub-SMQ MI, and SMQ cardiac failure, respectively. A total of 239 SR 5mcg patients and 245 SHH patients experienced an on treatment cardiac event. Occurrence of an on treatment cardiac event did not appear to affect the percentage of patients who experience AEs, SAEs, cardiac SAEs, death, and cardiac deaths when comparing SR 5mcg groups to placebo. These results are summarized in Table 57.

Table 57. Trial 205.452 (TIOSPIR). Adverse events following an initial on-treatment cardiac event.

	Cardiac Arrhythmias		Myocardial infarction		Cardiac failure	
	SR 5mcg N=92 n(%)	SHH N=84 n(%)	SR 5mcg N=72 n(%)	SHH N=68 n(%)	SR 5mcg N=75 n(%)	SHH N=93 n(%)
All adverse events	56 (65.5)	51 (67.1)	30 (52.6)	33 (60)	33 (66)	47 (69.1)
Cardiac AE	8 (9.5)	13 (17.1)	8 (14.0)	10 (18.2)	14 (28.0)	21 (30.9)
SAE	32 (38.1)	37 (48.7)	24 (42.1)	24 (43.6)	31 (62.0)	35 (51.5)
Cardiac SAE	7 (8.3)	12 (15.8)	8 (14.0)	9 (16.4)	13 (26.0)	19 (27.9)
Death	9 (10.7)	10 (13.2)	6 (10.5)	5 (9.1)	11 (22.0)	14 (20.6)
Death cardiac SOC	0	1 (1.3)	3 (5.3)	1 (1.8)	3 (6.0)	4 (5.9)
MACE (all)	6 (7.1)	1 (1.3)	3 (5.3)	3 (5.5)	8 (11.8)	23 (12.4)
Fatal MACE	2 (2.4)	1 (1.3)	2 (3.5)	2 (3.6)	4 (8.0)	13 (7.0)

Source: SCS; table 5.1.4:2; pg 149

While these results are suggestive that an acute cardiac does not increase the likelihood of an adverse event when comparing SR 5mcg to SHH, the number of patients who experienced an initial cardiac event was small, and subsequent events were also small in number. As such, it is difficult to make any definitive conclusions based on these results.

Reference ID: 3618244

Respiratory safety

Deaths most commonly occurred in the RTM SOC. Because of this, the patient population, and disease; respiratory events were further analyzed based on variety of respiratory related PVEs. For fatal events, this analysis did not reveal any imbalances in favor of SHH. Notably, for the PVE COPD exacerbation, pneumonia, COPD exacerbation with pneumonia, and respiratory failure; deaths were balanced when comparing percentages and rates between SR and SHH groups. No imbalances favoring SHH were apparent when looking at the individual PTs that constituted the PVEs. Results are summarized in Table 58. Note that this table does not include all PVE analyzed, only those for which there were recorded events. Note that for the COPD exacerbation related PVEs, rate ratios for SR 5mcg compared to SHH had point estimates of approximately 1. This is what one would expect given efficacy data from trial 205.452. A similar analysis using collapsed terms was also performed on SAEs, with similar results.

Table 58. Trial 205.452 (TIOSPIR). Deaths (adjudicated) by respiratory PVE (Death Analysis Set)

	SR 2.5mcg		SR 5mcg		SHH		Rate ratio	
	n (%)	rate/ 100 pt yrs	n (%)	rate/ 100 pt yrs	N (%)	rate/ 100 pt yrs	SR 2.5 mcg vs. SHH (95% CI)	SR 5mcg vs. SHH (95% CI)
Patients	5730		5711		5694			
COPD exacerbation (broad) with pneumonia PVE	136 (2.4)	1.0	140 (2.5)	1.1	141 (2.5)	1.1	0.96 (0.76, 1.21)	0.99 (0.78, 1.25)
COPD exacerbation (broad) PVE	111 (1.9)	0.8	116 (2.0)	0.9	117 (2.1)	0.9	0.94 (0.73, 1.22)	0.99 (0.76, 1.27)
Pneumonia PVE	25 (0.4)	0.2	24 (0.4)	0.2	24 (0.4)	0.2	1.03 (0.59, 1.81)	0.99 (0.56, 1.75)
Respiratory Failure (broad (PVE)	3 (0.1)	0.0	2 (0.0)	0.0	9 (0.2)	0.1	0.33 (0.09, 1.22)	0.22 (0.05, 1.02)
Respiratory disorder (lower)	140 (2.4)	1.1	144 (2.5)	1.1	154 (2.7)	1.2	0.9 (0.72, 1.14)	0.93 (0.74, 1.17)
Respiratory disorder (upper)	0	0.0	1 (0.0)	0.0	1 (0.0)	0.0	0.33 (0.07, 1.64)	0.33 (0.07, 1.64)

Source: trial 205.452 CSR; table 15.3.2.2:5 and 15.3.2.2:6;pp 355-363 and 364-370

Results from a similar analysis of mortality data from the vital status database and the SAE data from the clinical safety database also did not demonstrate imbalances favoring placebo for respiratory related adverse events. On the contrary, for deaths due to COPD exacerbation related PVEs had rate ratios with point estimates ranging from 0.6-0.87 when comparing SR 5mcg to placebo. Results from the SAE data were similar. Based on these analyses, no respiratory related safety signal was identified.

Neoplasm

Reference ID: 3618244

Mortality due to events in the SOC neoplasm was similar when comparing SR 5mcg to SHH treated patients in trial 205.452, however, in the vital status database, there was a numerical imbalance when comparing SR 5mcg to placebo. The rate ratio was 3.32 [95% CI (0.92, 12.02)] and number of events was low (SR 5mcg n=10, placebo n=3). The numerical imbalance was driven by the PT lung neoplasm malignant (SR 5mcg n=4, placebo n=0). When grouping together PTs related to lung neoplasms only (lung neoplasm PVE), the difference becomes marginally larger (SR 5mcg n=6, placebo n=1) with a rate ratio of 6.03 [95% CI (0.72, 50.29)].

When analyzing SAEs in the neoplasm SOC, small differences were observed when comparing SR 5mcg to SHH in trial 205.452 [SR 5mcg n=274 (4.8%), SHH n=250 (4.4%)] and when comparing SR 5mcg to placebo in the clinical safety database [SR 5mcg n=66 (2%), placebo n=44 (1.3%)]. When grouping SAEs using the lung neoplasm PVE, the differences were similar for both trial 205.452 [SR 5mcg n=113 (2%), SHH n=94 (1.7%)] and the clinical safety database [SR 5mcg n=26 (0.8%), placebo n=16 (0.5%)]. These small differences in the SOC neoplasms are of unclear significance. Given the latency period of lung cancers and length of the placebo controlled trials (≤48-weeks), it is unlikely that SR 5mcg was directly causative. Rather, given the small numbers, a patient population prone to lung-related cancers, and the wide 95% confidence intervals for the rate ratios; these numerical differences are likely due to chance.

Anticholinergic effects

The label for SHH currently states that its use may worsen the signs and symptoms associated with narrow-angle glaucoma and urinary retention. As such, AE data for SR was scrutinized for imbalances in these types of events. Additionally, as concerns regarding intestinal obstruction were raised during the review of SHH (see Dr. Theresa Michele's review dated 11/30/09 for NDA 21,395), AEs related to constipation and intestinal obstruction was also evaluated. Results from trial 205.452 did not reveal any imbalances for these events with regard to mortality when comparing SR 5mcg to SHH. The analysis of the causes of death in the vital status database also did not reveal imbalances favoring placebo. This is not surprising as these types of events are usually not fatal. With regard to SAEs, a small numerical difference was noted for the PVE prostatic disorder (SR 5mcg n=18, SHH n=7) with a rate ratio (SR 5mcg:SHH) of 2.57 with a 95% confidence interval of (1.07, 6.16). This was driven by the constituent preferred term benign prostatic hyperplasia. However, in the analysis of SAEs from the clinical safety database, the occurrence of events in the prostatic disorder PVE when comparing SR 5mcg to placebo was similar. This implies that the difference observed in trial 205.452 between SR 5mcg and SHH was likely related to chance. Otherwise SAEs potentially related to anticholinergic effects were generally similar when comparing SR 5mcg to both SHH (in trial 205.452) and placebo (in the clinical safety database). For all AEs (analysis performed in the clinical safety database) an imbalance was observed for dry mouth (PT and PVE) when comparing SR 5 mcg to placebo [rate ratio for

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PVE=2.49, 95% CI (1.81, 3.43)]. Otherwise, events were generally balanced between SR 5mcg and placebo groups.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Trial 205.452 did not collect data on all adverse events. As such, common adverse data is taken from the clinical safety database. The most common adverse event by far was COPD, followed by nasopharyngitis and dyspnea. The percentage of patients with the AE COPD was numerically lower in the SR 5mcg compared to placebo, which is consistent with the efficacy data from the three 48-week exacerbation trials. Based on rate ratios, the common AEs with the largest difference when comparing SR 5mcg to placebo was dry mouth. This is likely related to the known pharmacologic effect of tiotropium. Common adverse events are summarized in Table 59 by preferred term.

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Table 59. Clinical safety database. Adverse events occurring in ≥2% of patients (EOT+30days)

	SR 5mcg		Placebo		Rate ratio
	n(%)	rate/100 pt yrs	n(%)	rate/100 pt yrs	SR 5mcg vs. placebo (95% CI)
Number of patients	3282		3283		
Patients with AE	1768 (53.9)	105.33	1863 (56.7)	120.72	
COPD	933 (28.4)	41.94	1133 (34.5)	56.85	0.73 (0.67, 0.80)
Nasopharyngitis	293 (8.9)	11.50	270 (8.2)	11.04	1.04 (0.88, 1.22)
Dyspnea	190 (5.8)	7.28	232 (7.1)	9.40	0.77 (0.64, 0.94)
Cough	175 (5.3)	6.71	154 (4.7)	6.17	1.09 (0.88, 1.36)
Upper respiratory tract infection	152 (4.6)	5.79	184 (5.6)	7.41	0.78 (0.63, 0.97)
Dry mouth	117 (3.6)	4.46	43 (1.3)	1.69	2.63 (1.85, 3.73)
Bronchitis	113 (3.4)	4.27	136 (4.1)	5.42	0.79 (0.61, 1.01)
Headache	109 (3.3)	4.12	96 (2.9)	3.80	1.08 (0.82, 1.42)
Back pain	87 (2.7)	3.27	77 (2.3)	3.03	1.06 (0.78, 1.44)
Pneumonia	86 (2.6)	3.22	80 (2.4)	3.14	1.04 (0.76, 1.41)
Influenza	82 (2.5)	3.08	88 (2.7)	3.48	0.87 (0.65, 1.18)
Hypertension	78 (2.4)	2.92	67 (2.0)	2.64	1.10 (0.79, 1.52)
Sinusitis	75 (2.3)	2.81	67 (2.0)	2.63	1.06 (0.77, 1.48)
Oropharyngeal pain	75 (2.3)	2.82	58 (1.8)	2.28	1.22 (0.86, 1.72)
Diarrhea	69 (2.1)	2.58	79 (2.4)	3.11	0.83 (0.60, 1.14)
Dizziness	66 (2.0)	2.47	49 (1.5)	1.92	1.29 (0.89, 1.86)

Source: SCS supplement body report; table 2.1.3 and 2.1.4; pp 46 and 48

Pooled adverse event data from the 48-week exacerbation trials and from the 12-week bronchodilation trials demonstrated similar results.

7.4.2 Laboratory Findings

Lab data from the trials submitted with the initial NDA showed no meaningful difference between SR treated patients and those treated with placebo. In trials 205.372 and 205.452 submitted with this NDA, lab testing was only performed at screening.

7.4.3 Vital Signs

Vital sign data from the trials submitted with the initial NDA have been reviewed and no clinically significant differences were noted at baseline or during the treatment period between SR and placebo treatment groups. For this submission, in trial 205.452, vital signs were assessed only at visit 1 prior to randomization, while for 205.372, vital signs were assessed at clinic visits. For these new trials, no clinically significant differences were noted at baseline or during the treatment period between treatment groups.

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7.4.4 Electrocardiograms (ECGs)

ECG data from the efficacy and safety trials submitted with the initial NDA revealed no clinically significant changes in any of the ECG parameters. Similarly, no clinically significant changes were observed in Holter monitoring data. Evaluation of shift tables for outliers also showed balance between the tiotropium and placebo groups. ECG data was not collected during treatment in trial 205.452. ECG data from trial 205.372 is reviewed in section 5.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Trial 205.452 (TIOSPIR) included SR 2.5mcg and SR 5mcg groups. For overall mortality, there was no clear dose response. The same was true for adjudicated causes of death based on SOC. SAEs also demonstrated no clear dose response based on SOC.

7.5.2 Time Dependency for Adverse Events

The Applicant did not perform a specific analysis of safety data for time dependency and adverse events. However, the safety profile from the 12-week bronchodilator trials (205.251 and 205.252) and 48 week exacerbation trials (205.254, 205.255, and 205.372) were generally similar.

7.5.3 Drug-Demographic Interactions

For trial 205.452 (TIOSPIR), the Applicant performed multiple subgroup analyses based on demographics characteristics (age, gender, race, region, and body mass index) and found no meaningful differences in mortality. Similar analyses were performed for the vital status database with similar results. Results from trial 205.452 and clinical safety database are summarized in Figure 8 and Figure 9 . Note that this figure also includes subgroup analyses based on baseline cardiac disorders and cardiac arrhythmias. These will be discussed in the subsequent section.

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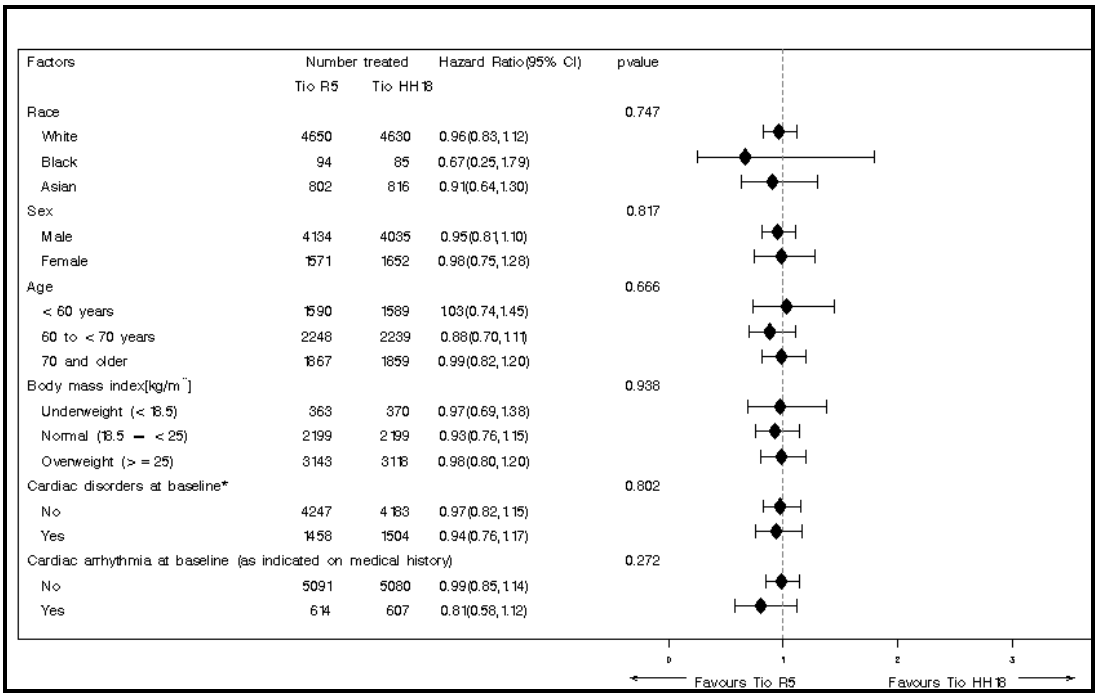
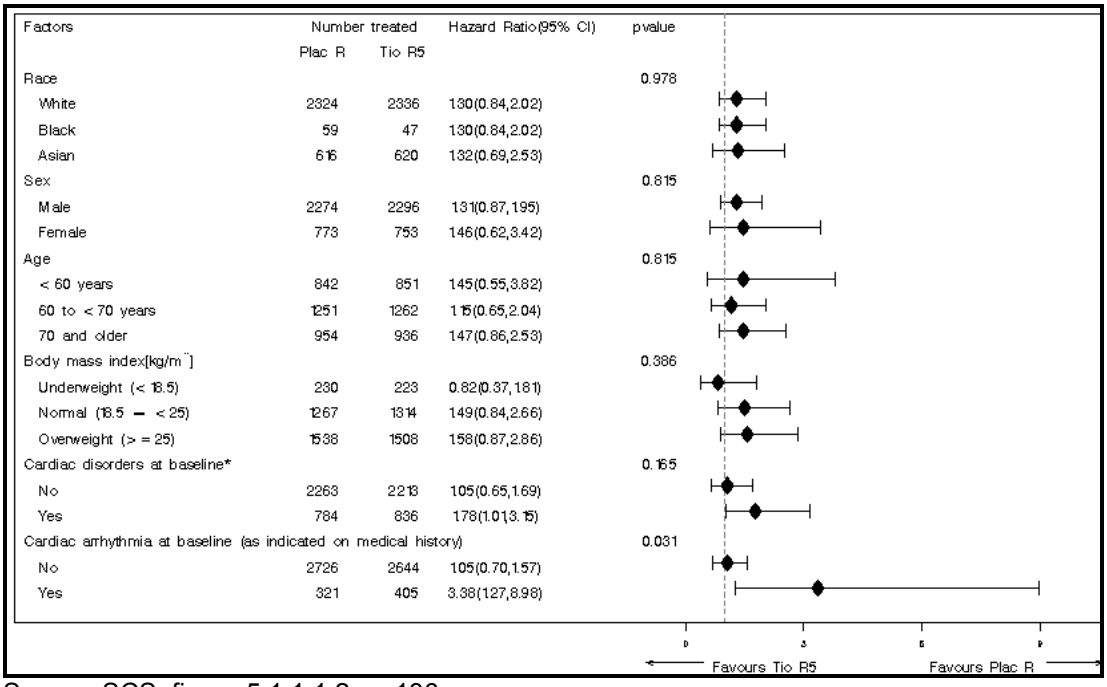
Figure 8. Trial 205.452 (TIOSPIR). Subgroup analyses



Source: SCS; figure 5.1.1.1:1; pg135

Figure 9. Vital status database. Subgroup analyses



Source: SCS; figure 5.1.1.1:2; pg136

Subgroup analyses were also performed based on region (USA/outside USA) and smoking history (current/ex-smoker). No significant effects on mortality were seen.

7.5.4 Drug-Disease Interactions

Subgroup analyses in trial 205.452 based on baseline cardiac disease and cardiac arrhythmia demonstrated that a larger percentage of patients with baseline cardiac disease or cardiac arrhythmia across treatment groups died compared to those without. However, when comparing SR 5mcg to SHH, the percentages were similar for each subgroup, with hazard ratios (SR 5mcg: SHH) near 1. However, when similar analyses were performed in the vital database, a nominally statistically significant difference was observed when comparing SR 5mcg to SHH (Figure 8 and Figure 9). For patients with baseline cardiac disease or cardiac arrhythmia, mortality was higher in SR 5mcg patients compared to placebo patients [HR=1.78 (95% CI (1.01, 3.15)) and HR=3.38 (95% CI (1.27, 8.98)), respectively]. This was not the case in the sub-groups without cardiac arrhythmia or cardiac disease. As this is a sub-group analysis with small total numbers, these findings must be interpreted with caution.

Subgroup analysis based on baseline GOLD criteria and history of exacerbations was also performed in both trial 205.452 and the vital status database. No significant differences were seen in terms of mortality.

Subgroup analysis based on baseline renal function (mild, moderate, severe) was also performed in the clinical safety database. This subgroup analysis of the clinical safety database did not reveal any significant differences in terms of all AEs, SAEs, or death for patients with normal, mild, or moderate renal impairment. However, for patients with severe impairment, a higher percentage of patients in the SR 5mcg group experienced fatal AEs [SR 5mcg=5 (22.5%), placebo=1 (5.9%)]. While this was observed, there were very few patients with severely impaired renal function [SR 5mcg n=17 (0.5%) and placebo n=22 (0.7%)]. As such, this observation must be interpreted with caution.

7.5.5 Drug-Drug Interactions

No formal drug interaction studies were included in this submission. However, in trial 205.452 and the vital status database, subgroup analysis was performed based on baseline use (yes/no) of inhaled corticosteroids and LABA. No effect was seen in terms of mortality.

7.6 Additional Safety Evaluations

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7.6.1 Human Carcinogenicity

No specific trials were conducted to assess carcinogenicity in humans

7.6.2 Human Reproduction and Pregnancy Data

No specific trials were conducted in pregnant women. There were no pregnancies reported in either trials 205.452 of 205.372.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Potential for withdrawal and rebound were not formally assessed. Based on the low systemic bioavailability, withdrawal and rebound are not expected. Overdose experience was reviewed by Dr. Theresa Michele in her reviewed dated 7/31/08. The Applicant has also included a case report from the literature where a 71-year old female accidentally took 90mcg of SHH and developed urinary retention and dry mouth.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

SR 5mcg is not marketed in the U.S. However, it has been marketed in Europe since 2007. Additionally, SHH was approved in Europe in 2001 and in the U.S. in 2004. Since marketing authorization until March 2013, SR 5mcg and SHH have accumulated approximately 1.6 million and 31 million patient years of exposure, respectively. Adverse event reporting rates (per 1 million patient-years) were generally similar or lower for SR 5mcg compared to SHH based on SOC. Findings were similar when analyzing reporting rates for cardiovascular related SMQs. Analysis of the postmarketing safety data did not reveal any new safety concerns.

Reference ID: 3618244

9 Appendices

9.1 Literature Review/References

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. Lee TA, Pickard S, Au DH *et al*. Risk of Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease. *Annals of Internal Medicine* 2008;149:380-90.
3. Tashkin DP, Celli B, Senn S. *et al*. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *NEJM* 2008; 359: 1543-54
4. Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. *NEJM.* 2010*;363:1097-99.*

9.2 Labeling Recommendations

Labeling negotiations are currently ongoing. Identified issues with the label include the presentation of safety data in section 6 and efficacy information in section 14. In the proposed label, the Applicant presents safety data from the pooled clinical safety database. While this was an acceptable approach to review safety, it is not optimal for the purposes of labeling. Because the majority of the safety data in the clinical safety database is derived from three 48-week exacerbation trials of similar design, because these trials represent the longest exposure in placebo controlled trials, and because safety results from these trials are representative of the clinical safety database; for the purposes of labeling, presentation of these data would more concisely and clearly show the safety profile of this product. An additional issue with section 6 is that the Applicant did not include the TIOSPIR in this section. As TIOSPIR was a mortality/safety trial, results from it should be included in section 6. Section 6 of the label will be amended to present safety data from the 48-week exacerbation trials and to include TIOSPIR mortality/safety data. Additionally, the Applicant has modeled section 14 of the Spiriva Respimat label on the Spiriva HandiHaler label. Given current labeling practices, this is an issue, as the Spiriva Handihaler label includes data that are no longer routinely included in LAMA labels. This includes figures depicting peak FEV1 response. Additionally, the Applicant has included mortality data from TIOSPIR in this section.

9.3 Advisory Committee Meeting

A Pulmonary-Allergy Advisory Committee was held on August 14, 2014 to discuss the safety and efficacy of Spiriva Respimat. The questions to the committee, summary of discussion, and voting results are as follows:

1. **Discussion Question:** Discuss the efficacy data for tiotropium bromide inhalation spray 5 mcg to support the proposed indication of the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) and for reducing COPD exacerbations.

Committee Discussion: *There was consensus among the panel members that the data demonstrated that Spiriva Respimat was effective in terms of bronchodilation and exacerbation reduction. However, some committee members noted that Spiriva Respimat did not demonstrate a unique efficacy benefit over the currently available Spiriva Handihaler. One member commented that Spiriva Resimat may be easier to use than Spiriva HandiHaler, especially in more elderly patients.*

2. **Voting Question**: 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?

    a. If not, what further data should be obtained?

YES= 14 NO=0 ABSTAIN=0

3. **Discussion Question:** Discuss the safety data for tiotropium bromide inhalation spray 5 mcg. Consider the following issues in the discussion: mortality, stroke, and myocardial infarction.

Committee Discussion: *The consensus among the committee members that in terms of all-cause mortality, Spiriva Respimat 5mcg was non-inferior to Spiriva HandiHaler. There was some concern regarding the numerical increase in fatal MI subcomponent of cardiovascular deaths, in Spiriva Respimat compared to Spiriva HandiHaler in TIOSPIR and compared to placebo in the placebo controlled databases. However, the majority felt that the overall numbers were small and that these events may have been related to chance due to multiple comparisons. One committee member also noted that examining the MI subcomponent of cardiovascular deaths individually may be problematic as it is possible that other subcomponents may also include MI deaths (e.g. sudden death). Some committee members were still concerned, as they felt that even a small number of events warranted concern and because of the finding was seen in both TIOSPIR and the placebo controlled databases.*

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4. **Voting Question:** 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?

   a. If not, what further data should be obtained?

   YES= 9 NO=4 ABSTAIN=0

5. **VOTE:** 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?

   a. If not, what further data should be obtained?

   YES= 10 NO=3 ABSTAIN=0

Committee Discussion: *The majority of the members agreed that the data supports approval of Spiriva Respimat for the proposed indication. The members who voted "Yes" commented that there was clear demonstration of efficacy and safety (in terms of all-cause mortality and cardiovascular). The 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.*

9.4 Clinical Investigator Financial Disclosure Review Template

Clinical Investigator Financial Disclosure
Review Template

Application Number: 021936

Submission Date(s): 3/24/14

Applicant: Boehringer-Ingelheim

Product: Tiotropium Respimat

Reviewer: Robert Lim

Date of Review: August 19, 2014

Covered Clinical Study (Name and/or Number): 205.372 and 205.452

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

Reference ID: 3618244

		applicant)
Total number of investigators identified: 5189 (PI and sub-investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 183 (PI)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

From trials 205.372 and 205.452, BI certified the absence of financial arrangement for 5189 primary and sub-investigators. From trial 205.372, there were (b) (6) investigators with significant payments of other sorts: (b) (6) . These significant payments of other sorts were determined to not have significant impact upon the conduct of this clinical trial, given that the study was randomized, double-blinded, placebo-controlled trial, with objective spirometric and exacerbation related endpoints, and since each investigator was only responsible for enrolling a small number of patients to this multi-center trial.

From trial 205.452, one investigator received significant payments of other sorts (b) (6) and one investigator's spouse is employed by BI (b) (6). (b) (6)). Given that the study was randomized, double-blinded, double-dummy, active controlled trial, with an objective mortality endpoints and since each investigator

was only responsible for enrolling a small number of patients to this large, multi-center trial; it was determined that this financial disclosure information did not significantly affect trial conduct.

From trials 205.372 and 205.452, BI performed due diligence on 183 primary investigators and financial interest was not certified. For 181 primary investigators, the reasons that this information was not certified was the site did not initiate the trial or the site did not enroll any patients. For the two remaining primary investigators, both from 205.372, the reason given was “unable to contact” and “deceased.”

Reference ID: 3618244

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/s/

ROBERT H LIM
08/28/2014

ANTHONY G DURMOWICZ
08/28/2014

SUMMARY REVIEW OF REGULATORY ACTION

Date:	September 16, 2008
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	21-936
Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission:	November 16, 2007
PDUFA Goal Date:	September 16, 2008
Proprietary Name:	Spiriva Respimat
Established Name:	Tiotoprium bromide
Dosage form:	Inhalation Spray
Strength:	2.5 mcg per spray
Proposed Indications:	Chronic obstructive pulmonary disease (COPD)
Action:	Complete response

1. Introduction

Boehringer Ingelheim Pharmaceuticals submitted this 505(b)(1) application for use of Spiriva Respimat as a long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The proposed dose is 5 mcg (2 inhalation of 2.5 mcg each). The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes approved for maintenance treatment of airflow obstruction in patients with COPD. These include beta-adrenergic agents, anticholinergic agents, combination products containing beta-adrenergic agents and anticholinergic agents, combination of long-acting beta-adrenergic agents and corticosteroids, and methlyxanthines. Advair Discus (fluticasone propionate and salmeterol) is also approved for reducing exacerbations in patients with COPD.

Tiotropium bromide is a long-acting anticholinergic with specificity for muscarinic receptors that is currently approved as Spiriva HandiHaler (tiotropium bromide inhalation powder) for maintenance treatment of bronchospasm associated 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 Boehringer Ingelheim proposes to introduce a novel reservoir type device, called the Respimat, to deliver tiotropium bromide. This drug

product is the first example in an NDA of the inhalation spray dosage form. The proposed indication for Spiriva Respimat is similar to Spiriva HandiHaler, which is maintenance treatment of bronchospasm associated with COPD. Spiriva Respimat also claims benefit for COPD exacerbation, which is mentioned in the proposed Clinical Studies section of the product label, but not mentioned as a separate indication in the proposed Indications and Usage section of the label. Advair Diskus is the only drug that has a reduction of exacerbation indication in COPD patients.

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 will place the cartridge containing the formulation into the Respimat Inhaler. To actuate the product, the patient will turn 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 will then press a trigger, which will release the spring to provide mechanical energy that will propel the formulation through a nozzle with two outlets that will form two jets of solutions. The two jets will converge on each other and create an aerosol cloud that will emit gently from the mouthpiece of the product. The product will need to be primed after the cartridge is placed in the Respimat Inhaler. The Respimat cartridge will allow 60 actuations after priming. Boehringer Ingelheim submitted adequate stability data to support the proposed expiry of (b) (4) months 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. 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. Boehringer Ingelheim 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. Boehringer Ingelheim 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 Boehringer Ingelheim 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.

Boehringer Ingelheim submitted results from one safety pharmacology study of the HERG channel in guinea pig papillary muscles. Review of this study did not show any safety issues.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutic 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), Boehringer Ingelheim 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

	Spiriva Respimat 5 mcg	Spiriva Respimat 10 mcg	Spiriva HandiHaler 18 mcg
AUC 0-24 ss, pg.hr/mL	67.4	143	62.3
Urinary excretion 0-12 hrs, ng	479	892	410

Boehringer Ingelheim 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 (b) (4) and filled in the cartridge and sealed (b) (4). Once the cartridge is inserted into the Respimat Inhaler the formulation is open to contamination from the environment. The formulation contains benzalkonium chloride as a preservative, which is adequate to address this concern.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Boehringer Ingelheim 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 design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 2. Selected clinical studies

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
Comparability assessment to Spiriva HandiHaler:							
127	Efficacy and safety Phase 2 dose-ranging	3 week	≥ 40	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	1999	France
249	Efficacy and safety Phase 3 Cross-over	4 week	≥ 40	SR 5 mcg QD SR 10 mcg QD SH 18 mcg QD Pbo QD	131 131 131 131	2004	US, Canada
250	Efficacy and safety Phase 3	4 week	≥ 40	SR 5 mcg QD SR 10 mcg QD	76 76	2003	Belgium, Netherlands

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N (ITT)	Study Year#	Countries
	Cross-over			SH 18 mcg QD Pbo QD	76 76		
Stand alone pivotal efficacy and safety studies for Spiriva Respimat:							
251	Efficacy and safety Phase 3 Parallel-group	12 week	≥ 40	SR 5 mcg QD SR 10 mcg QD A 36 mcg QID Pbo	88 93 89 91	2003	Germany, Italy, Switzerland, South Africa
252	Efficacy and safety Phase 3 Parallel-group	12 week	≥ 40	SR 5 mcg QD SR 10 mcg QD A 36 mcg QID Pbo	92 87 89 90	2003	US, Canada
254	Efficacy and safety Phase 3 Parallel-group	48 week	≥ 40	SR 5 mcg QD SR 10 mcg QD Pbo QD	332 332 319	2005	US, Canada, EU
255	Efficacy and safety Phase 3 Parallel-group	48 week	≥ 40	SR 5 mcg QD SR 10 mcg QD Pbo QD	338 335 334	2005	US, Canada, Africa, Australia
392	Follow-up of patients discontinued from 254 and 255	+ 48 week		SR 5 mcg QD SR 10 mcg QD Pbo	456	2005	US, Canada, Africa, EU, Australia
* SR = Spiriva Respimat; SH: Spiriva HandiHaler; A = Atrovent MDI; Pbo R = Placebo Respimat: Pbo H = Placebo HandiHaler; # Year study subject enrollment ended							

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 endpoint 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. The primary efficacy endpoint 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. The primary efficacy endpoint 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. The study had a 2-week run-in period followed by 48-week randomized treatment period, and then a 3-week follow-up period. The study had four co-primary efficacy endpoints 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. Boehringer Ingelheim 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.[1]

c. Efficacy findings and conclusions

The clinical program submitted with this application is large but typical 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, SGRQ, Mahler TDI, and COPD exacerbation. These four

[1] Cazzola M, MacNee W, Martizez 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.

components are briefly discussed below, although for the purpose of US registration purpose Boehringer Ingelheim stated that airflow obstruction and COPD exacerbation are relevant.

Airflow obstruction

Maintenance treatment of bronchospasm associated with COPD for Spiriva Respimat 5 mcg is supported by studies 127, 249, 250, 251, 252, 254, and 255. 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). Boehringer Ingelheim carried the 5 mcg and 10 mcg doses in further clinical studies (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). FEV1 time-response curve for these studies also provided similar results (data not shown in this review). The overall data support Boehringer Ingelheim'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 noninferior to Spiriva HandiHaler (with a noninferiority 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	

Treatment groups	n	Mean Trough FEV1 (L) Response on Day 21	Difference from placebo (L)
* 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						
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			

SGRQ

Boehringer Ingelheim 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		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 Boehringer Ingelheim 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			

Exacerbations

Reduction of COPD exacerbation statement in the product label is not supported by the submitted data for Spiriva Respimat 5 mcg. The submitted data show that of the two studies only one showed statistically significant superiority for Spiriva Respimat over placebo (Table 8). For a labeling statement of COPD exacerbation, supporting evidence from two studies will be required. Although pre-specified combined analyses of the two

studies shows statistical significance (data not shown), this is not adequate for labeling claim because the pooled studies are considered as one study. Boehringer Ingelheim submitted results of a study conducted in Veterans Affairs patients with Spiriva HandiHaler (study 205.266) to show replication of COPD exacerbation. That study is not adequate for the purpose of replication because it was conducted with a different product.

Table 8. Mean COPD exacerbations data

Treatment groups		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

8. Safety

a. Safety database

The safety database for Spiriva Respimat is relatively large. In addition to the previous studies that form the basis of approval for Spiriva HandiHaler for maintenance treatment of airflow obstruction in COPD patients which provides support for the systemic safety of tiotropium, this application contains data from a number of studies with Spiriva Respimat ranging in duration from 3 weeks to 1 year (Table 2).

b. Safety findings and conclusion

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. Two new major potential safety signals emerged during review of this application. These are increased frequency of death seen in Spiriva Respimat 48-week studies, and increased frequency of stroke seen in Spiriva HandiHaler and Spiriva Respimat studies. This application will not be approved in this review cycle because of these two safety signals.

Review of the safety data did not show any other new previously unknown safety signal for tiotropium. Laboratory data, ECG, and Holter monitoring did not suggest a safety signal.

The safety findings of death and stroke are discussed in the following section, followed by comment on the path forward to address these safety signals.

Death

The two 48-week clinical studies showed a mortality imbalance against Spiriva Respimat (Table 9). Review of the cases of death did not point to a particular cause or organ system. The causes of death were generally what would be expected in older patients with COPD, such as cardiac and respiratory system diseases. Death is expected to be related to systemic effect of tiotropium, and should occur with both Spiriva Respimat and Spiriva HandiHaler, and also with the short-acting anticholinergic ipratropium. From a mechanistic standpoint one could theorize that an anticholinergic drug may have cardiac effects that can result in mortality. This theory is supported by finding of the US Lung Health Study that evaluated the effects of smoking on decline in FEV1 and mortality or morbidity. Results of the study were suggestive of a possible link between use of inhaled ipratropium and increased cardiovascular death.[2] However, more recent meta-analyses of placebo controlled clinical studies with ipratropium and tiotropium did not show an increase in deaths.[3] A review of the placebo controlled clinical studies with Spiriva HandiHaler also did not show an increase in mortality. The finding of increased death in the two 48-week clinical studies with Spiriva Respimat is difficult to discard as a chance finding, but is also difficult to explain based on negative data from other sources.

Table 9. Death in 48 week studies with Spiriva Respimat

	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)

Boehringer Ingelheim made the Division aware of the mortality imbalance seen in the two 48-week studies in November 2005, well before submitting this application. The Division presented the finding to the Drug Safety Oversight Board (DSOB) on June 15, 2006. At that time data from within the study period were available and the retrospective follow-up data were not available (Table 9). The DSOB was not overly concerned because the overall death signal was driven largely by no death in the placebo arm in one study. No death in a large COPD study is highly unlikely. Also, there was an imbalance of discontinuation between the two treatment arms with approximately 30% of patients discontinuing from the placebo arm and approximately 20% patients discontinuing from each Spiriva Respimat arm. On the Division's advice Boehringer Ingelheim

[2] Anthonisen NR, Connett JE, et al. Hospitalization and mortality in the Lung Health Study. Am J Respir Crit Care Med 2002; 166:333-339.
[3] Salpeter SR, Buckley NS, et al. Meta-analysis: Anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med 2006; 21:1011-1019.

subsequently set up study 392 to obtain retrospective follow up data from patients discontinued from the two 48-week studies (Table 2). Boehringer Ingelheim was remarkably successful in their effort and obtained vital status on approximately 97% of discontinued patients. The additional death numbers modify the finding, but the mortality imbalance against Spiriva Respimat remains (Table 9).

The Division discussed the mortality data at an internal CDER Regulatory Briefing on July 18, 2008. The general opinion expressed by senior CDER staff was that the mortality signal seen in the two 48-week clinical studies are difficult to discard as a chance event or accept as real and additional clinical data is necessary to sort this out. Boehringer Ingelheim has just 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). This study will provide a large safety database for review. A final call on mortality will be deferred till formal Agency review of the UPLIFT study results.

Stroke

In November 2007, Boehringer Ingelheim submitted a pooled analyses of 29 placebo-controlled clinical studies with Spiriva HandiHaler (25 clinical studies) and Spiriva Respimat (4 studies) that showed an increased risk of stroke (Table 10). The analysis was performed as part of routine safety monitoring for tiotropium. The Agency issued an Early Communication regarding this potential serious safety signal in March 2008. [4] Specific detailed review of the studies submitted with this application for Spiriva Respimat do not show a stroke signal. As with the death signal discussed above, the stroke signal is also an open issue at this time. Review of the UPLIFT study, that will provide substantial safety data, will help address the stroke signal as well as the death signal.

Table 10. 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)

Path forward to address the safety findings

A large controlled study is necessary to address the concerns of death and stroke. It is possible that the UPLIFT study may serve as that study. Boehringer Ingelheim has completed the UPLIFT study and submitted preliminary results of the study to the Agency late in the review cycle. The study does not show an imbalance of death and

[4] Early Communication about an Ongoing Safety Review of Tiotropium.
Http://ww fda.gov/cder/drug/early_comm/tiotropium.htm

stroke. The preliminary findings are reassuring, but a formal Agency review of the data is necessary before the study can be used to support a regulatory action. It is expected that Boehringer Ingelheim will submit the UPLIFT study results for Agency review either as a part of the complete response to action on this application, or as a separate supplement. Our plan is to take the complete response including the UPLIFT study results, along with existing data, to an Advisory Committee for further discussion.

c. REMS/RiskMAP

Not relevant because Spiriva Respimat will not be approved in this cycle. A final decision will be made later prior to approval.

9. Advisory Committee Meeting

An advisory committee meeting was not convened for this application. Initially the Division tentatively planned for a Pulmonary and Allergy Drug Advisory Committee (PADAC) meeting for mid-June 2008 to discuss the known mortality signal with Spiriva Respimat. The Division later cancelled the Advisory Committee meeting because a decision was made that to fully discuss the mortality and stroke signal, full analysis of the UPLIFT study results is necessary. As mentioned above, our plan is to take this application to an Advisory Committee meeting during review of a complete response including the UPLIFT study results.

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 recommended by the clinical review team. These two 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 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

Boehringer Ingelheim submitted acceptable financial disclosure statements. A total of 19 investigators had significant financial interest in Boehringer Ingelheim 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 DDMAC, DMETS, or from other groups in CDER.

12. Labeling

a. Proprietary Name

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

b. Physician Labeling

The labeling was not reviewed in detail and not discussed with Boehringer Ingelheim during review of this application because the application cannot be approved due to the safety signals of death and stroke as discussed in section 8 above. Boehringer Ingelheim will need to revise the labeling to include the results of the UPLIFT study and other information provided in the complete response. It will be more useful to do a comprehensive label review and have discussions with the applicant with a label that is expected to be final or close to final and for a product that is headed towards approval.

c. Carton and Immediate Container Labels

These were also not reviewed in detail because the product will not be approved in this review cycle.

d. Patient Labeling and Medication Guide

Patient labeling was not reviewed in detail because the product will not be approved in this review cycle. There is no Medication Guide proposed for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The application will not be approved in this review cycle. The submitted data has failed to provide substantial evidence of safety for use of Spiriva Respimat in COPD patients. The submitted data is adequate to support efficacy for Spiriva Respimat 5 mcg for long-term maintenance treatment of bronchospasm associated with COPD, but not for reduction of COPD exacerbation.

The comments below are for the action letter.

1. The submitted data do not provide substantial evidence of safety to support the use of Spiriva Respimat in patients with chronic obstructive disease (COPD). The safety concerns are death and stroke. Increased frequencies of death were observed in patients treated with Spiriva Respimat compared to placebo in the two 48-week studies submitted with this application, particularly in study 205.255. Increased frequencies of stroke were observed in patients treated with tiotropium bromide compared to placebo in a pooled analysis of clinical study data with Spiriva HandiHaler and Spiriva Respimat.

To support the safety of Spiriva Respimat for use in COPD patients, provide data from an adequate and well-controlled study to address the concerns of death and stroke. The study should be of adequate duration and power that will allow evaluation of these two safety concerns. If study 205.235 (The UPLIFT study) is intended to be used to address these safety concerns, provide justification for use of safety data from Spiriva HandiHaler to support the safety of Spiriva Respimat.

2. The submitted data do not provide substantial evidence to support the proposed claim of reduction of COPD exacerbation. While the pre-specified combined analysis of the two 48-week clinical studies 205.254 and 205.255 show a decreased number of COPD exacerbations with Spiriva Respimat compared to placebo, replication of the finding is necessary to support a labeling claim. Results of the two individual 48-week studies are not sufficient for replication because only one of the two studies showed a statistically significant difference from placebo. The clinical study 205.266 is not acceptable for replication because the study was conducted with Spiriva HandiHaler, which is a distinct product in terms of efficacy.

   To support the proposed claim of reduction of COPD exacerbation, provide data from an adequate and well controlled clinical study that shows statistically significant reduction in COPD exacerbation with Spiriva Respimat compared to placebo.

b. Risk Benefit Assessment

The overall risk benefit assessment does not support approval of Spiriva Respimat for maintenance treatment of airflow obstruction associated with COPD and for reduction of COPD exacerbation. The two potential safety risks that have not been adequately addressed are death and stroke as discussed above in sections 8 and 13a. The reduction of exacerbation claim is not supported by a replicate study as discussed above in sections 7c and 13a.

c. Post-marketing Risk Management Activities

Not relevant because the application will not be approved.

d. Post-marketing Study Commitments

Not relevant because the application will not be approved.

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/s/

Badrul Chowdhury
9/16/2008 10:22:43 AM
MEDICAL OFFICER

Cross-Discipline Team Leader Review

Date	August 22, 2008
From	Sally Seymour, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA# 21,936
Applicant	Boehringer Ingelheim
Date of Submission	November 16, 2007
PDUFA Goal Date	September 16, 2008
Proprietary Name / **Established (USAN) names**	Spiriva Respimat tiotropium bromide inhalation spray
Dosage forms / Strength	Inhalation spray
Proposed Indication(s)	Long term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema
Recommended:	**Complete Response**

1. Introduction

On November 16, 2007, Boehringer Ingelheim (BI) submitted a 505(b)(1) application for Spiriva Respimat Inhalation Spray for the long term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The PDUFA date for this application is September 16, 2008. In this application, BI proposes a novel inhalation device, the Respimat inhaler, to deliver tiotropium bromide for oral inhalation. The product proposed for registration delivers 2.5mcg tiotropium ion per actuation, provided as tiotropium bromide. The proposed dose is 5mcg (two actuations) once daily. Another formulation of tiotropium bromide, Spiriva HandiHaler Inhalation Powder, was approved for the same indication on January 30, 2004, (NDA# 21-395).

To support this application, BI submitted an extensive clinical program as well as the necessary CMC, pharmacology/toxicology, and clinical pharmacology data. This memo will provide an overview of the application with a focus on issues that warrant further discussion, particularly the clinical program because of the potential safety signals of mortality and stroke. The Applicant also seeks a labeling claim that Spiriva Respimat reduces the number of COPD exacerbations, which would be a new claim for tiotropium bromide and this memo will also provide an expanded discussion regarding the support for this claim.

2. Background

Tiotropium bromide is a long acting anticholinergic, with specificity for muscarinic receptors that is currently approved as Spiriva HandiHaler. Spiriva HandiHaler is a dry powder capsule formulation approved for the long term, once-daily, maintenance treatment of bronchospasm

associated with COPD, including chronic bronchitis and emphysema (i.e. a bronchodilator for patients with COPD). The clinical development program for this type of indication is well established. In this application for Spiriva Respimat for the same indication, the Applicant submitted an appropriate clinical program. However, during this development program, there were several unique issues regarding the regulatory history including a mortality signal in the phase 3 program, a potential emerging safety stroke signal with tiotropium, and a labeling claim for COPD exacerbations. The background for these issues is outlined below; however, the primary discussion for the mortality and stroke issue is in Section 8 and the primary discussion for the COPD exacerbation claim is in Section 7

- A pre-NDA meeting was held with BI on April 20, 2005. During that discussion, the Division agreed to reordering of the analysis of the four primary efficacy variables for the two 48 week clinical trials. The new order is trough FEV1, SGRQ, TDI (pooled analysis), and COPD exacerbation (pooled analysis). While the Mahler TDI is included as a primary efficacy variable for international registration, the Division does not consider the Mahler TDI adequate to support a dyspnea claim; therefore, the TDI will not be one of the primary efficacy variables when the data is analyzed for registration in the United States. Therefore, for the US NDA, the Applicant may proceed to the exacerbations endpoint regardless of the significance of the TDI endpoint.

- On November 18, 2005, BI submitted an information amendment to the Spiriva Respimat IND (#65,127) that showed an imbalance in fatal adverse events, favoring placebo in both the one year clinical trials. BI requested a meeting in April 2006, to discuss the impact of this imbalance on the planned NDA. The Division responded to submitted questions on April 25, 2006, and BI cancelled the meeting. In the April 2006, responses, the Division noted that the Spiriva Respimat data must provide the primary basis of support; however, we will consider the Spiriva HandiHaler safety data. To discuss the impact of this safety signal on the approved product, Spiriva HandiHaler, the Division presented this issue at the Drug Safety Oversight Board (DSOB) Meeting on June 15, 2006. The DSOB commented that the mortality signal for Spiriva Respimat was weak because in one study there were no deaths in the placebo group and there was no specific pattern for the deaths. The large Spiriva HandiHaler database was reassuring and there was no suggestion of a problem with the HandiHaler. The DSOB recommended that BI follow up on the vital status for discontinued patients for analysis of the ITT population because there was significant differential discontinuation between the placebo and tiotropium treatment groups.

- On November 30, 2007, the Applicant submitted a document to the IND for Spiriva HandiHaler (IND# 46,687) that described a potential stroke safety signal found in a routine safety analysis of pooled data from controlled Spiriva HandiHaler and Spiriva Respimat clinical trials. Based upon BI's analysis of 29 pooled clinical trials, there was an increased risk of stroke with use of tiotropium bromide with a risk ratio of 1.37 (95% CI: 0.73, 15.6). Additional patient level data was requested from BI and the status of this analysis is described in Section 8. Because of 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 and Spiriva.

3. CMC/Device

In this NDA, BI proposes a novel device, the Respimat inhaler, to deliver tiotropium bromide. The Applicant has submitted the appropriate CMC information to support the proposed drug product and expiry. There are no major CMC issues precluding approval of Spiriva Respimat, but several issues worth addressing are discussed below, including changes in device throughout development, patient handling concerns, and microbiology issues.

The drug substance, tiotropium bromide, is a long acting anticholinergic currently approved as a dry powder for inhalation with the HandiHaler device. For the Spiriva Respimat drug product, tiotropium is formulated as a sterile aqueous solution with the excipients benzalkonium chloride (preservative), edetate disodium (stabilizer), hydrochloric acid (pH adjustment), and water for injection. The phase 3 clinical program included a 2.5mcg and 5mcg strength product; however, the proposed strength for commercialization is 2.5mcg tiotropium per actuation. The proposed dose is two actuations or 5mcg tiotropium per day. The product has 30 labeled doses or 60 actuations, which is a one month supply.

The Respimat device is complex and produces a spray using mechanical energy (spring) to force two streams of solution to aerosolize. There is no propellant in the product. The solution is contained in a cartridge shown in Figure 1, which is supplied separate from the Respimat inhaler, but in one package. Figure 1 shows the cartridge and the Respimat inhaler. To use the inhaler, the patient places the cartridge into the Respimat inhaler. Once the cartridge is in the inhaler, to ready the actuation, the patient turns the bottom of the inhaler by 180°, a small volume of inhalation solution is metered into a chamber and a spring is compressed. When the trigger is pressed, the metered inhalation solution is pressed through a nozzle (uniblock) with two outlets that form two jets of solutions. These two jets converge on each other and create an aerosol cloud, which results in the spray from the mouthpiece (Figure 2).

Figure 1

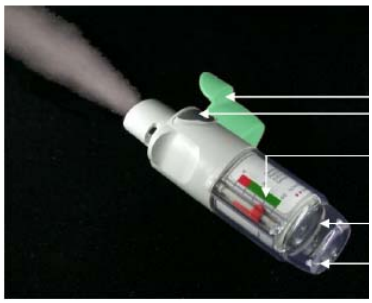


Figure 2

The phase 3 clinical program was conducted with an A4 version of the Respimat product and the to-be-marketed product is the A5 version, which includes a locking mechanism after 60

actuations. Typically the Division recommends pivotal studies be conducted with the to-be-marketed product; however, BI asserted that the addition of this locking mechanism is unlikely to affect product characteristics as it does not interfere with the creation of the aerosol. The CMC reviewer, Dr. Alan Schroeder, has determined that the in vitro characteristics of the A4 and A5 version are indeed similar, so the clinical data obtained with the A4 version can be relied upon to support the marketing of the A5 version.

The drug product has a dose indicator, which is combined with the locking mechanism that locks the inhaler to prevent further actuations after 30 doses has been reached. When 14 actuations remain, the dose indicator reaches the red color zone. Once the inhaler reaches 0, it locks and it is no longer possible to turn the lower portion of the inhaler to meter a dose; thus, the inhaler is no longer usable. The dose indicator is shown below in Figure 3. Only one cartridge is used per device.

Figure 3

A consultation from CDRH was requested because of the complexity of the manufacturing of the device. The CDRH reviewer, Sugato De, did not have any concerns regarding the manufacturing quality and control; however, he raised the concern regarding adequate performance testing with regards to human factors. To evaluate patient handling, BI conducted specific clinical handling/preference studies using a Respimat product. In addition, BI included assessment of patient's satisfaction with the device in the phase 3 clinical program as well as collected inhalers reported as malfunctioning in the phase 3 program. These assessments were reviewed in Dr. Theresa Michele's clinical review and did not suggest any significant problems with patients handling the Respimat device.

The CMC reviewer, Dr. Alan Schroeder, raised two concerns regarding patient handling: 1) the amount of pressure needed to insert the cartridge into the Respimat device and 2) a partial loading of a dose could happen if the patient did not rotate the bottom of the device a full 180°. Regarding the first concern, BI provided patient handling information in which patients judged the Respimat as easy to use. BI conducted one study specifically evaluating the ease of cartridge insertion in relation to age. In this study 94% of patients < 65 years of age and 76% of patients > 65 years of age could load the cartridge unaided. This study showed that the most common recorded difficulty was patients forgetting the next step rather than specific handling difficulties. BI also conducted a study looking at the effect of joint problems on Respimat handling, which showed that approximately 25% of patients with joint problems had difficulty assembling the inhaler properly. With regards to the partial filling, BI indicated that there is sufficient overfill if partial doses are actuated and that this issue could be addressed with labeling. BI noted that it was not advisable to include a ratcheting mechanism to prevent the Respimat base from turning backwards and emitting a partial dose, since patients may confuse the additional clicking sounds emitted by this mechanism with the click when the device is fully loaded. Dr. Schroeder's concerns are noted and the data submitted by BI does

show that it is possible that some patients, especially patients older than 65 years of age or patients with joint problems, may need assistance with assembling the inhaler. Appropriate labeling and patient instructions will be necessary to help ensure appropriate assembly and use of the product.

Dr. Schroeder concluded that the data submitted support the recommendation for initial priming of the product of a minimum of 4 sprays (the number of initial priming sprays is variable) and re-priming with one spray is adequate after 3 days of non-use. If the device is not used for more than 21 days, a minimum of 4 priming sprays are recommended. The Applicant provided data to show that at least 30 doses are available after priming prior to lock out. The Applicant submitted adequate stability data to support the proposed expiry of (b) (4) months and the use life of 3 months.

Dr. Schroeder requested a consultation from the pharmacology/toxicology review team regarding the safety of drug related impurities, degradation products, leachables, foreign particulates, and excipients. In a review dated May 6, 2008, Dr. Luqi Pei responded to the consultation request and did not note any safety concerns. Dr. Schroeder also requested a consultation from the microbiology reviewer, which is discussed in Section 6. Compliance of the manufacturing and testing facilities were adequate.

Dr. Schroeder concluded that the Applicant satisfactorily addressed the CMC issues raised during the review period and his follow-up review recommends Approval.

4. Nonclinical Pharmacology/Toxicology

BI submitted a full pharmacology/toxicology program to support the approval of Spiriva HandiHaler (NDA# 21-395), including chronic inhalation toxicity studies and a carcinogenicity study. The nonclinical safety of tiotropium bromide 18mcg was established in that program. Because the dose of tiotropium bromide in the Spiriva Respimat is 5mcg, the previously submitted nonclinical data for tiotropium is adequate to support the safety of tiotropium delivered via the Respimat. The nonclinical safety of the excipients, EDTA and benzalkonium chloride, have been established for inhalation products.

BI submitted one new safety pharmacology study of the HERG channel in guinea pig papillary muscles. The pharmacology/toxicology reviewer, Dr. Luqi Pei, reviewed the study and no nonclinical safety issues were identified. Previous nonclinical studies demonstrated that tiotropium is non-genotoxic and non-carcinogenic. Tiotropium adversely affects the fetal development when given to pregnant female rats and rabbits. Dr. Luqi Pei, recommends approval of the NDA and revisions to the proposed product label.

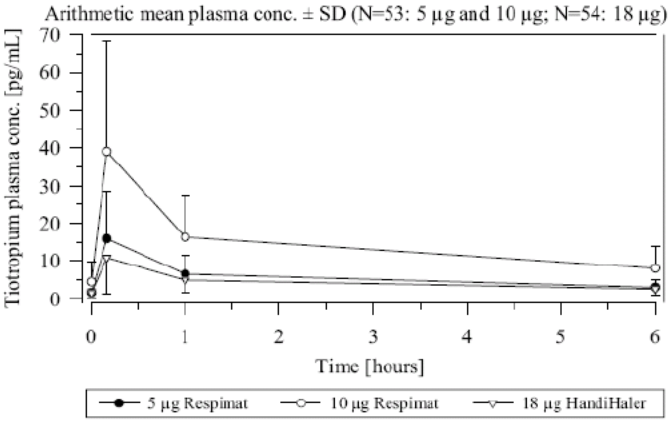
5. Clinical Pharmacology/Biopharmaceutics

BI submitted a full clinical pharmacology program to support the approval of Spiriva HandiHaler (NDA# 21-395) and referenced this NDA to support much of the clinical pharmacology of Spiriva Respimat. In addition, BI evaluated the pharmacokinetic profile of Spiriva Respimat in several clinical trials, which were reviewed in detail by the clinical pharmacology reviewer. One of the issues with the clinical pharmacology information submitted in this application is that two of the studies that included clinical pharmacology

assessments were conducted with an earlier version of Spiriva Respimat, version A3. (b) (4) However, because of the differences in device, the clinical pharmacology data obtained using the A3 device is not suitable for labeling purposes. This is not a major issue because BI also collected PK data in two of the phase 3 clinical trials with the A4 version of the device.

Since Spiriva Respimat is an inhalation spray intended for local effect in the pulmonary tract, the pharmacokinetic profile is primarily useful for safety determination. The clinical pharmacology data submitted in this application demonstrated that following inhalation, maximum tiotropium plasma concentrations were observed within 5 to 10 minutes and declined quickly. Renal is the major route of elimination. Steady state data was inconclusive, but suggested that steady state was not reached by 7 days.

Based upon limited PK sampling points from two clinical studies comparing Spiriva Respimat and Spiriva HandiHaler (Studies 205.249 and 205.250), comparable systemic exposure and urine excretion was observed for the Spiriva Respimat 5mcg and Spiriva HandiHaler 18mcg treatment groups at steady state. The figure below shows the mean plasma concentration following dosing in Study 205.249.



BI Trial No.: 0205.0249

Regarding special populations, there was a trend towards higher exposure in the elderly (>70 years) based upon results from a study with Spiriva HandiHaler assessing the effects of age on tiotropium pharmacokinetics. Renal clearance is significantly lower in the elderly. Renal impairment is associated with increased plasma concentration and reduced clearance. To determine if dosing adjustment is necessary in elderly patients and patients with renal impairment, it is useful to look to the Spiriva HandiHaler labeling in which dosing adjustment is not recommended in these populations. Spiriva HandiHaler dosing recommendations are relevant because the effects of age and renal impairment on PK are dependent on the drug substance and the systemic exposure for tiotropium Respimat 5mcg and Spiriva HandiHaler are similar and the drug clearance between the two devices in elderly patients or patients with renal impairment are expected to be similar. Therefore, dosage adjustment is not recommended in the elderly or patients with renal impairment for tiotropium Respimat. In addition, the mean age of patients in the phase 3 clinical trials was 64 years of age and the safety profile of tiotropium Respimat in this elderly population is generally supported (See

Section 8). The effects of hepatic impairment were not evaluated as tiotropium is primarily renally excreted.

A thorough QT study was conducted with Spiriva HandiHaler in a 12 day placebo and positive controlled study with Spiriva HandiHaler 18mcg and 54mcg once daily. The results of the study were reviewed by the Agency's QT IRT and determined that tiotropium does not have a significant effect on the QT interval as the largest upper limit of the two sided 90% CI for the mean difference between Spiriva and placebo was below 10msec. Relative to placebo, the maximum mean change from baseline in study-specific QT_c interval was 3.2msec and 0.8msec for Spiriva HandiHaler 18mcg and 54mcg, respectively. This information will be included in the product label for Spiriva HandiHaler and would be appropriate for tiotropium Respimat.

The clinical pharmacology reviewer, Dr. Yun Xu, found the NDA "acceptable" pending satisfactory agreement on the labeling.

6. Clinical Microbiology

This Application does not contain clinical microbiology data. However the inhalation solution is manufactured using (b) (4) and a microbiology consult was requested during the review period and information regarding CMC-microbiology is included in this section.

The inhalation solution in the sealed cartridge is manufactured using (b) (4). However, once the cartridge is inserted into the Respimat inhaler, there is a connection between the solution and the environment and the potential for contamination exists. To address this issue, the inhalation solution contains benzalkonium chloride as a preservative. A microbiology consult was requested to evaluate the (b) (4) manufacturing process and sterility process validation. During the review period, the microbiology reviewer, Anastasia Lolas, requested additional information regarding antimicrobial effectiveness testing, sterilization processes, and media fills. The Applicant satisfactorily addressed the microbiology issues and Ms. Lolas recommends Approval.

7. Clinical/Statistical- Efficacy

To support the safety and efficacy of Spiriva Respimat for the proposed indication, BI submitted a full clinical program including six phase 3 clinical trials and many supportive studies. The table below shows a summary of the design of the key clinical trials in the development program. Of these trials, one was a phase 2a dose-ranging trial (205.127) and the remaining 6 were phase 3 clinical trials. Two of the phase 3 clinical trials were 12 weeks duration (205.251 and 205.252) and included an active control, ipratropium bromide. Two of the clinical trials were one year duration (205.254 and 205.255). These four trials are considered the pivotal clinical trials and will be the focus of this memo. In addition, BI conducted two additional phase 3 clinical trials comparing tiotropium Respimat to the approved product, Spiriva HandiHaler. These clinical trials and the dose ranging trial will be briefly addressed in this memo.

Table 1 Summary of Tiotropium Respimat Clinical Development Program						
Study No.	**Description**	**Subjects**	**Design**	**Dose**	**Duration**	**Endpoints**
205.127 France Mar 1998 - Apr 1999	P2a PD and PK dose ranging study	202 subjects with COPD	R, DB, PC,	1.25mcg Tio Respimat QD 2.5mcg Tio Respimat QD 5mcg Tio Respimat QD 10mcg Tio Respimat QD 20mcg Tio Respimat QD 18 mg Spiriva HandiHaler QD Placebo Respimat QD Placebo HandiHaler QD	3 weeks	Trough FEV_1
205.249 United States Canada Nov 2002-Apr 2004	P3 cross over comparison of tiotropium inhalation powder and inhalation spray	131 subjects with COPD	R, DB, DD, AC, PC, XO trial	5mcg Tio Respimat QD 10mcg Tio Respimat QD 18 mg Spiriva HandiHaler QD Placebo Respimat QD Placebo HandiHaler QD	4 weeks	Trough FEV1 (non-inferiority)
205.250 Netherlands Belgium Aug 2002 – July 2003	P3 cross over comparison of tiotropium inhalation powder and inhalation spray	76 subjects with COPD	R, DB, DD, AC, PC, XO trial	5mcg Tio Respimat QD 10mcg Tio Respimat QD 18 mg Spiriva HandiHaler QD Placebo Respimat QD Placebo HandiHaler QD	4 weeks	Trough FEV1 (non-inferiority)
205.251 Multinational Nov 2002-Dec 2003	P3 12-week safety and efficacy trial	361 subjects with COPD	R, DB, DD, PC, AC, //	5mcg Tio Respimat QD 10mcg Tio Respimat QD 36mcg ipratropium bromide QID Placebo Respimat QD Placebo MDI QID	12 week	Trough FEV1
205.252 Multinational Nov 2002-Dec 2003	P3 12-week safety and efficacy trial	358 subjects with COPD	R, DB, DD, PC, AC, //	5mcg Tio Respimat QD 10mcg Tio Respimat QD 36mcg ipratropium bromide QID Placebo Respimat QD Placebo MDI QID	12 week	Trough FEV1
205.254 Multinational Feb 2003 – June 2005	P3 48 week safety and efficacy trial	983 subjects with COPD	R, DB, PC, //	5mcg Tio Respimat QD 10mcg Tio Respimat QD Placebo Respimat QD	48 week	Trough FEV1, SGRQ, TDI, exacerbations (combined)
205.255 Multinational Mar 2003 – June 2005	P3 48 week safety and efficacy trial	1007 subjects with COPD	R, DB, PC, //	5mcg Tio Respimat QD 10mcg Tio Respimat QD Placebo Respimat QD	48 week	FEV1, SGRQ, TDI exacerbations (combined)

Dose Ranging

To support dose selection for the phase 3 development program, BI conducted a randomized, double-blind, placebo controlled, 3 week, phase 2a dose-ranging trial in 200 patients with COPD (Study 205.127). Patients were randomized to one of the following 8 treatment groups: 1.25, 2.5, 5, 10, 20mcg and placebo Respimat once daily, 18mcg Spiriva HandiHaler once daily, placebo HandiHaler once daily. The primary efficacy endpoint was change from baseline trough FEV_1 and the results are shown in the following table.

Table 2 Results of Dose Ranging Study 205.127			
Treatment Group	**n**	**Mean Trough FEV_1 (L) Response* on Day 21**	**Difference from Placebo (L)**
Tiotropium Respimat 1.25 mcg QD	25	0.10	0.08
Tiotropium Respimat 2.5 mcg QD	28	0.05	0.03
Tiotropium Respimat 5 mcg QD	25	0.15	0.13**
Tiotropium Respimat 10 mcg QD	26	0.13	0.11
Tiotropium Respimat 20 mcg QD	26	0.15	0.13**
Placebo Respimat QD	24	0.02	
Spiriva HandiHaler 18mcg QD	25	0.23	0.32**
Placebo HandiHaler QD	23	-0.09	
*adjusted for baseline **statistically significant			

The results showed that the 5mcg and 20mcg tiotropium Respimat treatment groups 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 20mcg dose did not appear to show a benefit over the 5 and 10mcg doses; however, there was an increase in AEs (dry mouth) with higher doses. Based upon the results of this study, the Applicant chose to carry forward the 5mcg and 10mcg dose into the phase 3 program. It is difficult to compare the results for the HandiHaler and the Respimat as the HandiHaler placebo group had a significantly lower response compared to the Respimat placebo group.

Dosing interval

The once daily dosing interval for tiotropium Respimat is based upon the following: a) trough FEV_1 demonstrating bronchodilator effect at the end of the dosing interval; b) known once daily dosing interval of tiotropium from Spiriva HandiHaler product; and c) comparison of tiotropium Respimat with ipratropium bromide and Spiriva HandiHaler in the phase 3 program. Ipratropium bromide was included as an active comparator in Study 205.251 and 205.252 and the results show that for the trough FEV_1 response, both doses of tiotropium Respimat were numerically greater than for ipratropium bromide. Spiriva HandiHaler was included as a comparator in Studies 205.249 and 205.250 and the results show that for the trough FEV_1 response, both doses of Spiriva Respimat were similar to or numerically greater than the trough response with Spiriva HandiHaler.

Phase 3 Efficacy - Design

The four pivotal phase 3 clinical trials (251, 252, 254, and 255) were similar in design except for the duration and additional key efficacy variables in the 1 year clinical trials. The trials were randomized, double blind, placebo controlled, parallel group, and multinational and included two doses of Spiriva Respimat, 5mcg and 10mcg, administered once daily. The 12 week trials also included an active comparator, ipratropium bromide, dosed QID and thus these trials were also double dummy design. The phase 3 clinical trials enrolled patients with a diagnosis of moderate to severe COPD, with the following pertinent entry criteria: a) 40 years of age and older; b) $FEV_1/FVC \leq 70\%$ and $FEV_1 \leq 60\%$; and c) current or ex-smokers with a smoking history of > 10 years. Patients with a history of asthma or who were using oral corticosteroids in excess of 10mg of prednisone per day or 20mg every other day were excluded. Other pertinent exclusion criteria included: a) recent history of myocardial

infarction; b) unstable or life-threatening cardiac arrhythmia; c) narrow angle glaucoma; and d) known symptomatic prostatic hypertrophy.

The primary endpoint was the trough FEV_1. Trough FEV_1 is defined as the FEV_1 measured at the -10 minute time point at the end of 24 hour dosing interval. FEV_1 is an acceptable, reliable, validated efficacy variable for a bronchodilator. Trough FEV_1 is considered an acceptable primary endpoint and can also help provide support for the proposed dosing interval. Although there is no consensus on the minimal clinically important difference for trough FEV_1, we have some precedence with the Spiriva HandiHaler program, in which the trough FEV_1 response (change from baseline) was 110 to 130mL.

The two 48 week clinical trials included the following 3 additional primary endpoints, which are further described below:

- St. George's Respiratory Questionnaire (SGRQ) at 48 weeks
- Mahler TDI at 48 weeks (pooled 48 week studies)
- number of COPD exacerbations (pooled 48 week studies)

The St. George's Respiratory Questionnaire (SGRQ) is a widely used patient reported outcome (PRO) instrument used to measure health impairment in patients with pulmonary disease. Patients complete a questionnaire that contains 50 items compiled into an overall score addressing 3 domains: symptoms, activity, and impact. A treatment difference of 4 units in the total score is generally considered the minimum clinically important difference. Currently, there are no pulmonary medications with an SGRQ labeling claim and BI is not seeking an SGRQ labeling claim. Therefore, there will be minimal discussion of this efficacy variable.

The Mahler TDI is an interviewer administered questionnaire consisting of two parts, the baseline dyspnea index (BDI) determined at baseline and a transition dyspnea index (TDI) determined at subsequent visits to measure changes in the following domains: functional impairment, magnitude of task, and magnitude of effort. The Mahler TDI was included for international registration, but because of limitations of the Mahler TDI, the Division does not consider the instrument adequate to support a dyspnea claim. This issue was discussed at a pre-NDA meeting on April 20, 2005. In that meeting, the Division agreed to skip the Mahler TDI endpoint for the efficacy analysis of the 48 week trials. The limitations of the Mahler TDI were discussed during review of the Spiriva HandiHaler NDA at a September 6, 2002, Pulmonary Allergy Drugs Advisory Committee Meeting. There will be minimal discussion of this efficacy variable.

The fourth primary efficacy variable was the number of COPD exacerbations. BI seeks a labeling claim for reduction of exacerbations in the product label. There is no standard, well-accepted definition of COPD exacerbation.[1] In the 48 week clinical trials, COPD exacerbation was defined as "a complex of respiratory events/symptoms with a duration of three days of more requiring a change in 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

[1] Cazzola M, MacNee W, et. al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008; 31: 416-418.

- sputum production (volume)
- occurrence of purulent sputum
- cough
- wheezing
- 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)

The onset of an exacerbation was defined by the onset of the first recorded symptom. The end of the exacerbation was recorded as defined by the investigator. Although there is no well-accepted definition of COPD exacerbation, the definition used in this clinical program is reasonable as it includes both symptoms and treatment and is consistent with definitions in the literature. It should be clarified that in this application, the number of COPD exacerbations actually refers to an incidence rate per year on a subject level.

One other product (Advair Diskus) has a labeling claim (and indication) for the reduction of COPD exacerbations, thus there is a regulatory pathway for this type of claim. While the definition used by BI is not exactly the same as used in the Advair clinical trials, the definition has many of the same elements. It should be noted that for the COPD exacerbation claim, BI pre-specified combining the two 48 week clinical trials. During the pre-NDA stage the Division informed BI that this was acceptable, but the COPD exacerbation findings would need to be replicated to support a labeling claim. In this NDA, BI also submitted the results of a 6 month study with Spiriva HandiHaler to replicate the COPD exacerbation findings. The use of efficacy data from Spiriva HandiHaler is not acceptable for substantiation of the findings of COPD exacerbation as the HandiHaler is a different drug product. Because the dose, formulation, and delivery system are all very different for this locally acting product, extrapolation of efficacy is not acceptable. However, since BI has two 48 week clinical trials in which COPD exacerbations were assessed, these trials were also reviewed individually to see if the trials support the COPD exacerbation claim.

In addition to the key primary efficacy variables discussed above, additional supportive secondary efficacy variables were assessed in all four phase 3 trials including the following: FEV_1 peak and AUC, FVC, peak expiratory flow rate (PEFR), rescue albuterol use, and COPD symptoms.

<u>Phase 3 Efficacy Results</u>

In general, patients enrolled in the phase 3 trials were primarily white males with a mean age around 65 and a baseline pre-bronchodilator FEV_1 of approximately 1 liter (~40% predicted). The demographic profile was generally balanced between treatment groups in the trials. There was a difference in patient disposition between treatment groups because the placebo group had a higher percentage of patients who discontinued, the primary reason being worsening of COPD.

FEV_1

The first primary endpoint in the four pivotal phase 3 trials was the trough FEV_1 response at the end of the treatment period and the results are shown in the table below. Both the 5mcg and 10mcg tiotropium Respimat treatment groups were statistically significant compared to placebo in each of the four pivotal phase 3 trials. Generally the tiotropium Respimat 10mcg treatment group demonstrated a greater numerical response compared to the tiotropium Respimat 5mcg treatment group, but the clinical significance of this difference is uncertain.

Table 3 Mean* Trough FEV_1 (L) Response at End of Treatment Period

Full analysis set**	**Tiotropium Respimat 5mcg**	**Tiotropium Respimat 10mcg**	**Placebo**
Study 205.251			
Trough FEV_1	1.34	1.41	1.23
Difference from Placebo	0.11 $p = 0.003$	0.18 $p < 0.0001$	
Study 205.252			
Trough FEV_1	1.11	1.10	0.99
Difference from Placebo	0.12 $p < 0.0001$	0.12 $p = 0.0001$	
Study 205.254			
Trough FEV_1	1.17	1.19	1.03
Difference from Placebo	0.14 $p < 0.0001$	0.16 $p < 0.0001$	
Study 205.255			
Trough FEV_1	1.14	1.16	1.02
Difference from Placebo	0.11 $p < 0.0001$	0.14 $p < 0.0001$	

* adjusted for center, smoking status, and baseline
** all randomized patients with baseline data and at least one adequate endpoint following at least 5 days of treatment

In the two 48 week clinical trials, there were 4 co-primary efficacy variables: trough FEV_1 response, SGRQ, Mahler TDI, and COPD exacerbations. Trough FEV_1 response was addressed in the above section. The Applicant specified a stepwise analysis plan FEV_1 response, SGRQ, Mahler TDI, and COPD exacerbations. Each of the additional primary endpoints will be discussed below.

SGRQ

The Division would consider a labeling claim regarding SGRQ. While the Applicant did not seek an SGRQ labeling claim, the results for both tiotropium groups in the 48 week studies were significant compared to placebo. However, the minimum clinically important difference of 4 was not achieved in either study for the tiotropium 5mcg group as shown in the table below. Therefore, the submitted data do not support an SGRQ labeling claim, but are supportive of the efficacy of tiotropium Respimat.

Table 4 Mean* SGRQ Total Score at End of 48 Week Treatment Period						
	Study 205.254			Study 205.255		
	Tio Resp 5mcg N=318	Tio Resp 10mcg N=315	Placebo N=275	Tio Resp 5mcg N=310	Tio Resp 10mcg N=304	Placebo N=276
LS Mean*	39.6	38.7	42.9	39.8	40.0	43.5
Difference from Placebo	-3.3	-4.2		-3.7	-3.4	
pvalue vs. pbo	0.001	<0.0001		0.0004	0.001	
* adjusted for center, smoking status, and baseline; per-protocol missing data imputed using LOCF						

Mahler TDI

The third primary efficacy variable was the Mahler TDI. Because the Division has determined the Mahler TDI is not adequate for a dyspnea claim, the Division agreed that for the US NDA, the Mahler TDI would be skipped for the efficacy analysis. However, as the Mahler TDI is a widely used instrument, it is worth briefly mentioning the findings. Analysis of the Mahler TDI was based upon the combined data from the two 48 week clinical trials. The results for the TDI focal score at the end of the 48 week treatment showed that both doses of tiotropium Respimat were statistically significant compared to placebo. This finding is supportive of the efficacy of tiotropium Respimat.

COPD Exacerbations

From a statistical standpoint, trough FEV_1 and SGRQ were both statistically significant compared to placebo for both tiotropium treatment groups in both 48 week studies; therefore, it is valid to address the COPD exacerbation efficacy variable, which is the focus of the remaining efficacy discussion. As discussed above, the efficacy endpoint of number of COPD exacerbations refers to an incident rate per year on a subject level i.e (number of COPD exacerbations for each subject/number of days of exposure) * 365.25 days per year. This is described in detail in Dr. Ruthanna Davi's statistical review.

BI pre-specified that for the efficacy endpoint of COPD exacerbations, the data would be analyzed based upon the combined data from the two 48 week clinical trials. The protocol specified analysis plan was the Wilcoxon-Mann-Whitney test. As shown in the table below, for the pooled analysis, the results were highly statistically significant for both tiotropium groups compared to placebo. In addition, other measurements of exacerbation, such as time to first exacerbation were also supportive. However, the Division requires replication to support a labeling claim. BI submitted the results of the VA study with Spiriva HandiHaler (205.266) to replicate the COPD exacerbation findings. Because the VA study was conducted with a different drug product, the results are not adequate for replication of the efficacy findings for tiotropium Respimat. The Division evaluated the results of the two individual 48 week studies to see if there is adequate support for replication of the COPD exacerbation claim using the same statistical approach (Wilcoxon-Mann-Whitney) and the results are shown in the table below.

Table 5 Mean Exacerbation Rate* Per Year									
	Study 205.254			Study 205.255			Pooled		
	Tio R5 n=332	Tio R10 n=332	Pbo n=319	Tio R5 n=338	Tio R10 n=335	Pbo n=334	Tio R5 n=670	Tio R10 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	
*(number of exacerbations in subject/number of days of treatment received by subject) times 365.25 days per year; Wilcoxon Mann Whitney test									

While the tiotropium groups in Study 205.255 were statistically significant compared to placebo, the tiotropium groups in Study 205.254 were not; therefore, there is no replication of the findings in the individual studies. This is not surprising given the fact that the individual studies were not powered to show a difference for COPD exacerbations.

It should be noted that the Applicant was requested to submit the statistical analysis for the individual studies. The Applicant submitted results for COPD exacerbation for the individual studies and the results were different than the results shown above in that tiotropium was statistically significant compared to placebo in both individual studies. This is because the Applicant used a Poisson regression model with correction for overdispersion (increased variance in data compared to mean). While this is a valid method of analysis, the use of the Wilcoxon-Mann-Whitney is preferred as this was the prespecified analysis plan for the combined studies. In addition, because a different statistical approach (Poisson regression) provided different results, this calls into question the robustness of the data. Ideally, the data would be robust enough so that using different valid methods of analysis would yield similar results.

Overall, the Applicant has essentially one study supporting the COPD exacerbation claim (pooled 48 week studies or Study 205.255) and will need to replicate the findings to support the claim.

Efficacy Conclusions

- The submitted data support the proposed bronchodilator indication for both 5mcg and 10mcg tiotropium Respimat. While the 10mcg group generally demonstrated a greater numerical response than the 10mcg group, the difference between the 5mcg and 10mcg groups is of questionable clinical relevance.
- The submitted data do not support an SGRQ labeling claim. While the results were statistically significant for both the 5mcg and 10mcg treatment groups compared to placebo in the two 48-week clinical trials, the minimal important difference of 4 was not achieved in either study for the tiotropium Respimat 5mcg treatment group.
- The submitted data do not support a dyspnea claim as the Division has determined that the Mahler TDI is not adequate to support a dyspnea claim due to limitations in the development of the instrument. BI is not seeking a dyspnea claim.
- The submitted data do not support a COPD exacerbation labeling claim as the Applicant has one study supporting the COPD exacerbation claim (pooled 48 week studies or Study 205.255) and will need to replicate the findings to support the claim.

8. Safety

The submitted safety data are not adequate to support the safety of tiotropium Respimat for the proposed indication. Safety determination was based primarily on the submitted controlled clinical trials with tiotropium Respimat. In addition, because tiotropium is already marketed as Spiriva HandiHaler, safety data from the Spiriva HandiHaler program was considered as well. The safety data from the clinical program with tiotropium Respimat showed a mortality imbalance favoring placebo in the long-term studies. A pooled meta-analysis of controlled clinical trials with tiotropium submitted by BI in November 2007, suggested a potential stroke safety signal with tiotropium. These two safety signals warrant additional clinical data and will be discussed below.

The primary source for safety data came from the key clinical trials with tiotropium Respimat in the development program, which are outlined in Table 1. The number of COPD patients exposed to at least one dose of tiotropium Respimat was over 2000. Of these patients, over 500 patients had exposure for approximately one year. Thus, the exposure exceeds the minimum ICH guidelines for population exposure to assess clinical safety for long term treatment of non-life-threatening diseases (ICH-E1A). The phase 3 clinical trials included two doses of tiotropium Respimat 5mcg and 10mcg, which is useful to assess for a dose response with any noted safety signals. Safety assessments in the clinical program included the following: adverse events, laboratories, ECGs, and Holter monitoring (subset).

<u>Deaths</u>

The 48 week clinical trials demonstrated a mortality imbalance favoring placebo. BI informed the Division of this mortality imbalance in November 2005, prior to submitting the NDA. Because the Division was concerned about the fact that another drug product with tiotropium, Spiriva HandiHaler, was available on the US market, the Division presented the preliminary mortality data from the tiotropium Respimat program to the Drug Safety Oversight Board (DSOB) on June 15, 2006. The DSOB noted the following:

> *The potential safety signal for Spiriva Respimat is weak because the signal is present in one (study 255) of two very similar studies and the rate of death in the placebo group of study 255 was zero, a very unusual finding in a COPD population. The difference in mortality seen in study 255 is likely due to this unusually low mortality rate in the placebo group. The causes of death show no sensible pattern and the HandiHaler data are reassuring.* – DSOB minutes, June 15, 2006

The DSOB recommended that BI obtain vital status follow up data on 100% of patients that dropped out of the tiotropium Respimat studies. Because there was differential discontinuation, follow up vital status data may help to determine if randomization to tiotropium permitted longer participation of more severely affected patients with COPD thus explaining the imbalance in deaths. BI subsequently submitted a new protocol to obtain retrospective vital status information on patients discontinued from the two 48 week clinical trials.

The data from the 48 week clinical trials submitted in this NDA showed a mortality imbalance favoring placebo, primarily in Study 205.255. In Study 205.255, the primary reason for the imbalance in mortality was that there were no deaths observed in the placebo group during the clinical trial. It should be noted that there was differential discontinuation with approximately

30% of the placebo group discontinuing compared to approximately 20% in the tiotropium groups in the 48 week trials. The Applicant obtained retrospective follow up vital status on over 97% of the patients in the 48 week clinical trials, which is commendable considering the trials were multi-national. The follow up mortality data showed two deaths in the placebo group in Study 205.255. The additional vital status data modified the mortality data, but the imbalance favoring placebo remains. The table below shows the fatal adverse events in each 48 week clinical trial and for the pooled 48 week clinical trials and includes the additional retrospective follow up data obtained by the Applicant.

Table 6 Fatal Adverse Events in 48 Week Clinical Trials with Tiotropium Respimat

Number Fatal Adverse Events (%)*	Tiotropium 5 mcg	Tiotropium 10 mcg	Placebo	Relative Risk vs. Placebo (95% CI)**	
				Tiotropium 5 mcg	Tiotropium 10 mcg
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 Retro F/U	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 Retro F/U	7 (1.8%)	10 (2.8%)	2 (0.6%)	3.4 (0.7, 16.5)	5.0 (1.1, 22.9)
Studies 254 & 255 (n)	670	667	653		
Within Study	12 (1.9%)	16 (2.5%)	5 (0.9%)	2.1 (0.7, 5.9)	2.9 (1.1, 8.0)
With Retro F/U	15 (2.1%)	18 (2.5%)	9 (1.4%)	1.6 (0.7, 3.6)	1.9 (0.9, 4.3)

*Kaplan Meier estimates at 48 weeks
**Estimated by Cox proportional hazards regression wit treatment as independent variable, stratified by study for pooled analysis

Dr. Theresa Michele reviewed the mortality data in detail. Review of the causes of death did not suggest a particular signal. The main causes of death were related to the cardiac and respiratory system or were undetermined. The causes of death were generally what would be expected in an older population with COPD and did not clearly identify a specific signal. When deaths were evaluated by country it was noted that there were a large number of deaths of unknown cause in Russia.

Serious adverse events (SAEs) did not necessarily suggest a safety signal and did not support a particular cause of death. There was an increase in pneumonia SAEs in the Spiriva Respimat treatment groups (2.1% Tio 5mcg, 1.6% Tio 10mcg) compared to placebo (0.9%) in the 48 week trials, but there was no increase in fatal adverse events due to pneumonia.

From a mechanistic standpoint, one could theorize that an anticholinergic may have cardiac effects that could increase mortality. An increase in cardiac fatal events was noted with ipratropium compared to placebo in the Lung Health Study[2], which was a long term (5 year), randomized clinical trial in approximately 6000 smokers to evaluate the effects of smoking intervention +/- ipratropium bromide on rate of decline of FEV_1 and respiratory or cardiac morbidity and mortality. The 5 year results showed an increase in cardiovascular deaths with ipratropium compared to placebo, but these results were not adjusted for multiplicity and there was not a correlation with compliance. Recent meta-analyses of placebo controlled clinical trials with anticholinergics (tiotropium and ipratropium) do not suggest an increase in

[2] Anthonisen NR, Connett JE, et. al. Hospitalization and Mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002; 166: 333-339.

respiratory related deaths.[3] A review of placebo controlled clinical trial data with Spiriva HandiHaler does not show an increase in mortality. The available data do not suggest an increase in mortality with Spiriva HandiHaler. Death is considered a systemic effect and the systemic exposure of tiotropium is similar for Spiriva HandiHaler 18mcg and tiotropium Respimat 5mcg. Thus, the Spiriva HandiHaler data is supportive of the safety of tiotropium Respimat 5mcg. However, tiotropium Respimat 10mcg has a higher systemic exposure as discussed in Section 5 and the Spiriva HandiHaler data is not helpful to support the safety of tiotropium Respimat 10mcg.

Regardless how the mortality data is analyzed, the imbalance in Study 205.255 cannot be completely explained. One way to interpret this data is that the increase in mortality is not a real signal because the imbalance is due to an unusually low number of deaths in the placebo group in Study 205.255, not an increase in mortality in the tiotropium Respimat groups, and if there were a real signal Study 205.254 would also show a similar trend. However, as pointed out by the statistical review team, while Study 205.254 does not confirm the findings in Study 205.255, Study 205.254 does not necessarily refute the findings as this is difficult to do given the sample size and variability of the data. Additional clinical data is necessary to elucidate whether the mortality imbalance is a real signal.

Stroke Adverse Events

In November 2007, BI submitted a pooled analysis of 29 placebo controlled clinical studies with Spiriva HandiHaler (25 clinical trials) and tiotropium Respimat (4 clinical trials), which was performed as part of routine safety. BI noted an increased risk of stroke (RR 1.37, 95% CI 0.73-1.56) in patients treated with tiotropium compared to placebo. This analysis is not adjusted for multiplicity. While the results are not statistically significant, the Division issued an Early Communication regarding this potential serious safety signal in March 2008.[4] Although the increase in stroke is primarily noted with Spiriva HandiHaler, since tiotropium Respimat contains the same API, tiotropium, stroke is an adverse event of interest for this tiotropium Respimat review. The safety data was reviewed with a focus on stroke and the tiotropium Respimat data do not show a stroke signal. That being said, the potential stroke signal with tiotropium is not resolved and additional long term safety data is necessary to further evaluate the potential stroke safety signal.

In the Early Communication, it was noted that the Applicant recently completed a large, 4 year, placebo controlled clinical trial with Spiriva HandiHaler – Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) in 6000 patients with COPD. Data from UPLIFT will be helpful to further evaluate the potential stroke safety signal with Spiriva HandiHaler. BI submitted preliminary results from UPLIFT during the review period, which did not show an increase in stroke with Spiriva HandiHaler; however, the final study has not been submitted for review.

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[3] Salpeter SR, Buckley NS, et. al. Meta-analysis: Anticholinergics, but not b-agonists, Reduce Severe Exacerbations and Respiratory Mortality in COPD. *J Gen Intern Med* 2006; 21: 1011-1019.

[4] Early Communication about an Ongoing Safety Review of Tiotropium http://www fda.gov/cder/drug/early_comm/tiotropium.htm

Other Safety Findings

In terms of discontinuations, there were more discontinuations in the placebo group, primarily due to worsening of COPD/COPD exacerbations. Review of adverse event data is consistent with the known safety profile of tiotropium, primarily an increase in dry mouth and nasopharyngitis. Dry mouth showed a dose related increase (Tio 5mcg 7.2%, Tio 10mcg 14.5%, and placebo 2%) and is the primary reason that the Applicant proposes to market tiotropium Respimat 5mcg. Laboratory and ECG results did not suggest a safety signal. Twenty-four hour Holter monitoring was performed on a subset of patients (582) in the 48 week clinical trials at baseline, 16 weeks, and 40 weeks. The results did not show any clinically significant changes.

Safety Conclusions

Dr. Theresa Michele has concluded that the submitted data are not adequate to support the safety of tiotropium Respimat because of the imbalance in mortality and the outstanding potential stroke safety signal with tiotropium. Dr. Michele recommends a **Complete Response** action. I concur with Dr. Michele. The two safety signals were discussed at a Regulatory Briefing on July 18, 2008, and the panel generally agreed with the Division's plan to take a Complete Response action (See Section 11). To support the safety of tiotropium Respimat for the proposed indication, BI will need to provide additional long term safety data to demonstrate the safety of tiotropium Respimat with regards to mortality and stroke.

As noted above, the Applicant recently completed UPLIFT, which will provide long term safety data with Spiriva HandiHaler. Because of the size and duration of UPLIFT, this study will double the existing safety database for Spiriva HandiHaler. Data from this clinical program may be supportive of the safety of Spiriva Respimat for the following reasons: 1) both products contain the same API, tiotropium bromide; 2) the events of concern (mortality and stroke) are events related to systemic exposure and the exposure of Spiriva HandiHaler 18mcg is very similar to the exposure of tiotropium Respimat 5mcg (See Section 5); and 3) the stroke signal is primarily from the Spiriva HandiHaler data; thus, if the data from UPLIFT does not show a stroke safety signal, the issue regarding stroke should be resolved. Because of the safety concerns outlined above, this NDA is worthy of discussion at a public Advisory Committee meeting once BI responds to the Complete Response.

9. Advisory Committee Meeting

When this application was submitted, a Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was tentatively planned for mid-June because the Division was aware of the mortality signal noted in the phase 3 program for tiotropium Respimat and thought this safety signal would be worthy of discussion in a public forum. However, as the review proceeded, the Division became aware of an emerging potential safety signal of stroke with Spiriva HandiHaler. Boehringer Ingelheim submitted a document on November 30, 2007, that described an increased risk of stroke (RR 1.37, 95% CI 0.73-1.56) based upon data from 29 pooled clinical trials with Spiriva HandiHaler and tiotropium Respimat as discussed in Section 8. Because of the two potential safety signals and the knowledge that the results from a 4 year controlled clinical trial in 6000 patients with COPD with Spiriva HandiHaler (UPLIFT) would be available later this year, we decided to cancel the advisory committee meeting because

approval of the application this cycle was unlikely. The decision to cancel the advisory committee was made mid February and communicated to the Applicant.

10. Pediatrics

As a new dosage form, this application triggers PREA. The Applicant submitted a waiver for pediatric study requirements as COPD is a disease of adults. The request for a waiver is reasonable and the pediatric study requirements will be waived.

11. Other Relevant Regulatory Issues

Interaction with the Applicant prior to NDA submission identified some potential safety issues with this Application. Therefore, a DSI audit was requested. One site was chosen from each of the 48-week clinical trials. A site in Moscow Russia (Dr. Eugen Shmelev) from Study 205.254 was chosen because it had the second highest enrollment and had the largest number of unexplained deaths. A site in Charleston, South Carolina was chosen as it had the highest enrollment in Study 205.252 and the highest US enrollment in Study 205.255. Results of the DSI audit showed some regulatory violations at both sites (failure to maintain adequate and accurate case histories, failure to ensure the investigation was conducted according to the investigational plan), but none of the violations were deemed to be likely to affect the data integrity.

A Regulatory Briefing was held on June 18, 2008, to discuss the impact of the mortality signal in this NDA as well as the emerging stroke safety signal with Spiriva HandiHaler. The Regulatory Briefing panel is an advisory panel and had the following is a summary of the discussion points. There were mixed feelings regarding the mortality signal as some members did not think this was a true signal because it is driven by the results of one study and primarily because the number of deaths in the placebo group was so small (Study 255) and if it were a true signal, the second study should also show a trend of a signal. Other members were more concerned regarding the signal because even though the placebo group rate of death was low in Study 255, the rate was still within the confidence intervals of Study 254, so the studies were not contradicting each other. There was a consensus that the Division should wait until we have further information about these safety signals before considering approval, especially since this is not a novel medication. There was a consensus that the Division should not rely on the preliminary results of UPLIFT as we have not received the full study report and have not had the opportunity to review the data. Finally, there was some discussion about whether the Division should accept data with Spiriva HandiHaler to evaluate the mortality signal seen in the tiotropium Respimat program.

12. Labeling

The Applicant submitted the proposed label in the PLR format. The proposed tradename is Spiriva Respimat, which was reviewed by DMETS. Because the decision is to not approve this NDA due to the safety signal described in Section 8, labeling negotiations were not conducted with the Applicant. That being said, a labeling review was performed and high level labeling comments are included in Dr. Theresa Michele's clinical review.

13. Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The recommended regulatory action is **Complete Response**. The submitted data are adequate to support the proposed bronchodilator indication, but the submitted data are not adequate to support the safety of tiotropium Respimat. A mortality imbalance was noted in the 48 week clinical trials and a potential stroke signal was identified from analysis of pooled placebo controlled clinical trials with tiotropium. Because of these two outstanding potential safety signals, additional long term safety data are required to support approval.

In addition, the submitted data are not adequate to support the proposed exacerbation labeling claim. While the pre-specified combined analysis of the two 1 year clinical trials (205.254 and 205.255) demonstrated a significant decrease in the number of COPD exacerbations compared to placebo, replication of the findings is necessary to support the labeling claim.

- Risk Benefit Assessment

The data submitted do not support a favorable benefit-risk assessment for tiotropium Respimat for the proposed indication. Although the submitted data demonstrate the efficacy of tiotropium Respimat for the proposed bronchodilator indication, the safety data are not sufficient to support approval because of the unresolved potential mortality signal and potential stroke signal with tiotropium. Tiotropium Respimat is not a novel therapy in that Spiriva HandiHaler is currently available in the US market. Therefore, there is no urgency to approve this drug product with the outstanding safety signals.

- Recommendation for Postmarketing Risk Management Activities

This section is not applicable since the recommended regulatory action is **Complete Response**.

- Recommendation for other Postmarketing Study Commitments

This section is not applicable since the recommended regulatory action is **Complete Response**.

- Recommended Comments to Applicant

<u>Deficiencies</u>
1. The submitted data do not provide substantial evidence that tiotropium Respimat is sufficiently safe for the proposed indication because of two potential safety signals, mortality and stroke adverse events. An increased number of deaths were observed in the tiotropium Respimat treatment groups compared to placebo in the 48-week clinical trials, primarily in Study 205.255. Differential drop outs among the treatment groups do not completely explain the mortality imbalance, and therefore mortality is an unresolved safety issue. In a pooled analysis of tiotropium clinical trial data, you identified an increase in stroke events in patients receiving tiotropium compared with patients receiving placebo. This potential safety signal

was communicated to the public by FDA as an Early Communication on March 18, 2008, and is an outstanding safety issue with tiotropium.

2. The submitted data do not provide substantial evidence that tiotropium Respimat is sufficiently effective for the proposed claim that "Spiriva Respimat significantly reduces the number of COPD exacerbations compared to placebo (b) (4) While the pre-specified combined analysis of the two 1 year clinical trials (205.254 and 205.255) demonstrated a significant decrease in the number of COPD exacerbations compared to placebo, replication of the findings is necessary to support the labeling claim. Evaluation of the individual clinical trials did not demonstrate robust results that are sufficient for replication of the findings, since only one study showed a statistically significant improvement compared to placebo. The VA clinical trial (205.266) that you submitted in this application is not acceptable for replication of findings since this trial was conducted with Spiriva HandiHaler, which is a different product and efficacy cannot be extrapolated.

Information Needed to Resolve the Deficiencies

1. To support the safety of tiotropium Respimat for the proposed indication, provide data to demonstrate the safety of tiotropium Respimat with regards to mortality and stroke. If you intend to use the recently completed 4-year placebo-controlled trial with Spiriva HandiHaler (UPLIFT; Protocol 205.235) to fulfill this requirement, you will need to justify the use of Spiriva HandiHaler data to support the safety of tiotropium Respimat.

2. To support approval of tiotropium Respimat for the proposed labeling claim of reduction in COPD exacerbations, submit placebo controlled clinical trial data that demonstrates tiotropium Respimat reduces COPD exacerbations to replicate the efficacy findings shown in the pooled 48 week clinical trials (205.254 and 205.255).

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/s/

Sally Seymour
8/22/2008 02:54:14 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-936
Submission Code	000
Letter Date	November 16, 2007
Stamp Date	November 16, 2007
PDUFA Goal Date	September 16, 2008
Reviewer Name	Theresa M. Michele, MD
Review Completion Date	July 31, 2008
Established Name	tiotropium bromide
(Proposed) Trade Name	Spiriva Respimat
Therapeutic Class	anticholinergic bronchodilator
Applicant	Boehringer Ingelheim
Priority Designation	S
Formulation	inhalational spray
Dosing Regimen	5 mcg QD (2 actuations of 2.5 mcg each)
Indication	long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema
Intended Population	adults

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This is a 505(b)(1) application for Spiriva Respimat Inhalation Spray for the long term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. In this application, Boehringer Ingelheim (BI) proposes a novel inhalation device, the Respimat inhaler, to deliver tiotropium bromide oral inhalation. Tiotropium bromide is an anticholinergic/antimuscarinic that is currently approved as a dry powder inhaler, Spiriva HandiHaler Inhalation Powder (NDA# 21-395), for the same indication at a dose of 18mcg once daily. The Spiriva Respimat product proposed for registration delivers 2.5mcg tiotropium bromide per actuation. The proposed dose is 5mcg (two actuations) once daily.

To support this application, BI submitted an extensive clinical development program. Sufficient data to support approval is provided from an efficacy perspective; however, a potential adverse mortality signal was demonstrated in the 1-year Phase 3 trials. In addition, a potential stroke signal with tiotropium was identified from controlled clinical trials with Spiriva HandiHaler. Additional safety data from a long-term placebo-controlled clinical trial are required to support approval. From a clinical perspective, the recommended regulatory action is "**complete response**," i.e. non-approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

This section does not apply as the recommended regulatory action is complete response.

1.2.2 Required Phase 4 Commitments

This section does not apply as the recommended regulatory action is complete response.

1.2.3 Other Phase 4 Requests

This section does not apply as the recommended regulatory action is complete response.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

BI proposes Spiriva Respimat for the following indication: the long-term once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. In addition, BI also seeks a labeling claim regarding a reduction of COPD exacerbations. To support the proposed claims, the application included a total of 12 clinical trials, as well as a number of other clinical reports summarizing various related clinical trial data such as data from combined trials.

There were four primary pivotal trials in the application, two replicative 12-week trials (205.251 and 205.252) and two replicative 1-year trials (205.254 and 205.255). The four pivotal trials were multicenter, randomized, double-blind, placebo controlled clinical trials and included two doses of Spiriva Respimat, 5mcg and 10mcg once daily. The two 12-week clinical trials also included an active comparator, ipratropium bromide, which is an approved short-acting anticholinergic metered dose inhaler. The primary efficacy variable in the pivotal trials was trough forced expiratory volume in one second (FEV_1). In addition, the two one year pivotal trials included COPD exacerbations as a primary efficacy variable. To support the COPD exacerbation claim, the Applicant pre-specified analysis of the data from the combined 1-year clinical trials. In addition, key information reports related to the 1-year trials which were reviewed in detail include a retrospective follow up study of patients discontinuing from the 1-year trials (Protocol 205.392) and a combined safety and efficacy analysis of the 1-year trials (Protocol 205.9992).

Dose selection for the Respimat program was performed in stages. In the initial safety study in healthy volunteers (205.112), a maximum tolerated dose of 20 mcg daily was determined based on the increased incidence of anticholinergic side effects (primarily dry nose and mouth). A Phase 2 dose-ranging study was then conducted in patients with COPD (Protocol 205.127). A total of five dosage groups of tiotropium solution using the Respimat device (1.25, 2.5, 5, 10, and 20 mcg) were evaluated compared to a Respimat placebo. In addition, one dosage group of tiotropium dry powder (18 mcg) using the HandiHaler device was evaluated compared to a HandiHaler placebo. On the basis of this study, two doses, 5 mcg and 10 mcg, were chosen for evaluation in Phase 3 trials. All six Phase 3 trials evaluated both 5 and 10 mcg doses. Based on the results of the Phase 3 trials, a dose of 5 mcg once daily is proposed for approval.

1.3.2 Efficacy

1.3.2.1 Bronchodilator effect

The results of the Phase 3 clinical trials including the primary endpoint trough FEV_1 are sufficient to form the basis of approval for Spiriva Respimat 5mcg once daily for the indication maintenance treatment of bronchospasm associated with COPD. In all four primary pivotal

studies (205.251, 205.252, 205.254, and 205.255) a small, clinically insignificant efficacy advantage of tio R10 was demonstrated over tio R5, suggesting that tio R5 is at the plateau of the dosing curve.

In each of the four pivotal studies (205.251, 205.252, 205.254, and 205.255), both tiotropium 5 mcg (tio R5) and tiotropium 10 mcg (tio R10) were superior to placebo for the primary endpoint, trough FEV_1 response at the end of treatment. In addition, in the 12-week studies (205.251 and 205.252) both tiotropium groups were superior to ipratropium for trough FEV_1 at the end of treatment. While tio R10 was generally numerically superior to tio R5, the differences were generally small and not statistically significant. Overall, these data are sufficient to support an efficacy claim for the maintenance treatment of bronchospasm associated with COPD. Because the primary endpoint was evaluated at the end of the 24-hour dosing interval, the active pharmaceutical ingredient, tiotropium bromide, is currently approved for once daily dosing, and the pharmacodynamic response with tiotropium Respimat is similar to the approved Spiriva HandiHaler, a once daily dosing regimen for tiotropium Respimat is supported.

For the 1-year studies (205.254 and 205.255), the differences between the tiotropium groups and placebo were also highly statistically significant ($p<0.0001$) for mean FEV_1 $AUC_{(0\text{-}3h)}$ response and mean FEV_1 $peak_{(0\text{-}3h)}$ response throughout the treatment period. A similar treatment difference was observed by Day 85 in the 12-week trials (205.251 and 205.252). Based on the 1-year studies (205.254 and 205.255), the effects of tiotropium on FEV_1 appeared to reach steady state after 15 days of dosing.

In the 1-year studies (205.254 and 205.255), the forced vital capacity (FVC) results generally paralleled the FEV_1 results. The difference in FVC between the tiotropium groups and placebo were statistically significant ($p<0.0001$) at all time points post-dose on all test days. In general, the tio R10 group showed some improvement over the tio R5 group, but the differences were small and not significant. In the 12-week studies, results were more variable, but a significant difference from placebo was demonstrated for most time points.

Other secondary efficacy variables including peak expiratory flow rate (PEFR), St. George Respiratory Questionnaire (SGRQ), and Mahler Transitional Dyspnea Index (TDI) were generally supportive of efficacy of Spiriva Respimat.

In the 1-year studies for all treatment groups combined, albuterol was used an average of 2.5-2.7 occasions/day at baseline. Compared to placebo, both tiotropium groups showed a significant decrease in the use of albuterol rescue throughout the study, ranging from 0.3-1.0 fewer rescue uses per day.

1.3.2.2 COPD exacerbations

Efficacy was assessed with respect to COPD exacerbations with two replicative 1-year double-blind, placebo-controlled clinical trials (205.254 and 205.255). These trials had identical protocols and a pre-specified combined analysis for the fourth primary endpoint, number of COPD exacerbations occurring in a year. Secondary endpoints related to COPD exacerbations were also combined.

As a second study in support of the COPD exacerbation indication, the application included a 6-month double-blind trial in a US Veterans Affairs population comparing Spiriva HandiHaler (tio HH18) to placebo (Protocol 205.266). Similar but not identical endpoints to the Respimat 1-year trials (Protocols 205.254 and 205.255) were included. Because Spiriva Respimat and Spiriva HandiHaler are different drug products, the HandiHaler data cannot be used to support the Spiriva Respimat efficacy claim. Thus, the VA clinical trial (Protocol 205.266) was not reviewed for this application.

Looking at the two studies individually, one study shows a significant improvement over placebo and one study shows borderline significance. Since reduction of COPD exacerbations is an important claim, the results are not sufficient to demonstrate reproducibility of results in two studies.

Looking at the two 1-year studies combined, as they were designed, the efficacy results regarding COPD exacerbations are much more robust, although insufficient to support an efficacy claim as a single study. In conjunction with a second Spiriva Respimat study demonstrating efficacy with regards to COPD exacerbations, this combination study would support a COPD exacerbation claim.

1.3.3 Safety

The safety data submitted in the Spiriva Respimat clinical program are not sufficient to support approval. A potential mortality signal was noted in the one year clinical trials. While the remainder of the safety data, including adverse events, laboratory, and ECG data, are generally supportive of the safety of Spiriva Respimat, the potential mortality signal cannot be completely explained. Therefore, additional long term safety data of adequate duration and power to evaluate mortality and stroke with tiotropium will be necessary to resolve this safety issue.

Overall, 3173 patients, 3103 of whom had COPD, participated in the Spiriva Respimat clinical trials, and 2077 were exposed to at least one dose of Spiriva Respimat. Of these, 1061 were exposed to the 5 mcg dose. The total number of patients exposed to any dose of Spiriva Respimat included 519 patients for more than 330 days, and 591 were exposed for more than 200 days. Similar exposure times were seen for the 10 mcg dose. The overall exposure is adequate to meet the ICH guidelines for new drug products. In addition, a large safety database is available with Spiriva HandiHaler, a product that contains the same chemical entity with a different delivery mechanism.

1.3.3.1 Mortality

An increased number of deaths was observed in the tiotropium Respimat treatment groups compared to placebo for the 1-year studies, primarily in Protocol 205.255. For the studies combined, a total of 12 deaths in the tio R5 group, 17 in the tio R10 group, and 5 in the placebo group were reported during the study. In 205.255, there were no deaths in the placebo group during the treatment period. The fatal adverse events were reviewed in detail and no pattern or potential mechanism of action of these events could be identified. The overall percentage of

patients in the tiotropium groups who died during the 1-year studies is not unexpected for the patient population, whereas the death rate in the placebo groups is unexpectedly low.

Follow up and evaluation of patients who discontinued prematurely demonstrated that a portion of this mortality imbalance can be explained by differential drop outs. For Protocols 205.254 and 205.255 combined, the relative risk of death for the tio R5 group compared to placebo was 2.1 (95% CI 0.7-5.9) during the study; relative risk decreased to 1.6 (0.7-3.6) when deaths identified in the retrospective follow up are included. The relative risk of death for the tio R10 group compared to placebo was 2.9 (95% CI 0.7-5.9) during the study; relative risk decreased to 1.9 (0.7-3.6) when deaths identified in the retrospective follow up are included. Thus, even with the follow up vital status data, the remainder of the signal cannot be explained with available data.

The analysis of drop outs (Protocol 205.392) was potentially confounded by use of anticholinergic medications (primarily Spiriva HandiHaler) and LABAs in a large portion of the treatment group after discontinuation. In addition, vital status could not be collected from approximately 10% of discontinued patients, which may contribute to the remaining imbalance.

Adverse events leading to death in the Respimat program are not unexpected for the patient population. The only potential exception is the large number of deaths of unknown cause. No obvious safety signal can be linked to death. Even attributing all deaths from unknown causes to a particular adverse event (e.g. myocardial infarction or stroke) does not lead to a notable imbalance. Deaths were generally distributed evenly across countries when corrected for enrollment with the exception of a large number of deaths of unknown cause in Russia.

Comparison of the Spiriva Respimat trials to randomized, placebo-controlled parallel group trials in the HandiHaler program demonstrates a similar fatal adverse event rate for the tiotropium treatment groups; however, the placebo group in the Spiriva Respimat program, particularly in Study 205.255, has a lower fatal adverse event rate. The clinical trial database for Spiriva HandiHaler does not suggest a mortality signal.

The Applicant has recently completed a large, 4-year clinical trial comparing Spiriva HandiHaler to placebo (UPLIFT—Understanding Potential Long-term Impacts on Function with Tiotropium, Protocol 205.235). This study will provide long-term safety data with Spiriva HandiHaler. Although UPLIFT was conducted with Spiriva HandiHaler rather than Spiriva Respimat, the study will provide useful information to place the mortality data in the Spiriva Respimat program in perspective. The results of UPLIFT with Spiriva HandiHaler are applicable to the Spiriva Respimat program because the products contain the same active pharmaceutical ingredient, tiotropium bromide, and Spiriva HandiHaler 18 mcg and Spiriva Respimat 5 mcg have similar systemic exposure. The study report for UPLIFT is expected in the fourth quarter of 2008.

1.3.3.2 Other safety data

For the combined 1-year studies (205.254 and 205.255), 17.2% of patients overall experienced a serious adverse event, 16.1% in the tio R5 group, 18.7% in the tio R10 group, and 16.8% in the placebo group. The most common serious adverse events were COPD exacerbations, pneumonia, and cardiac events. COPD exacerbations were balanced among the groups, occurring in 4.9% tio

R5, 6.0% tio R10, and 5.7% placebo. Serious adverse events of pneumonia were increased in the tiotropium groups compared to placebo, whereas cardiac events were balanced

The most common adverse event associated with discontinuation was COPD exacerbation across all of the studies. Discontinuation due to COPD exacerbation occurred most frequently in the placebo group in the 1-year and most frequently in the ipratropium group for the 12-week studies. Focusing on the 1-year studies, there were 3.3% of patients in the tio R5 group, 3.9% in the tio R10 group, and 9.6% of patients in the placebo group who discontinued due to the adverse event of COPD exacerbation. Other adverse events leading to discontinuation occurred much less frequently. The next most common of these were dyspnea, cardiac disorders overall, nervous system disorders, neoplasms, and pneumonia. Of these, dyspnea occurred more frequently in the placebo group, pneumonia was slightly increased in the tiotropium groups, and the others were balanced among the groups.

Other adverse events were not unexpected for the patient population. Across the studies as a whole, the most common adverse events were in the respiratory system, including COPD exacerbation, nasopharyngitis, and dry mouth. Dry mouth was the most common drug-related AE, occurring in a dose-related fashion in the 1-year studies. This is a known anticholinergic effect and is reported in the Spiriva HandiHaler label.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. No particular stroke-related adverse event was definitively increased in the tiotropium groups in the combined 1-year studies (205.254 and 205.255). Combining terms of cerebral infarction, CVA, transient ischemic attack, and cerebrovascular insufficiency gives 3 events in the tio R5 group, 6 in the tio R10 group, and 3 in the placebo group. Although stroke was not identified as a signal in the Spiriva Respimat program, concern remains regarding stroke with tiotropium and additional long term controlled safety data is necessary to evaluate this potential risk.

In the 1-year studies (205.254 and 205.255) a subset of 582 patients from this study received additional 12-lead ECG measurements and 364 of these received 24-hour Holter monitoring studies that were reviewed centrally. No clinically significant changes in any of the ECG parameters were observed. For heart rate, a small decrease of 2-3 bpm compared to baseline was observed across all treatment groups. Similarly, no clinically significant changes were observed in Holter monitoring data. Evaluation of shift tables for outliers also showed balance between the tiotropium and placebo groups.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen is “5 mcg once daily administered as two inhalations of 2.5 mcg once daily.” This regimen and choice of doses is supported by Phase 3 data. See Section 5.3 for a complete discussion. The primary endpoint in the six Spiriva Respimat Phase 3 trials, trough FEV_1 response, confirmed that an improvement of lung function was maintained for 24 hours at steady state for both tio R5 and tio R10.

In all four primary pivotal studies (205.251, 205.252, 205.254, and 205.255) a small, clinically insignificant efficacy advantage of tio R10 was demonstrated over tio R5, suggesting that tio R5 is at the plateau of the dosing curve. In the 1-year studies, a clear dose-effect was demonstrated for anticholinergic adverse effects of dry mouth and urinary tract infection. The most sensitive of these measures, dry mouth, was doubled in the tio R10 group as opposed to the tio R5 group (14.5% versus 7.2%). On the basis of this aggregate safety data in conjunction with comparable efficacy between the groups, the Applicant selected the 5 mcg dose (2 actuations, 2.5 mcg per actuation) for marketing.

1.3.5 Drug-Drug Interactions

Patients in the Spiriva Respimat Phase 3 studies were permitted to be on regularly scheduled doses of inhaled corticosteroids, xanthenes, low dose oral corticosteroids, and as needed albuterol. No interactions were observed between these drugs and tiotropium Respimat with regards to either efficacy or safety. No formal drug-drug interaction studies were submitted with this program.

1.3.6 Special Populations

Because Spiriva HandiHaler and Spiriva Respimat contain the same active pharmaceutical ingredient, language regarding pregnancy, labor and delivery, and nursing mothers has been taken directly from the approved Spiriva HandiHaler label for the Spiriva Respimat label. Renal impairment was associated with increased plasma concentration and reduced clearance, although dosing adjustment is not recommended in patients with renal impairment. No overall increase in adverse events or differences in efficacy were observed in geriatric patients. Although geriatric patients are known to have decreased renal excretion of tiotropium, no dose adjustment is proposed. This is consistent with Spiriva HandiHaler labeling.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

This NDA is submitted in support of Spiriva (tiotropium bromide) inhalation spray delivered via the Respimat device. The proposed trade name is Spiriva Respimat. In early development, the drug was identified as Ba679.

Tiotropium bromide dry powder inhaler (HandiHaler inhalation device, 18 mcg tiotropium) was approved on January 30, 2004 (NDA 21-395) for the long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema in adults. The proposed indication for Spiriva Respimat is the same as for the HandiHaler. The proposed dose is two inhalations once daily for a total dose of 5 mcg (2.5 mcg/actuation). Tiotropium is a specific antagonist at muscarinic acetylcholine receptors, often called anticholinergic.

2.2 Currently Available Treatment for Indications

There are several drug classes available for relief of bronchospasm in patients with COPD. These include beta-adrenergic agents, anticholinergic agents, combination beta-agonists/anticholinergics, methylxanthines, and combination corticosteroid/long-acting beta-agonists. See Table 1 for a list of currently available products. In the anticholinergic category, ipratropium (short-acting) and tiotropium (long-acting, Spiriva HandiHaler) are available.

Table 1: Currently available drugs for the treatment of COPD

Drug class	Generic name	Brand name	Formulation	Dosing frequency
Beta-agonists (short-acting)	albuterol	many	MDI/inhalation solution	Q 4-6 hr
Beta-agonists (long acting)	salmeterol	Serevent Diskus	DPI	BID
	formoterol	Foradil Aerolizer	DPI	BID
	formoterol	Brovana	inhalation solution	BID
anticholinergic (short acting)	ipratropium	Atrovent and others	MDI/inhalation solution	QID
anticholinergic (long-acting)	tiotropium	Spiriva HandiHaler	DPI	QD
methylxanthine	theophylline	many	tablet/ extended release capsule/ oral elixir/ oral syrup/ injectable	QD
combination products	ipratropium/albuterol	Combivent	MDI	QID
	ipratropium/albuterol	Duoneb and others	inhalation solution	QID
	fluticasone/salmeterol	Advair Diskus	DPI	BID

2.3 Availability of Proposed Active Ingredient in the United States

A formulation of tiotropium bromide in the HandiHaler device formulation was approved on January 30, 2004, for the chronic treatment of bronchospasm associated with COPD, and is marketed in the US as well as many countries worldwide.

2.4 Important Issues With Pharmacologically Related Products

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic bronchodilator. It is manufactured by Boehringer Ingelheim (the Applicant) and is approved for use in patients with COPD as Spiriva HandiHaler. Spiriva HandiHaler consists of a capsule dosage form containing a dry powder formulation of tiotropium bromide intended for oral inhalation only with the HandiHaler inhalation device. Spiriva HandiHaler has been relatively

safe in the COPD patient population. It is intended as a one-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm, i.e. rescue therapy. According to the product label for Spiriva HandiHaler, the product may worsen symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction and should be used with caution in patients with any of these conditions. As a predominantly renally excreted drug, patients with moderate to severe renal impairment treated with Spiriva HandiHaler should be monitored closely. In addition, immediate hypersensitivity reactions and paradoxical bronchospasm are listed in the warnings section of the Spiriva HandiHaler label. The most common adverse events occurring in patients in 1-year placebo and active controlled trials were upper respiratory tract infection (41-43%), dry mouth (12-16%), accidents (5-13%), pharyngitis (7-9%), non-specific chest pain (5-7%), and urinary tract infection (4-7%).

In March 2008, the Agency released an Early Communication regarding a potential stroke signal with tiotropium. This is discussed in detail in Section 7.1.6.

Ipratropium bromide is a short-acting, anticholinergic bronchodilator that is also manufactured by Boehringer Ingelheim and is approved for use in patients with COPD. The drug substance is marketed as a metered dose inhaler in two formulations: as the sole active agent (Atrovent HFA) and as a combination product with albuterol sulfate (Combivent Inhalation Aerosol). Ipratropium bromide is also approved as an inhalation solution and a nasal spray. Ipratropium bromide has proved to be relatively safe in the COPD patient population. According to the product label for Atrovent HFA, the product should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction. These precautions are based on the potential systemic anticholinergic effects of the drug, and cases of precipitation or worsening of narrow-angle glaucoma and acute eye pain have been reported. Cases of hypotension and allergic-type reactions have also been reported. The most common adverse events occurring in a 1-year active-controlled trial were upper respiratory tract infection (34%), bronchitis (23%), COPD exacerbation (23%), sinusitis (11%), urinary tract infection (10%), influenza-like symptoms (8%), back pain (7%), headache (7%), and dyspnea (7%).

2.5 Presubmission Regulatory Activity

The applicant's opening IND for tiotropium in the Respimat device was submitted on June 28, 2002 (IND 65,127). DPAP held a type C meeting with the sponsor on December 29, 2004 to discuss the possibility of a labeled indication for relief of dyspnea in COPD patients. Limitations of the self-administered computerized Mahler Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) instrument Boehringer Ingelheim proposed to support the dyspnea indication had been previously discussed in the September 6, 2002 DPAP Advisory Committee meeting for tiotropium HandiHaler. Although the sponsor addressed many of the concerns raised by the Advisory Committee, the Division advised the applicant that the BDI/TDI could not be utilized to support a dyspnea indication due to fundamental inherent weaknesses of the instrument. A pre-NDA was held with the sponsor in April 2005.

An imbalance in deaths in the 1-year studies was noted upon unblinding. The Applicant submitted a summary of mortality data from these trials to the FDA in November 2005. Because

there was a marketed product containing the same drug substance (tiotropium HandiHaler), this issue was reviewed by the Drug Safety Oversight Board on June 15, 2006. The committee concluded that "the potential safety signal for Spiriva Respimat is weak because the signal is present in one of two very similar studies (study 255) and the rate of death in the placebo group of study 255 was zero, a very unusual finding in a COPD population. The difference in mortality seen in study 255 is likely due to this unusually low mortality rate in the placebo group. The causes of death show no sensible pattern and the HandiHaler data are reassuring."

On December 4, 2007, the Division denied a submission by the sponsor to issue a pediatric Written Request for tiotropium Respimat (b) (4) .

2.6 Other Relevant Background Information

As of November 2, 2007, registration dossiers for tiotropium Respimat were submitted to 31 countries. The Decentralized Procedure in the European Union was successfully completed on July 24, 2007, with a positive opinion in all 25 participating countries. As of the time of the NDA submission, 10 European countries have issued national approval documents, the earliest of which occurred on August 20, 2007. In addition, applications are under regulatory review in Australia, Canada, Switzerland, South Africa Japan, and Turkey. Tiotropium Respimat has not been withdrawn from the market for any reason nor have any applications been withdrawn for any reason.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

3.1.1 Respimat product and device summary

In this NDA, BI proposes a novel device, the Respimat inhaler to deliver tiotropium bromide. Tiotropium Respimat product is contained in a plastic container that is crimped into an aluminum cylinder forming a cartridge. The inhalation solution is a sterile aqueous solution of tiotropium bromide monohydrate and two excipients, benzalkonium chloride (BAC) and edetate disodium (EDTA). The pH of the solution is adjusted with hydrochloric acid (b) (4) . The Respimat is a hand-held, pocket-sized, multi-dose, oral inhalation device that generates a slow-moving aerosol cloud of medication from the aqueous solution. The Respimat cartridge allows 60 actuations (30 doses, following priming). The solution is expelled mechanically rather than by a propellant gas. The delivery device provides both a dose indication and a locking mechanism after the declared number of doses to prevent tail-off of dosing. [Module 2, Section 2.2, page 1]

The Respimat device is complex and produces a spray using mechanical energy (spring) to force two streams of solution to aerosolize. There is no propellant in the product. The solution is contained in a cartridge (see Figure 1), which is supplied separate from the Respimat inhaler, but

in one package. To use the inhaler, the patient places the cartridge into the Respimat inhaler. Once the cartridge is in the inhaler, the patient turns the bottom of the inhaler by 180° to ready the actuation. A small volume of inhalation solution is metered into a chamber, and a spring is compressed. When the trigger is pressed, the metered inhalation solution is pressed through a nozzle (uniblock) with two outlets that form two jets of solution. These two jets converge on each other and create an aerosol cloud, which results in the spray from the mouthpiece. See Figure 2.

Figure 1: Respimat cartridge

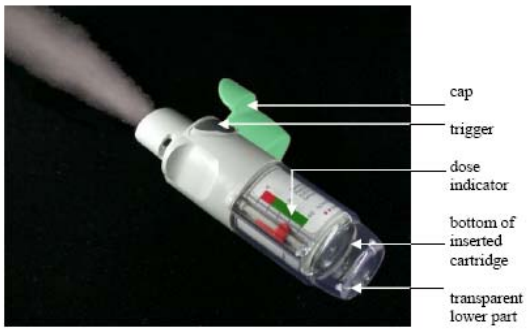


Figure 2: Respimat inhaler device

The Phase 3 clinical program was conducted with an A4 version of the Respimat product and the to be marketed product is the A5 version, which includes a locking mechanism after 60 actuations. Typically the Division recommends pivotal studies be conducted with the to be marketed product; however, BI asserted that the addition of this locking mechanism is unlikely to affect product characteristics as it does not interfere with the creation of the aerosol. The CMC reviewer, Dr. Alan Schroeder, has determined that the in vitro characteristics of the A4 and A5 version are indeed similar, so the clinical data obtained with the A4 version can be relied upon to support the marketing of the A5 version.

The Phase 2 clinical program, primarily study 205.127, the dose ranging study, utilized the A3 Respimat device. According to the Applicant, all three versions of the inhaler have the same nozzle type and are identical in terms of aerodynamic performance of the emitted aerosol sprays.

(b) (4)

(b) (4)

According to Dr. Alan Schroeder, the CMC reviewer, the drug product used for Protocol 205.127 used a slightly higher (b) (4) and higher (b) (4) than the drug product used in other pivotal clinical batches. There are limited data comparing the performance of the Respimat A3 device with the Respimat A4 device. Based on these limited data, the A3 inhaler appears to be similar in delivered dose to A4 and A5 and appears to have a generally similar in aerodynamic particle size distribution (APSD) profile.

The Respimat A5 has a dose indicator, which is combined with the locking mechanism that locks the inhaler to prevent further actuations after 30 doses has been reached. Once the inhaler is locked, it is no longer possible to turn the lower portion of the inhaler meter a dose; thus, the inhaler is no longer usable. The dose indicator is shown above in Figure 2. Only one cartridge is used per device.

A consultation from CDRH was requested because of the complexity of the manufacturing of the device. The CDRH reviewer, Sugato De, did not have any concerns regarding the manufacturing quality and control; however, he raised a concern regarding adequate performance testing with regards to human factors. The CMC reviewer, Dr. Schroeder, also raised two concerns regarding patient handling: 1) the amount of pressure needed to insert the cartridge into the Respimat device, and 2) a partial loading of a dose could happen if the patient did not rotate the bottom of the device a full 180°. Regarding the first concern, BI referred to the patient handling information in which patients judged the Respimat as easy to use. With regards to the partial filling, BI indicated that there is sufficient overfill if partial doses are actuated and that this issue could be addressed with labeling. BI noted that it was not advisable to include additional noise indications for turning of the bottom of the Respimat device as patients may confuse this with the click when the device is fully loaded.

3.1.2 Respimat device performance in Phase 3 trials

Device performance characteristics were evaluated as part of the Phase 3 12-week studies (205.251 and 205.252). In study 205.252, a device satisfaction and preference questionnaire was also completed by a subset of patients at the 14 US sites in the trial. The results of device performance characteristics are discussed in detail in the individual study results presented in Sections 10.1.2 and 10.1.3. In general the Respimat device performed well, with few reported problems. In the device satisfaction questionnaire, greater satisfaction was shown with the Respimat device as compared to a standard MDI for the attributes of: 1) ability to tell the amount of medication left in the container, 2) inhaler durability, and 3) inhaler is environmentally friendly. Patients scored the MDI significantly higher than the Respimat in terms of overall convenience with carrying the inhaler.

3.1.3 Respimat patient preference study

Study 215.1357 was an open label crossover study comparing Berodual (20 mcg ipratropium/50 mcg fenoterol fixed dose combination) delivered via the Respimat A5 device to Berodual MA (metered aerosol) using HFA 134a as propellant. Each product was given TID or QID on a daily basis for 7 weeks before crossing over to the over device. The primary objective of the study was to investigate patient's acceptability and preference for the Respimat device versus the conventional Berodual MA device. Ease of handling and assembly of the Respimat inhaler at home under "real life" conditions was also evaluated. The study enrolled 245 patients ≥18 years of age with asthma, COPD, or mixed respiratory conditions who were using Berodual MA on a daily basis at baseline.

A significant number of patients preferred the Respimat over the standard MA device (80.6% preferred Respimat versus 19.4% preferred MA, $p < 0.001$). On a 7-point scale (1=very dissatisfied, 7=very satisfied), the mean overall satisfaction for Respimat was 6.2 versus 5.4 for MA. The Respimat scored significantly higher than the MA device on 14 of 15 attributes tested. The only one for which there was no difference was "convenience of carrying."

Nearly all patients were able to correctly assemble and use the Respimat inhaler after completing training (96.4%). Only 48.2% assembled the device properly and demonstrated correct inhaler technique on the first attempt; however, only 11% required more than 3 attempts. Of those patients not demonstrating correct inhaler technique on the first attempt, more than 50% had difficulties with "inhale slowly" and "continue inhalation." At the end of treatment, 96.9% of patients retained and could correctly demonstrate Respimat inhaler technique. Most patients (193/222, 86.9%) rated the Respimat as "easy" to assemble.

Reviewer comment:

Berodual MA is approved in Europe for the treatment of bronchospasm associated with both asthma and COPD. Berodual Respimat was the first pulmonary medication available using the Respimat device. It was first launched in Germany in January 2004. While this patient handling study is not with Spiriva Respimat, the data are useful to evaluated patient handling with the Respimat device.

3.1.4 Respimat market research (handling) studies

3.1.4.1 Respimat market research study design

Handing tests with Respimat version A3 or A4 were conducted in a total of 514 patients in 5 different studies. These studies are summarized in Table 2. [Module 5, Volume 1.27, Summary Report U04-1260, pages 8-9]

Table 2: Respimat handling studies

Study Code	Type of Study	Device Version	Patient Population	N	Age Groups (years)	Gender	Joint problems	Country
MRS # 01	Market Research Study	A4	Asthma	63+	16-45: 59% 46-69: 41%	M 48% F 52%	25%	UK
MRS # 02	Market Research Study	A4	Asthma: 88% COPD: 4%	187*	16-50: 55% > 50: 45% mean: 47	M 40% F 60%	35%	USA UK Germany
MRS # 03 (215.1349)	Evaluation following Clinical Study	A3	COPD	48	37-62: 46% ≥ 63: 54% mean: 64	M 75% F 25%	8%	Germany
MRS # 04	Market Research Study	A4	Asthma: 98% COPD: 3%	87	16-64: 71% ≥ 65: 29%	M 45% F 55%	32%	UK
MRS # 05 (244.2484)	Evaluation following Clinical Study	A3	COPD	129	≤ 65: 43% > 65: 57% mean: 66	M 55% F 45%	39%	Canada

Three of the studies (#01, 02, and 04) were pure market research studies, which used face-to-face interviews to collect handing data. In these studies, patients did not inhale from the Respimat device. During the course of the interview, each patient was shown the assembly and handling of the Respimat inhaler. Patients were then required to assemble and handle the device themselves, while interviewers observed and recorded their ability to achieve each step. Study MRS #01 evaluated a number of different design features for the device, including cartridge size, locking button, and memory aids. Study MRS #02 evaluated patients' preferences regarding a refillable Respimat version versus a disposable Respimat version. Study MRS #04 specifically evaluated the effect of age and joint problems on handling along with various memory aids regarding changing of canisters. All three studies recruited patients who were currently using some form of pulmonary inhalation device (DPI/MDI). [Module 5, Volume 1.28, Summary Report U04-1260, Appendices 1, 2, and 4]

Two of the studies (#3 and 5) were conducted in COPD patients who had actually used the Respimat device for a period of 12-weeks (Study 215.1349) and six-months (Study 244.2484). A potential confounder for this data is that patients were required to demonstrate competency in using the Respimat inhaler as an inclusion criterion for these two clinical trials.

Reviewer comment:

(b) (4)

The A5 version of the device proposed for approval is a single use unit. Once the canister is inserted, the device is not to be reused with a different canister.

3.1.4.2 Respimat market research study results

Effect of age on Respimat handling

Study MRS#04 evaluated the effect of age on handing of the Respimat A4 inhaler. In this study, 71% of patients were between 16 and 64 years of age, and 29% were aged 65 years or older. Following a demonstration by the interviewer, each patient was required to assemble and prepare the Respimat device using a new, unpierced cartridge. The majority of patients (88%) were able to achieve assembly and preparation by the second attempt. Patients younger than 65 years of age had fewer difficulties in assembling and preparing the inhaler than patients 65 years of age or older. See Table 3.

Table 3: Study MRS #04 number of attempts necessary to complete assembly and handling of the Respimat (A4) inhaler

No. of attempts	Total N=87	< 65 years N=62	≥ 65 years N=25
		% of patients	
First attempt	28	29	24
Second attempt	60	65	48
Third attempt	5	5	4
Gave up	8	2	24

Patients were also asked to assess the ease of cartridge insertion on a rating scale of 1.0 (extremely difficult) to 10.0 (extremely easy). The mean assessment of the patients was 7.2. Older patients assessed cartridge insertion to be easier (average 7.6) than patients younger than 65 years (average 7.0). However, interviewer assessment demonstrated that only 76% of older patients correctly inserted the cartridge unaided compared to 94% of younger patients.

Respimat assembly was divided into seven separate steps: 1) press safety catch to remove transparent base, 2) insertion of cartridge, 3) ticking cartridge number *[Reviewer comment: does not apply to current Respimat device]* 3) replacement of transparent base, 4) priming, 5) priming process, and 6) priming completion. Most patients remembered to perform the respective steps without any prompting from the interviewer, although the elderly had more difficulties and needed more advice in general. Of the individual steps pertaining to the current device, the most difficulties were recorded with priming, with 78% of patients overall (82% of patients <65 years and 68% of patients ≥65 years) successfully achieving the step unaided. The most frequently

recorded difficulties were associated with patients forgetting the next step in the procedure rather than actual handling difficulties.

[Module 5, Volume 1.27, Summary Report U04-1260, pages 10-12]

Effect of joint problems on Respimat handling

Study MRS#04 also evaluated the effect of joint problems on handing of the Respimat A4 inhaler. In this study, 32% of patients were reported to have arthritis, rheumatism, or other joint disabilities. Of the patients with joint problems, 79% were able to assemble the inhaler properly on the first or second attempt, compared to 92% of patients without joint problems.

The step that appeared to be the most difficult for patients with joint problems as opposed to those without joint problems was insertion of the cartridge. This step was completed correctly unaided by 75% of those with joint problems compared to 95% of those without joint problems. In agreement with this data, patients with joint problems assessed cartridge insertion to be more difficult than patients without joint problems. The mean assessment of patients without joint problems was 7.7 as opposed to 6.2 in those with joint problems. Only 9 patients assessed cartridge insertion to be particularly difficult (ratings 1-3). Six of these patients suffered from joint difficulties.

[Module 5, Volume 1.27, Summary Report U04-1260, pages 12-19]

Respimat handling following a clinical trial

In comparison to pure market research studies using face-to-face interviews (MRS #01, #02, and #04), data derived from market research studies following clinical trials in COPD (MRS#03 and #05) demonstrated that 97-98% of patients found the Respimat inhaler easy or very easy to use. Since competence in using the Respimat inhaler was an inclusion criterion for the studies, this result is not surprising. Most patients felt confident in using the inhaler within 2-3 days. See Table 4. [Module 5, Volume 1.27, Summary Report U04-1260, pages 19-27]

Table 4: Study MRS #03 and #05 time required for patients to be confident in using the Respimat device (A3)

Time required to be confident	MRS #03 N=48 % of patients	MRS #05 N=129 % of patients
Immediately	40	67
1 day	36	22
2-3 days	19	0
1 week	2	8
>1 week	2	4

Reviewer comment:

Based on these market research studies as well as the 12-week Phase 3 studies (205.251 and 205.252), the Applicant has conducted adequate research regarding patients handing of the Respimat device. Overall, the results demonstrate that most patients are able to assemble and

use the Respimat device without difficulty. Cartridge insertion poses the greatest difficulty in assembly, particularly for patients with joint problems. In addition, a significant subset of older patients had some problems remembering all of the steps required for device assembly. Because device assembly only occurs once per month when the medication is dispensed, patients with particular difficulty could have the new device assembled by a family member, pharmacist, or health care provider and still be able to use the device independently on a daily basis. It will be important to have clear patient instructions for use for patients to properly assemble and use the device.

3.2 Animal Pharmacology/Toxicology

The sponsor intends to rely on animal pharmacology and toxicology studies that were submitted and reviewed as part of the HandiHaler program (NDA# 21-395). The nonclinical safety of tiotropium bromide 18mcg was established in that program. One additional safety pharmacology study is submitted, "Study CO2001/254/275/PH2: Effects of tiotropium bromide on HERG-mediated potassium current in HEK293 cells and on action potential configuration in isolated guinea pig papillary muscle." The pharmacology/toxicology reviewer, Dr. Luqi Pei, reviewed the study and no nonclinical safety issues were identified.

BI submitted a full pharmacology/toxicology program to support the approval of Spiriva HandiHaler including chronic inhalation toxicity studies and a carcinogenicity study. These nonclinical studies demonstrated that tiotropium is non-genotoxic and non-carcinogenic. Tiotropium adversely affects the fetal development when given to pregnant female rats and rabbits. Because the dose of tiotropium bromide in the Spiriva Respimat is 5mcg, the previously submitted nonclinical data for tiotropium is adequate to support the safety of tiotropium delivered via the Respimat. The nonclinical safety of the excipients, EDTA and benzalkonium chloride, have been established for inhalation products.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of data for this review are the clinical trials contained in the original NDA submission (21,936), dated November 16, 2007. Additional data is taken from the 4-month safety update submission dated March 18, 2008. Finally, a number of responses by the Applicant to FDA requests regarding this submission contain clinical data. Primary ones are dated April 11, 2008; May 7, 2008; May 21, 2008; July 2, 2008 (IND 46,687 Serial No. 0293); and July 15, 2008 (IND 46,687 Serial No. 0294).

4.2 Tables of Clinical Studies

Table 5 and Table 7 display the pertinent clinical trials in the Spiriva Respimat program. The clinical trials that were considered critical to evaluate the safety and efficacy of Spiriva Respimat

are shown in Table 5. Additional clinical studies of interest that may be briefly discussed in this review are shown in Table 7. Key information reports related to the 1-year studies that were also reviewed in detail are presented in Table 6.

Table 5: Spiriva Respimat Program clinical studies reviewed in detail

ID #	Study type	Study duration	Patient age	Treatment groups	N (ITT)	Study Year†	Countries
205.127	Dose ranging	3 wk	≥40 yrs	tio R1.25, R2.5, R5, R10, R20 QD tio HH 18 QD Placebo R, HH	202	1999	France
205.251	Efficacy and safety COPD	12 wks	≥40 yrs	tio R5 QD tio R 10 QD ipratr 36 mcg QID placebo	88 93 89 91	2003	Germany Italy Switzerland S Africa
205.252	Efficacy and safety COPD	12 wks	≥40 yrs	tio R5 QD tio R10 QD ipratr 36 mcg QID placebo	92 87 89 90	2003	US Canada
205.254	Efficacy and safety COPD	48 wks	≥40 yrs	tio R5 QD tio R10 QD placebo	332 332 319	2005	EU N America
205.255	Efficacy and safety COPD	48 wks	≥40 yrs	tio R5 QD tio R10 QD placebo	338 335 334	2005	EU N America Africa Australia

†Year patient enrollment ended

Table 6: Spiriva Respimat Program related clinical information studies reviewed in detail

ID #	Study type	Treatment groups	N (ITT)	Study Year†	Countries
205.392	retrospective follow up of patients discontinuing from Protocols 205.254 and 205.255	tio R5 QD tio R10 QD placebo	456	2005 (2008)	EU N America Africa Australia
205.9992	Efficacy and safety COPD; combined analysis of Protocols 205.254 and 205.255	tio R5 QD tio R10 QD placebo	670 667 653	2005	EU N America Africa Australia

†Year patient enrollment ended; (year follow up ended)

Table 7: Spiriva Respimat Program clinical studies not reviewed in detail

ID #	Study type	Study duration	Patient age	Treatment groups†	N (ITT)	Study Year#	Countries
205.112	rising dose safety study (healthy volunteers)	14 d	21-50 yrs (males)	tio R10 QD tio R20 QD tio R40 QD placebo	9 9 9 9	1996	Germany
205.138	ocular administration (healthy volunteers)	single dose	21-50 yrs (males)	tio ocular 0.02 tio ocular 0.04 tio ocular 0.08 tio ocular 0.16 tio ocular 0.28 tio ocular 0.40 placebo	6 6 6 6 6 6 12	1998	Germany
205.248	crossover safety (asthma)	single dose	≥18 yrs	R placebo pH 3.4 R placebo pH 7 MDI placebo	34	2001	France
205.249	cross over comparison, COPD	4 wks	≥40 yrs	tio R5 QD tio R10 QD tio HH18 QD placebo	131 131 131 131	2004	US Canada
205.250	cross over comparison, COPD	4 wks	≥40 yrs	tio R5 QD tio R10 QD tio HH18 QD placebo	76 76 76 76	2003	Belgium Netherlands
205.266	efficacy for COPD exacerbations open label	6 mo	≥40 yrs	tio HH18 QD placebo	914 915	2003	US (VA)
215.1357	cross over patient preference (mixed resp conditions)	7 wks	≥18 yrs	Berodual R Berodual MA	245	2003	Germany

† tio R5 = tiotropium Respimat 5mcg total daily dose (2.5 mcg/spray); tio R10 = tiotropium Respimat 10 mcg total daily dose (5 mcg/spray); ipratr = ipratropium bromide 36 mcg (2 inhalations of 18 mcg) four times a day; tio HH18 = tiotropium HandiHaler 18 mcg one inhalation daily; Berodual R=20 mcg ipratropium/50 mcg fenoterol TID/QID via Respimat; Berodual MA= 20 mcg ipratropium/50 mcg fenoterol TID/QID via HFA metered dose inhaler

Year study subject enrollment ended

4.3 Review Strategy

There were four primary pivotal studies in the application, two replicative 12-week studies (205.251 and 205.252) and two replicative 1-year studies (205.254 and 205.255). See Table 5. These studies were reviewed in detail for both safety and efficacy. Key information reports

related to the 1-year studies were also reviewed in detail. These included a retrospective follow up study of patients discontinuing from the 1-year trials (Protocol 205.392) and a combined safety and efficacy analysis of the 1-year studies (Protocol 205.9992). See Table 6. Finally, the primary dose-ranging study (205.127) was reviewed in detail. Summaries of these reviews can be found in Section 10.1, except for the retrospective follow up study (Protocol 205.392) which is found in Section 7.2.9.1 because the final study report was submitted as part of the 4-month safety update.

The application included 7 clinical trials which were not reviewed in detail because they do not contain efficacy information relevant for approval. Five of these studies did include relevant safety information which is summarized in the Integrated Summary of Safety. See Section 7.1.12 for summaries of Protocols 205.138 and 205.248, and Section 7.1.16 for a summary of Protocol 205.112. Data from Protocols 205.249 and 205.250 were included as appropriate throughout the Integrated Summary of Safety. Pharmacokinetic data from Protocols 205.249 and 205.250 can be found under Section 5.

The two other clinical trials (205.266 and 215.1357) do not contain data from tiotropium Respimat. Protocol 205.266 was a placebo controlled study evaluating the effect of Spiriva HandiHaler on COPD exacerbations. The applicant intended this study to provide supportive pivotal efficacy data for the Respimat program; however, because it contains only data with the HandiHaler it cannot be used to support an efficacy claim for the Respimat. Therefore, this study was not reviewed under this NDA. It is reviewed in detail under the efficacy supplement for Spiriva HandiHaler (NDA 21,395 SE-024). Protocol 215.1357 is an open-label crossover patient preference trial comparing Berodual Respimat to Berodual MA (ipratropium/fenoterol). Handling data relevant to the Respimat device from this trial are reviewed under Section 3.1.3.

Reviewer comment:

The Applicant considers two replicative 4-week crossover studies comparing Respimat to HandiHaler (205.249 and 205.250) to be pivotal. These studies were intended as bridging studies between the two devices in order to permit HandiHaler exacerbation data to be used to support efficacy for the Respimat program. Although both Spiriva Respimat and Spiriva HandiHaler contain the same drug substance, the Division of Pulmonary and Allergy Drug Products considers them to be different products from an efficacy standpoint because they use a different delivery device and formulation. Therefore, the bridging studies were reviewed primarily for safety rather than as pivotal efficacy studies in this Application.

4.4 Data Quality and Integrity

A request for DSI consultation was submitted. In choosing sites for audit, no outliers were identified with regard to financial disclosure, protocol violations, or site specific efficacy. Sites in Russia were notable for having most of the unexplained deaths in the study (safety signal). Two sites were identified for inspection. The first site (Russia) was the second highest enroller for the pivotal 48 week Study 205.254, with 48 subjects. In addition, this site had the largest number of unexplained deaths in the study (4 deaths, 3 of which were unexplained). All deaths occurred in tiotropium Respimat groups. The second site (US) was the high enroller for the

pivotal 12 week Study 205.252, with 27 subjects. In addition, this site was also the highest US enroller for the pivotal 48 week Study 205.255, with 27 subjects.

As of the date of finalization of this review, DSI audit is pending.

4.5 Compliance with Good Clinical Practices

The Applicant states that the reviewed studies were conducted using Good Clinical Practices. In addition, the studies were all approved by the appropriate IRB and followed ICH guidelines. [Module 2, Vol 1.1, Section 2.5, page 11] The Applicant also provides debarment certification. [Module 1, Vol 1.1, Section 1.33]

4.6 Financial Disclosures

The Applicant provided financial disclosures for investigators participating in Phase 3 trials: 205.249, 205.250, 205.251, 205.252, 205.254, 205.255, and 205.266. The majority of investigators did not have financial interests requiring disclosure. There were a total of 19 investigators with financial interests totaling >$25,000. Of these, 5 participated in Study 205.266, which is not reviewed as part of this application, and 3 participated in Study 205.249, which does not form the primary basis for safety or efficacy in this application. This leaves 11 investigators with financial interests requiring disclosure in the 4 pivotal trials 205.251, 205.252, 205.254, and 205.255.

For the two 12-week studies, there were no investigators with financial interests who participated in Protocol 205.251. For study 205.252, one sub-investigator at a site (b) (6) and one primary investigator at a site in the United States reported owning >$50,000 worth of Pfizer stock including stock owned by other family members. The sites enrolled (b) (4) patients ((b) (4) of total) and (b) (4) patients ((b) (4) of total), respectively. Neither of the sites were high enrollers for the study. Based on the large treatment difference observed in this study, it is unlikely that either site could have significantly influenced the study results.

For the two 1-year studies, one investigator participating in Protocol 205.254 and 6 investigators at 4 sites participating in Protocol 205.255 declared a financial interest totaling >$25,000. For Protocol 205.254 one sub-investigator at a site (b) (6) reported owning >$50,000 worth of Pfizer stock including stock owned by other family members. (b) (6) . This site enrolled (b) (4) patients into the study ((b) (4) of total). For study 205.255, one sub-investigator (b) (6), and 3 primary investigators and 2 sub-investigators in the US declared financial interests. The sub-investigator (b) (6) reported having an asthma nurse on staff who received sponsorship from Boehringer Ingelheim. The site enrolled (b) (4) patients or (b) (4) of patients in the study. At one site in the US, both the primary and sub-investigator reported receiving >$25,000 in speaking honoraria from Boehringer Ingelheim and Pfizer. This site enrolled (b) (4) patients, or (b) (4) of the total for the study. At a second US site, the primary investigator reported receiving >$25,000 in speaking honoraria from Boehringer Ingelheim. The sub investigator at this site reported owning >$50,000 in Pfizer stock, held as a long-term investment. This site enrolled (b) (4) patients ((b) (4) of total). The primary investigator at

the third US site also reported holding >$50,000 worth of Pfizer stock as a long-term investment. (b) (6). His site enrolled (b) (4) patients (b) (4) of total). Given the large number of patients enrolled in these studies, it seems unlikely that any single investigator could significantly skew the results.

Reviewer comment:

Spiriva HandiHaler and Spiriva Respimat are owned by Boehringer Ingelheim, but are co-marketed by Pfizer. Four of the 7 sites with investigators having financial interests were reported due to long-term holdings of Pfizer stock.

5 CLINICAL PHARMACOLOGY

The Applicant submitted a full clinical pharmacology program to support the approval of Spiriva HandiHaler (NDA# 21-395) and referenced this NDA to support much of the clinical pharmacology of Spiriva Respimat. In addition, BI evaluated the pharmacokinetic profile of Spiriva Respimat in one Phase 1 rising dose safety study in healthy volunteers (Protocol 205.112), one Phase 2 dose ranging study (Protocol 205.127) and two replicative Phase 3 studies comparing two doses of Spiriva Respimat to Spiriva HandiHaler (Protocols 205.249 and 205.250). Protocol 205.127 is reviewed in detail in Section 10.1.1; this study collected only urinary excretion levels, not blood levels of tiotropium.

One issue with the clinical pharmacology information submitted in this application is the two early studies that included clinical pharmacology assessments (Protocols 205.112 and 205.127) were conducted with an earlier version of Spiriva Respimat, version A3. (b) (4) (b) (4) (b) (4) According to Dr. Alan Schroeder, the CMC reviewer, the drug product used for Protocol 205.127 used a slightly (b) (4) (b) (4) and higher (b) (4) than the drug product used in other pivotal clinical batches. There are limited data comparing the performance of the Respimat A3 device with the Respimat A4 device. Based on these limited data, the A3 inhaler appears to be similar in delivered dose to A4 and A5 and appears to have a generally similar in aerodynamic particle size distribution (APSD) profile. However, because of the differences in device, the clinical pharmacology data obtained using the A3 device is not suitable for labeling purposes. In contrast, although there are small differences, it is reasonable to rely on the data from this dose ranging trial to support initial dose selection which was taken into the Phase 3 studies. The applicant explored two different doses (tio R5 and tio R10) in Phase 3, lessening potential concern regarding device differences in the dose ranging study.

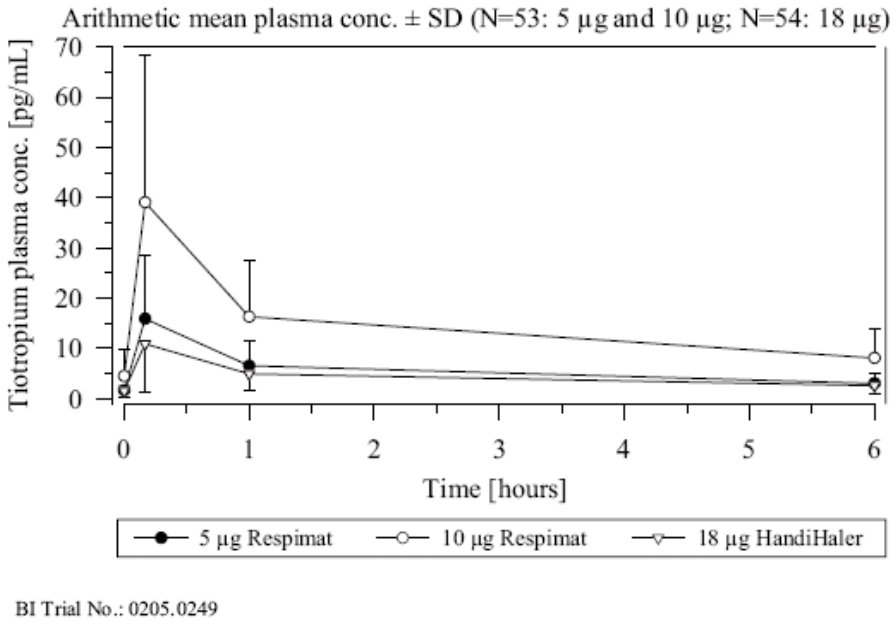
5.1 Pharmacokinetics

Since Spiriva Respimat is an inhalation spray intended for local effect in the pulmonary tract, the pharmacokinetic profile is primarily useful for safety determination. The clinical pharmacology data submitted in this application demonstrated that following inhalation, maximum tiotropium

plasma concentrations were observed within 5 to 10 minutes and declined quickly. Renal is the major route of elimination. Approximately 20% of the inhaled dose is excreted unchanged in urine and the amount of tiotropium excreted in urine increased with increased dose in a dose-proportional fashion. Steady state data were inconclusive, but suggested that steady state was not reached by 7 days.

Based upon two clinical studies comparing Spiriva Respimat and Spiriva HandiHaler (Studies 205.249 and 205.250), comparable systemic exposure and urine excretion was observed for the Spiriva Respimat 5mcg and Spiriva HandiHaler 18mcg treatment groups at steady state. Figure 3 shows the mean plasma concentration following dosing in Study 205.249. Similar results were obtained in Study 205.250.

Figure 3: Protocol 205.249 tiotropium mean plasma concentrations



Regarding special populations, there was a trend towards decreased excretion resulting in higher systemic exposure in the elderly (>70 years). Renal clearance is significantly lower in the elderly; however, dosage adjustment is not recommended as the clinical studies were conducted in an older population. There was not enough data available on races other than Caucasians to draw any conclusions. Renal impairment was associated with increased plasma concentration and reduced clearance. Again, dosing adjustment is not recommended in patients with renal impairment. The effects of hepatic impairment were not evaluated as tiotropium is primarily renally excreted. [Module 2, Volume 1.2. Section 2.7.2 Summary of Biopharmaceutical and Associated Analytical Methods]

Reviewer comment:

Data regarding renal impairment were taken from a combined analysis of Protocol 205.249 and 205.250. These studies only enrolled patients with mild-moderate renal impairment. The

exclusion criteria contained the statement "Precaution: as with all predominantly renally excreted drugs, tiotropium use must be monitored closely in patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min)." The Spiriva HandiHaler label contains the following statement regarding dosing with regards to renal impairment: "No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given Spiriva should be monitored closely." In addition, the clinical pharmacology section of the Spiriva HandiHaler label states: "Since tiotropium is predominantly renally excreted, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance after both intravenous infusion and dry powder inhalation. Mild renal impairment (CrCl 80-80 mL/min), which is often seen in elderly patients, increased tiotropium plasma concentrations (39% increase in AUC_{0-4} after intravenous infusion). In COPD patients with moderate to severe renal impairment (CrCl <50 mL/min), the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82% increase in AUC_{0-4}), which was confirmed by plasma concentrations after dry powder inhalation."

Although data regarding safety in patients with severe renal impairment is not provided as part of the Respimat program, systemic exposure after a 5 mcg Respimat dose is comparable to the HandiHaler 18 mcg dose. In addition, based on HandiHaler data, it is reasonable to expect that plasma levels in patients with severe renal impairment will be approximately double that of the Respimat 5 mcg dose group, or similar to that observed in the Respimat 10 mcg dose group. The applicant presents a substantial safety database for the Respimat 10 mcg dose group. Dry mouth is the most notable dose-related adverse event in the tio R10 dose groups. Therefore, no renal dose adjustment is required based on data presented. A cautionary statement regarding renal impairment will be added to the label, similar to the language in the Spiriva HandiHaler label.

5.2 Pharmacodynamics

5.2.1 Pharmacodynamics and safety

With regards to safety, the Applicant conducted a "thorough QT study" using tiotropium HandiHaler 18 mcg, tiotropium HandiHaler 54 mcg (3 times the approved dose), and moxifloxicin as a positive control. Results of this study are summarized in Section 7.1.9.4.

5.2.2 Pharmacodynamics and efficacy

Since Spiriva Respimat is an inhalation spray intended for local effect in the pulmonary tract, pharmacodynamic relationships for efficacy with regard to blood levels are not informative. Pharmacodynamic relationships for efficacy with regards to dose were evaluated as part of the 12-week Phase 3 studies (205.251 and 205.252). See Sections 10.1.2 and 10.1.3.

In the 12-week studies, responders were defined as patients with a 15% increase in FEV_1 over baseline. Using this criterion for the two studies, 62-68% of patients in the tio R10 group, 62-

68% of patients in the tio R5 group, and 57-65% of patients in the ipratropium groups were responders at some time point on Test Day 85. At 30 minutes after dosing on Day 1, only 33-42% of the tio R5 group and 45-52% of the tio R10 group showed a 15% increase in FEV_1, with the percent of responders gradually increasing to peak at 3-5 hours.

The median onset of response was slightly longer for tio R10 than for ipratropium (16.5-27.6 versus 13.1-18.5 minutes), and approximately double for tio R5 (30.1-59.2 minutes). Duration of action was 181-276 minutes (3.0-4.6 h) for ipratropium, and could not be measured for the tiotropium groups, since both showed a significant trough response.

When response is defined more stringently according to the American Thoracic Society Criteria (ref Pelligrino, 2005) of 12% increase over baseline and an increase of at least 200 mL, the mean FEV_1 increase on Day 1 does not cross a response threshold until 2 hours for tio R5 and one hour for tio R10. This is reduced to one hour for tio R5 and 5 minutes for tio R10 at Day 85.

For Protocol 205.251, an increase in all FEV_1 parameters (trough, peak and AUC (0-6h)) was observed with each successive week of the study for both tio R10 and tio R5, suggesting that steady state was not reached. However, there appeared to be a leveling off of effect by Test Day 85 (Week 12). In Protocol 205.252, both tiotropium groups achieved a steady state in terms of FEV_1 response by the end of the first week of dosing.

Reviewer comment:

Pharmacodynamic features of bronchodilators are customarily described in the label. The onset of action of bronchodilators is often defined as the time point after the first dose at which the mean FEV_1 reaches a clinically significant threshold. FDA has defined this threshold according to ATS standards as 12% and at least 200 mL. This threshold was used for the label for Serevent DISKUS COPD indication (NDA 20-692/S-016, approved March 2002) and Spiriva HandiHaler COPD indication (NDA 21-395, approved January 2004).

While the response reaches 12% change from baseline at 30 minutes for both tiotropium groups, it is not >200 mL. Using the common mean baseline value of 1.225 L for patients in this study, an improvement in FEV_1 of 16.3% is required to reach 200 mL.

While onset of action occurred within 2 hours of dosing after the first dose of tiotropium, the effects of tiotropium on FEV_1 did not appear to reach steady state within the 12 weeks of the study. Given that the maximum treatment response is not seen until after multiple dosing of tiotropium, the use of the first dose to describe the onset of action may not be optimal.

The Applicant proposes the following statement regarding pharmacodynamics in the label: "Pharmacodynamic steady state was reached by day (b)(4) *with once daily treatment." This statement is not supported by available data.*

5.3 Exposure-Response Relationships

5.3.1 Dose selection

Dose selection for the Respimat program was performed in stages. In the initial safety study in healthy volunteers (205.112), a maximum tolerated dose of 20 mcg daily was determined based on the increased incidence of anticholinergic side effects (primarily dry nose and mouth). See Section 7.1.16. A Phase 2 dose-ranging study was then conducted using doses of up to 20 mcg daily in patients with COPD (Protocol 205.127). See Section 10.1.1. On the basis of this study, two doses, 5 mcg and 10 mcg, were chosen for evaluation in Phase 3 trials. All six Phase 3 trials evaluated both 5 and 10 mcg doses. Based on the results of the Phase 3 trials, a dose of 5 mcg once daily is proposed for approval.

Protocol 205.127 was a randomized, intraformulation double-blind, placebo controlled parallel group dose ranging study in patients with COPD. A total of five dosage groups of tiotropium solution using the Respimat device (1.25, 2.5, 5, 10, and 20 mcg) were evaluated compared to a Respimat placebo. In addition, one dosage group of tiotropium dry powder (18 mcg) using the HandiHaler device was evaluated compared to a HandiHaler placebo. The objective of this study was to determine pharmacodynamic and pharmacokinetic profiles of a range of doses of tiotropium in order to determine the optimal dose inhaled as a solution from a Respimat device once a day for three weeks in patients with COPD. Results demonstrated a numerical increase in trough FEV_1 at Week 3 in all tiotropium groups (Respimat and HandiHaler) relative to placebo. The rank order of response among the Respimat groups was tio R5, tio R20, and tio R10. The difference from placebo was only significant in the tio R5 and tio R20 groups. However, the difference in the tio R10 group was comparable to the tio R5 and tio R20 groups with a p=0.06 compared to placebo. The tio R2.5 and tio R1.25 groups did not demonstrate a clinically important response, with a difference of <150 mL. Based on these findings, the Applicant chose to take two doses, tio R5 and tio R10, forward into Phase 3 studies.

In all four primary pivotal studies (205.251, 205.252, 205.254, and 205.255) a small, clinically insignificant efficacy advantage of tio R10 was demonstrated over tio R5, suggesting that tio R5 is at the plateau of the dosing curve. These data are in concurrence with the pharmacokinetic data from Protocols 205.249 and 205.250, which demonstrated a comparable systemic exposure for tio R5 and tio HH18, whereas tio R10 had a higher exposure. Safety data did not reliably differentiate between doses in shorter term studies. In the 1-year studies, a clear dose-effect was demonstrated for anticholinergic adverse effects of dry mouth and urinary tract infection. The most sensitive of these measures, dry mouth, was doubled in the tio R10 group as opposed to the tio R5 group (14.5% versus 7.2%). On the basis of this aggregate safety data in conjunction with comparable efficacy between the groups, the 5 mcg dose (2 actuations, 2.5 mcg per actuation) was selected for marketing.

Reviewer comment:

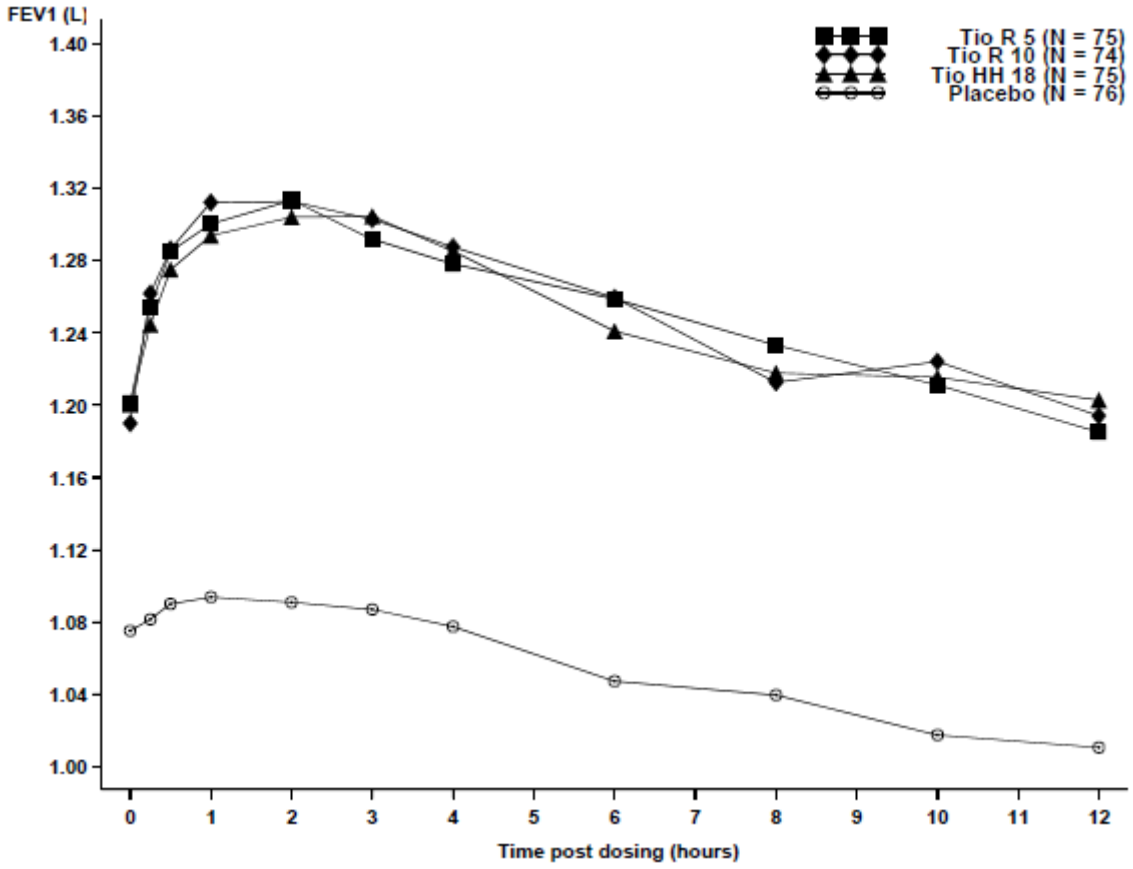
Based on the data provided in the Phase 3 trials, the selected dose of 5 mcg is supported. The difference from placebo in mean trough FEV_1 response in the 12-week studies is approximately

the same as the difference in trough FEV_1 response found in pivotal trials at the end of 13 weeks of treatment for Spiriva HandiHaler (18 mcg).

5.3.2 Dosing regimen

The rationale for once daily dosing for tiotropium was established during the Spiriva HandiHaler program. The primary endpoint in the six Spiriva Respimat Phase 3 trials, trough FEV_1 response, confirmed that an improvement of lung function was maintained for 24 hours at steady state for both tio R5 and tio R10. From a pharmacokinetic standpoint, once daily dosing is also supported by a half-life of approximately 5 days. In addition, Protocols 205.249 and 205.250 demonstrated comparable efficacy between the approved once daily dose of tio HH18 and tio R5 dosed once daily. See Figure 4 for a representative FEV_1 response curve. In comparison to short-acting ipratropium dosed four times daily conducted as part of the 12-week Phase 3 studies 205.251 and 205.252, tio R5 showed significantly better improvement in FEV_1 trough response on all days tested.

Figure 4: Protocol 205.250 mean FEV_1 [L] time response curve on Day 29



5.3.3 Tolerance

Tolerance effects were assessed as part of the 1-year Phase 3 trials (205.254 and 205.255). Efficacy endpoints were measured on Days 1, 15, 57, 169, 225, and 337. In both studies, the pairwise differences for FEV_1 between both the active groups and placebo were statistically significant ($p<0.0001$) at all time points post-dose on all test days. The trough response compared to placebo was maintained at similar levels at all time points measured, suggesting that tolerance does not occur with tiotropium. However, trough FEV_1 in all groups declined slightly over the 48 week study. A generally similar profile was also observed for other measured endpoints.

Reviewer comment:

Based on these results, no evidence of tolerance to tiotropium Respimat occurred. The slight decline in FEV_1 observed across all groups over the course of the study is expected because COPD is a progressive disease. The proposed Respimat label contains the following statement (b) (4) *Based on presented data, this statement is supported.*

5.3.4 Rebound effect

Rebound effect was assessed as part of all four pivotal Phase 3 trials (205.251, 205.252, 205.254, and 205.255). In both 12-week and 1-year trials, efficacy endpoints were assessed off therapy at the end of the treatment period. Primary data on rebound comes from the two 12-week trials. After the end of therapy, patients were followed for an additional 3 weeks during which they continued to perform daily PEFRs and record rescue albuterol use. Based on this data, there was no rebound effect; however, PFT data were not collected. Patients instead appeared to have a gradual tapering off of effect.

Reviewer comment:

The sponsor evaluated rebound only with PEFR. PEFR is generally regarded as a secondary, supportive endpoint; therefore, data provided are not sufficiently robust to support a claim regarding rebound. The Applicant has not proposed any labeling statements regarding rebound effects.

6 INTEGRATED REVIEW OF EFFICACY

BI has proposed an indication of the maintenance treatment of bronchospasm associated with COPD for Spiriva Respimat. In addition, BI proposed language in the clinical trials section regarding the prevention of COPD exacerbations and reduction in rescue medication use. The bronchodilator indication and COPD exacerbation labeling claim will be discussed in detail in Section 6.1 and 6.2, respectively. Rescue medication use is discussed under Section 6.1. Statements regarding tolerance and pharmacodynamic steady state are discussed under Section

5.2.2. As the statistical review was not available at the time of finalization, all data presented in this review are from the Applicant.

6.1 Indication: maintenance treatment of bronchospasm

The proposed indication is stated as "Spiriva Respimat is indicated for the long-term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema." In the clinical studies section, the Applicant also makes the following claim, (b) (4)

6.1.1 Methods

Efficacy was assessed with two sets of replicative studies: two 12-week studies (205.251 and 205.252) and two 1-year studies (205.254 and 205.255). Both sets of studies evaluated trough FEV_1 at the end of the treatment period as the first primary endpoint. Dyspnea using the Mahler Transitional Dyspnea Index (BDI/TDI) and quality of life using the St. George Respiratory Questionnaire were also assessed. The Applicant is not requesting claims regarding the latter two endpoints. Non-spirometric endpoints were generally in favor of the treatment groups across all studies. Because they are not being used to support labeling claims, they are not discussed in the Integrated Summary of Efficacy other than rescue therapy use. Information regarding non-spirometric endpoints is presented in detail under the individual study reports in Section 10.1.

In addition, the Applicant considers two replicative 4-week crossover studies comparing Respimat to HandiHaler (205.249 and 205.250) to be pivotal. These studies were intended as bridging studies between the two devices in order to permit HandiHaler exacerbation data to be used to support efficacy for the Respimat program. Although both Spiriva Respimat and Spiriva HandiHaler contain the same drug substance, the Division of Pulmonary and Allergy Drug Products considers them to be different products from an efficacy standpoint because they use a different delivery device and formulation. Therefore, the bridging studies were reviewed primarily for safety rather than as pivotal efficacy studies in this Application.

6.1.2 General Discussion of Endpoints

6.1.2.1 Spirometric primary efficacy endpoints

The primary endpoint for the 12-week studies (205.251 and 205.252) was trough FEV_1 response after 12 weeks of treatment. The primary endpoint for the 1-year studies (205.254 and 205.255) was trough FEV_1 response after 48 weeks of treatment. Trough FEV_1 was defined as the FEV_1 measured at the -10 minute time point at the end of the dosing interval 24 hours post drug administration. Trough FEV_1 response was defined as the change from baseline in trough FEV_1.

Baseline FEV_1 was the pre-treatment FEV_1 value measured at Visit 2 in the morning 10 minutes prior to administration of the first dose of study medication.

Pulmonary function testing was to occur both prior to and following test-drug administration on prespecified visits. Spirometry was performed according to ATS criteria. The highest FEV_1 and FVC of three maneuvers were recorded regardless of whether they came from the same or different maneuvers. For each patient, PFTs started at approximately the same time of day ±30 minutes in the morning between 7 and 10 am. Although not an enrollment criteria, reversibility was tested at baseline after administration of 400 mcg albuterol aerosol.

A number of medications were appropriately restricted prior to PFT testing:

- short-acting theophylline (at least 24 hour washout)
- long-acting theophylline (at least 48 hour washout)
- short-acting anticholinergic bronchodilators (at least 8 hour washout)
- short-acting beta-adrenergic bronchodilators (at least 8 hour washout)
- long-acting beta-adrenergics (at least 48 hour washout)
- inhaled corticosteroids (not to be taken 1 hour prior)
- study medications (not to be taken prior to test-day pre-dose PFTs)

In addition, patients were to refrain from strenuous exercise, smoking, caffeinated or ice-cold beverages, cold temperatures, dust, and environmental smoke the morning prior to spirometry.

Reviewer comment:

FEV_1 is a well-accepted, validated, reproducible efficacy variable and is the basis of approval of the majority of medications for asthma and COPD. Trough FEV_1 has been used as a primary efficacy variable to support the efficacy of the other tiotropium inhalation product, Spiriva HandiHaler, and can be used to assess the bronchodilator response at the end of the dosing interval. The use of trough FEV_1 response as the primary endpoint in the Spiriva Respimat program is appropriate.

6.1.2.2 Spirometric secondary efficacy endpoints

Secondary spirometric endpoints in the Phase 3 studies included:

- Trough FEV_1 response at various time points throughout the study
- Trough FVC response at various time points throughout the study
- FEV_1 and FVC area under the curve $(AUC)_{0\text{-}6h}$ and peak response
- Individual FEV_1 and FVC measurements at each time point

- Onset and duration of therapeutic response and percentage of responders after 0 and 12 weeks (12-week studies only)

[Module 5, Volume 1.6, Study report 205.251, page 38-39] [Module 5, Volume 1.11, Study report 205.254, pages 81-82]

Therapeutic response was determined based on FEV_1. A response was considered to have been achieved if an FEV_1 measurement of at least 1.15 times the Test Day 1 baseline value was recorded at any time during the first 2 hours of observation (15% increase). The onset of the therapeutic response was defined as the linear interpolation of the time of the first therapeutic response and the time of the observation just prior to the first therapeutic response (even if that was the baseline observation). If no therapeutic response was achieved within the first 2 hours following dosing, then the onset was flagged with the value 361 minutes. Termination of the therapeutic response was identified by the first fall below 1.15 times baseline FEV_1 on two consecutive measurements following a therapeutic response. Alternatively, response termination was identified by a single point if the initial measured value falling below 1.15 times pre-dose FEV_1 occurred at the 6-hour observation. If a response had been observed and was still present at the 6-hour time point, the termination of therapeutic response was flagged with the value of 361 minutes. Duration of the therapeutic response was defined as termination of response minus onset of response. See Section 5.2.2 for further discussion.

6.1.2.3 Rescue medication use

Weekly mean number of occasions of rescue therapy (albuterol) used per day was included as a secondary endpoint in all four pivotal trials (205.251, 205.252, 205.254, and 205.255).

The patient received a diary card at each visit. This card was used to record twice daily PEFR, test medication use, and rescue albuterol use. An additional card was given to record health-related comments. The card was returned and reviewed with the patient at each visit. Daily diary card data for PEFR and rescue medication use were excluded during steroid and theophylline bursts for COPD exacerbations. Weekly summary data from the diary card were imputed from neighboring weeks if less than 4 observations were recorded in a week. In patients discontinuing the study early due to worsening COPD, the missing data were imputed by the least favorable data prior to discontinuation. Missing data for patients missing a visit or discontinuing for other reasons were estimated by their last observed data.

6.1.3 Study Design

All of the studies that form the primary basis of this review (205.251, 205.252, 205.254, and 205.255) were randomized, double-blind, placebo-controlled parallel group trials that included two doses of Spiriva Respimat, tio R5 and tio R10. Two were 12-week trials (205.251 and 205.252) that primarily evaluated bronchodilator efficacy, and two were 1-year trials (205.254 and 205.255) that evaluated both bronchodilator efficacy and COPD exacerbations. The two 12-week trials (205.251 and 205.252) also included an ipratropium active control group. All patients received as needed albuterol MDI inhalers as a rescue medication.

The enrollment criteria and patient population for all of these trials was generally similar. Patients were older adults with a diagnosis of moderate to severe COPD (FEV_1 ≤60% predicted). All were current or former smokers. Both of the 1-year trials were multinational and both included patients from the US. In contrast, one of the 12-week studies was conducted in Europe while the other was conducted in North America.

6.1.4 Efficacy Findings

6.1.4.1 Trough FEV_1

In each of the four pivotal studies (205.251, 205.252, 205.254, and 205.255), both tiotropium groups were superior to placebo for the primary endpoint, trough FEV_1 response at the end of treatment. In addition, in the 12-week studies (205.251 and 205.252) both tiotropium groups were superior to ipratropium for trough FEV_1 response at the end of treatment. The treatment difference from placebo ranged from 0.109 to 0.142L for tio R5 and 0.115 to 0.177L for tio R10. This difference was statistically significant in all cases at $p < 0.005$. Means were adjusted for center, smoking status at entry and baseline value. While tio R10 was generally numerically superior to tio R5, the differences were generally small and not statistically significant. The mean treatment differences and 95% confidence intervals for each study are presented in Table 8.

Table 8: Spiriva Respimat Pivotal Studies FEV_1 trough response [L] treatment difference

Protocol number	Treatment comparison	Test day	Treatment difference Mean	SE	95% C.I.	p-value*
205.251	Tio R5 – Placebo	85	0.109	0.037	(0.036, 0.181)	0.0034
	Tio R10 – Placebo	85	0.177	0.036	(0.106, 0.249)	<.0001
205.252	Tio R5 – Placebo	85	0.124	0.029	(0.067, 0.181)	<.0001
	Tio R10 – Placebo	85	0.115	0.029	(0.057, 0.173)	0.0001
205.254	Tio R5 – Placebo	337	0.142	0.019	(0.104, 0.181)	<.0001
	Tio R10 – Placebo	337	0.161	0.020	(0.123, 0.200)	<.0001
205.255	Tio R5 – Placebo	337	0.113	0.017	(0.078, 0.147)	<.0001
	Tio R10 – Placebo	337	0.140	0.017	(0.106, 0.175)	<.0001

* Based on a two sided test

All values in this table are based on an ANCOVA analysis with terms for treatment, smoking status at entry, center, and baseline value. A separate ANCOVA is fitted at each time point.

6.1.4.2 FEV_1 AUC and peak response

For the 1-year studies (205.254 and 205.255), the mean FEV_1 $AUC_{(0\text{-}3h)}$ response for the tiotropium groups ranged from 0.181 to 0.272L above the baseline value and was generally consistent throughout the treatment period. The response for the placebo group was approximately 0.200L less than that seen for the active treatment groups. The differences between the tiotropium groups and placebo were highly statistically significant ($p<0.0001$). A similar treatment difference was observed by Day 85 in the 12-week trials (205.251 and 205.252).

For the 1-year studies (205.254 and 205.255), the mean FEV_1 $peak_{(0\text{-}3h)}$ response for the tiotropium groups ranged from 0.258 to 0.360L above the baseline value and was generally consistent throughout the treatment period. The response for the placebo group was approximately 0.200L less than that seen for the active treatment groups. The differences between the tiotropium groups and placebo were highly statistically significant ($p<0.0001$). A similar treatment difference was observed by Day 85 in the 12-week trials (205.251 and 205.252).

For Protocol 205.251, the effects of tiotropium on FEV_1 did not appear to reach steady state within the 12 weeks of the study. For Protocol 205.252, the effects of tiotropium on FEV_1 appeared to reach steady state by Day 8 of the study. For both of the 1-year studies (205.254 and

205.255), the effects of tiotropium on FEV_1 appeared to reach steady state after 15 days of dosing.

The Applicant proposes the following language in the label: (b) (4) (b) (4) (b) (4) See Table 9 and Table 10. See also Section 5.3.3 for a discussion of tolerance.

Table 9: Spiriva Respimat pivotal studies peak response [L] on each test day

Response	Test Day	Tio R5 (N = 324) Mean (SE)		Tio R10 (N = 324) Mean (SE)		Placebo (N = 307) Mean (SE)	
Protocol 205.251							
Peak(0-6h)	1	0.324	(0.022)	0.356	(0.021)	0.211	(0.021)
	8	0.306	(0.026)	0.351	(0.026)	0.196	(0.026)
	29	0.344	(0.032)	0.385	(0.031)	0.183	(0.031)
	57	0.345	(0.033)	0.452	(0.033)	0.200	(0.033)
	85	0.349	(0.032)	0.432	(0.032)	0.179	(0.032)
Protocol 205.252							
Peak(0-6h)	1	0.277	(0.015)	0.291	(0.015)	0.116	(0.015)
	8	0.304	(0.021)	0.314	(0.021)	0.053	(0.022)
	29	0.288	(0.021)	0.303	(0.021)	0.085	(0.022)
	57	0.270	(0.023)	0.313	(0.024)	0.077	(0.024)
	85	0.303	(0.023)	0.286	(0.024)	0.088	(0.024)
Protocol 205.254							
Peak (0-3h)	1	0.289	(0.011)	0.317	(0.011)	0.126	(0.011)
	15	0.342	(0.013)	0.347	(0.013)	0.129	(0.014)
	57	0.331	(0.014)	0.360	(0.014)	0.118	(0.015)
	113	0.322	(0.015)	0.327	(0.015)	0.094	(0.016)
	169	0.326	(0.015)	0.318	(0.015)	0.098	(0.015)
	225	0.318	(0.015)	0.315	(0.015)	0.090	(0.016)
	281	0.301	(0.015)	0.309	(0.015)	0.079	(0.016)
	337	0.288	(0.015)	0.305	(0.015)	0.064	(0.016)
Protocol 205.255							
Peak (0-3h)	1	0.274	(0.009)	0.298	(0.009)	0.120	(0.009)
	15	0.328	(0.012)	0.342	(0.012)	0.115	(0.013)
	57	0.317	(0.014)	0.330	(0.014)	0.110	(0.014)
	113	0.313	(0.013)	0.318	(0.013)	0.096	(0.014)
	169	0.300	(0.014)	0.317	(0.014)	0.090	(0.014)
	225	0.279	(0.014)	0.315	(0.014)	0.079	(0.014)
	281	0.267	(0.013)	0.278	(0.013)	0.061	(0.013)
	337	0.258	(0.014)	0.281	(0.014)	0.061	(0.014)

The common baseline mean obtained at the -10 minute time point of Test Day 1 was 1.225L for Protocols 205.251 and 205.252, 1.077 for Protocol 205.254, and 1.060L for Protocol 205.255.

The means are adjusted for center, smoking status at entry and baseline value.

A separate ANCOVA was fitted at each time point.

Table 10: Spiriva Respimat pivotal studies FEV_1 response [L] on Day 1

Day 1 Time point		Tio R5 Mean	Tio R5 Change from Baseline	Tio R5 % Change	Placebo Mean	Placebo Change from Baseline	Placebo % Change
Protocol 205.251							
Mins:	5	1.279	0.054	4.4	1.259	0.034	2.8
	15	1.346	0.121	9.9	1.291	0.066	5.4
	30	1.375	0.150	12.2	1.306	0.081	6.6
Hrs:	1	1.392	0.167	13.6	1.311	0.086	7.0
	2	1.440	0.215	17.6	1.326	0.101	8.2
	3	1.454	0.229	18.7	1.329	0.104	8.4
	4	1.455	0.230	18.8	1.327	0.102	8.3
	5	1.458	0.233	19.0	1.328	0.103	8.4
	6	1.457	0.232	18.9	1.322	0.097	7.9
Protocol 205.252							
Mins:	5	1.079	0.064	6.3	1.015	0	0
	15	1.119	0.104	10.2	1.034	0.019	1.9
	30	1.156	0.141	13.9	1.040	0.025	2.5
Hrs:	1	1.180	0.165	16.2	1.058	0.043	4.2
	2	1.208	0.193	19.0	1.048	0.033	3.3
	3	1.214	0.199	19.6	1.028	0.013	1.3
	4	1.220	0.205	20.2	1.034	0.019	1.9
	5	1.221	0.206	20.3	1.020	0.005	0.5
	6	1.218	0.203	20.0	1.016	0.001	0.1
Protocol 205.254							
Mins:	5	1.138	0.061	5.7	1.096	0.019	1.8
	30	1.224	0.147	13.6	1.110	0.033	3.1
Hrs:	1	1.267	0.190	17.6	1.121	0.044	4.1
	2	1.310	0.233	21.6	1.132	0.055	5.1
	3	1.321	0.244	22.7	1.132	0.055	5.1
Protocol 205.255							
Mins:	5	1.116	0.056	5.3	1.073	0.013	1.2
	30	1.214	0.154	14.5	1.091	0.031	2.9
Hrs:	1	1.257	0.197	18.6	1.101	0.041	3.9
	2	1.284	0.224	21.1	1.117	0.057	5.4
	3	1.289	0.229	21.6	1.116	0.056	5.3

Means are adjusted for center, smoking status at entry, and baseline value. A separate ANCOVA was fitted to each time point.

Reviewer comment:

The AUC and peak FEV_1 from the 1-year studies are not completely comparable to those obtained in the 12 week studies. For the 12-week studies (205.251 and 205.252), AUC and peak FEV_1 were measured over 6 hours rather than 3 hours as in the 1-year studies (Protocols 205.254 and 205.255).

The labeling statement (b) (4) *parallels labeling for Spiriva HandiHaler. Although descriptions of response* (b) (4) *are not typical bronchodilator labeling claims, in this case the data may be useful to the prescribing physician in order to assure that patients are not using this product as an acute reliever medication. Based on the results of the combined 1-year trials (205.254 and 205.255 presented as Protocol 205.9992) the Applicant's statement regarding* (b) (4) *change from placebo are accurate, although this reviewer calculated the percentage change as slightly lower (11% and 17% respectively). This small difference might be due to use of the baseline mean for the tio R5 group as opposed to the baseline mean for the group as a whole used by the reviewer for the denominator in this calculation. [Module 5, Volume 1.22, Study report 205.9992, page 145, Table 15.2.1:3]*

The Applicant proposes the following figures in the label:

(b) (4)

Reviewer comment:

Since the studies are evaluated as stand alone efficacy trials with respect to FEV_1, (b) (4) *In general, the Division prefers to include figures from one representative trial.* (b) (4)

(b) (4)

6.1.4.3 FVC

In the 1-year studies (205.254 and 205.255), the FVC results generally paralleled the FEV_1 results. The difference in FVC between the tiotropium groups and placebo were statistically significant ($p<0.0001$) at all time points post-dose on all test days. In general, the tio R10 group showed some improvement over the tio R5 group, but the differences were small and not significant. In the 12-week studies, results were more variable, but a significant difference from placebo was demonstrated for most time points. See Table 11 for trough FVC results.

Table 11: Spiriva Respimat Pivotal Studies FVC trough response [L] treatment difference

Protocol number	Treatment comparison	Test day	Treatment difference			p-value*
			Mean	SE	95% C.I.	
205.251	Tio R5 – Placebo	85	0.073	0.064	(-0.053, 0.199)	ns
	Tio R10 – Placebo	85	0.146	0.064	(0.021, 0.271)	0.02
205.252	Tio R5 – Placebo	85	0.191	0.067	(0.059, 0.232)	0.005
	Tio R10 – Placebo	85	0.230	0.068	(0.096, 0.364)	0.0008
205.254	Tio R5 – Placebo	337	0.178	0.039	(0.102, 0.254)	<.0001
	Tio R10 – Placebo	337	0.323	0.039	(0.247, 0.400)	<.0001
205.255	Tio R5 – Placebo	337	0.240	0.037	(0.168, 0.312)	<.0001
	Tio R10 – Placebo	337	0.252	0.037	(0.180, 0.324)	<.0001

* Based on a two sided test; ns=not significant

All values in this table are based on an ANCOVA analysis with terms for treatment, smoking status at entry, center, and baseline value. A separate ANCOVA is fitted at each time point.

6.1.4.4 Rescue medication use

In the 12-week studies (205.251 and 205.252) for all treatment groups combined, albuterol was used an average of 2.6-2.9 occasions/day at baseline. All active treatment groups showed a numerical decrease in the use of albuterol rescue throughout the study, ranging from 0.1-1.0 fewer rescue uses per day compared to placebo. The difference was statistically significant compared to placebo for tio R10 for most weeks, but not for tio R5 (significant only a few weeks in 1 of 2 trials) or ipratropium (not significant in either trial). [Module 5, Volume 1.6, Study report 205.251, pages 105-106] [Module 5, Volume 1.9, Study report 205.252, pages 108-109]

In the 1-year studies for all treatment groups combined, albuterol was used an average of 2.5-2.7 occasions/day at baseline. Compared to placebo, both tiotropium groups showed a significant decrease in the use of albuterol rescue throughout the study, ranging from 0.3-1.0 fewer rescue uses per day. [Module 5, Volume 1.11, Study report 205.254, pages 135-136] [Module 5, Volume 1.14, Study report 205.255, pages 132-133]

Reviewer comment:

The labeling language proposed by the Applicant is supported by the Phase 3 data. The reduction in rescue medication use observed in the 12-week studies was similar in magnitude to that of the 1-year studies. It did not reach statistical significance in the 12-week trials due to the smaller sample size enrolled.

6.1.4.5 Efficacy in special populations

Efficacy was analyzed in a variety of special groups and situations for the 1-year trials (205.254 and 205.255). These included intrinsic factors of gender, age, race, and disease severity. Extrinsic factors of steroid use at baseline, xanthene use at baseline, and smoking status were also assessed. Efficacy measurements of spirometry, TDI, SGRQ, and COPD exacerbations were evaluated. [Integrated Summary of Efficacy, Module 2, Volume 1.2, Section 2.7.3., pages 169-199]

Gender analysis

In the 1-year studies, approximately 75% of patients were male. The response profiles suggest that tio R5 and tio R10 were effective for both men and women. There was a suggestion that bronchodilator effect in men was greater for tio R10 than for tio R5, although the difference was small. There was no suggestion of a difference between tio R10 and tio R5 for women.

Age analysis

In the 1-year studies (205.254 and 205.255), 55% of patients were 65 years of age or older at the time of the screening visit. The response profiles suggest that tio R5 and tio R10 were effective for both patients under 65 years of age and for those 65 years and older. The Applicant notes that the treatment effects was more pronounced in the younger age group for FEV_1, SGRQ and TDI, but was more pronounced in the older age group for COPD exacerbations.

Reviewer comment:

This analysis was likely confounded by disease severity. Since COPD is a progressive disease, older patients are more likely to have more severe COPD at baseline. Severe disease tends to have a smaller absolute response to bronchodilators and present with an increased number of exacerbations. This pattern was observed for the tiotropium interaction with disease severity.

Race analysis

Since 98% of patients reporting race in the 1-year studies were white, meaningful subgroup analyses could not be made.

Disease severity analysis

Patients were divided into 3 subgroups to assess interactions with disease severity based on the Global Obstructive Lung Disease (GOLD) criteria for post-bronchodilator FEV_1. Groups included: GOLD Stage I and II ($FEV_1 \geq 50\%$ predicted), GOLD Stage III (FEV_1 30 - <50% predicted), GOLD Stage IV (FEV_1 <30% predicted). The mean baseline FEV_1 for patients in the 1-year studies (205.254 and 205.255) was 1.34, 0.97, and 0.67L for patients categorized as Stage I/II, III, and IV, respectively. Not surprisingly, those patients with the highest baseline FEV_1 had the largest treatment effect. However, patients receiving tiotropium had an improvement in FEV_1 compared to placebo across all disease severities. Patients in the most severe disease category had the largest number of COPD exacerbations and the greatest effect of tiotropium in decreasing exacerbations.

Drug interaction analysis

No difference was observed in response to tiotropium between patients taking xanthenes and not taking xanthenes. Likewise, there was no difference in response between patients taking low dose oral or inhaled steroids and those who were not, and also no difference based on active smoking status.

6.1.5 Clinical Microbiology

No clinical microbiology data is applicable to this NDA.

6.1.6 Efficacy Conclusions: maintenance treatment of bronchospasm indication

The results of the Phase 3 clinical trials including the primary endpoint trough FEV_1 are sufficient to form the basis of approval for Spiriva Respimat 5mcg once daily for the indication maintenance treatment of bronchospasm associated with COPD. In all four primary pivotal studies (205.251, 205.252, 205.254, and 205.255) a small, clinically insignificant efficacy advantage of tio R10 was demonstrated over tio R5, suggesting that tio R5 is at the plateau of the dosing curve.

In each of the four pivotal studies (205.251, 205.252, 205.254, and 205.255), both tiotropium groups were superior to placebo for the primary endpoint, trough FEV_1 at the end of treatment. In addition, in the 12-week studies (205.251 and 205.252) both tiotropium groups were superior to ipratropium for trough FEV_1 at the end of treatment. While tio R10 was generally numerically superior to tio R5, the differences were generally small and not statistically significant. Overall, these data are sufficient to support an efficacy claim for the maintenance treatment of bronchospasm associated with COPD. Because the primary endpoint was evaluated at the end of the 24-hour dosing interval and the active pharmaceutical ingredient, tiotropium bromide, is currently approved for once daily dosing, a once daily dosing regimen for tiotropium Respimat is supported.

For the 1-year studies (205.254 and 205.255), the differences between the tiotropium groups and placebo were also highly statistically significant ($p<0.0001$) for mean FEV_1 $AUC_{(0\text{-}3h)}$ response and mean FEV_1 $peak_{(0\text{-}3h)}$ response throughout the treatment period. A similar treatment difference was observed by Day 85 in the 12-week trials (205.251 and 205.252). Based on the 1-year studies (205.254 and 205.255), the effects of tiotropium on FEV_1 appeared to reach steady state after 15 days of dosing.

In the 1-year studies (205.254 and 205.255), the FVC results generally paralleled the FEV_1 results. The difference in FVC between the tiotropium groups and placebo were statistically significant ($p<0.0001$) at all time points post-dose on all test days. In general, the tio R10 group showed some improvement over the tio R5 group, but the differences were small and not significant. In the 12-week studies, results were more variable, but a significant difference from placebo was demonstrated for most time points.

Other secondary efficacy variables including peak expiratory flow rate (PEFR), St. George Respiratory Questionnaire (SGRQ), and Mahler Transitional Dyspnea Index (TDI) were generally supportive of efficacy of Spiriva Respimat.

In the 1-year studies for all treatment groups combined, albuterol was used an average of 2.5-2.7 occasions/day at baseline. Compared to placebo, both tiotropium groups showed a significant decrease in the use of albuterol rescue throughout the study, ranging from 0.3-1.0 fewer rescue uses per day.

Reviewer comment:

The results of the Phase 3 studies including the primary endpoint trough FEV_1 are sufficient to form the basis of approval for Spiriva Respimat 5mcg once daily for the indication maintenance treatment of bronchospasm associated with COPD. The labeling language regarding rescue medication use proposed by the Applicant is supported by the Phase 3 data.

6.2 Indication: prevention of COPD exacerbations

Although the Applicant has not formally listed prevention of COPD exacerbations as an indication, the Applicant has proposed the following language in the clinical studies section of the label: (b) (4) ”

6.2.1 Methods

Efficacy was assessed with two replicative 1-year double-blind, placebo-controlled clinical trials (205.254 and 205.255). These studies had identical protocols and a pre-specified combined analysis for the fourth primary endpoint, number of COPD exacerbations occurring in a year. Secondary endpoints related to COPD exacerbations were also combined.

As a second study in support of the COPD exacerbation indication, the Application completed Protocol 205.266, a 6-month double-blind trial in a US Veterans Affairs population comparing Spiriva HandiHaler (tio HH18) to placebo (Protocol 205.266). Similar but not identical endpoints to the Respimat 1-year trials (Protocols 205.254 and 205.255) were included.

Reviewer comment:

Although both Spiriva Respimat and Spiriva HandiHaler contain the same drug substance, the Division of Pulmonary and Allergy Drug Products considers them to be different products from an efficacy standpoint because they use a different delivery device and formulation. As such, support of the Respimat efficacy claim with HandiHaler data is not appropriate and depends on the data submitted with Spiriva Respimat.

In the pre-NDA meeting held with the Applicant on April 14, 2005, the Division provided the following guidance: “If you show a statistically and clinically significant reduction in COPD

exacerbations in the combined one-year trials (205.254 and 205.255) and substantiate the finding in a second clinical trial, we would consider describing the finding in the product label. Whether 205.266 provides adequate data to substantiate the finding will be a review issue. In addition, the exact wording in the product label will be a review issue."

Since the second study submitted in the NDA in support of a COPD exacerbation claim cannot be used to support efficacy, the application was reviewed in two different ways to determine if an efficacy claim could be supported with available data. These included: 1) consideration of combined clinical trial data resulting in a single clinical trial to support the indication, and 2) consideration of data from each trial separately resulting in two smaller clinical trials to support the indication. The Division requested the separate trial analyses from the Applicant as these were not submitted as part of the original NDA, since the statistical analysis plans for the studies specified combining the data for this endpoint.

6.2.2 General Discussion of Endpoints

Endpoints related to COPD exacerbations included the following:

- number of COPD exacerbations occurring in a year (Primary)
- number of patients with at least one COPD exacerbation, time to first exacerbation, and number of exacerbation days
- number of patients with at least one hospitalization for COPD exacerbations, time to first hospitalization associated with COPD exacerbations, number of hospitalizations, and number of hospitalization days due to COPD exacerbations during the treatment period

For the purposes of this study, COPD was defined as "a complex of respiratory events/symptoms with a duration of three days of more requiring a change in 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
- 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)

The onset of an exacerbation was defined by the onset of the first recorded symptom. The end of the exacerbation was recorded as defined by the investigator.

Reviewer comment:

The definition of COPD includes both a change in symptoms and a treatment requirement. Inclusion of both components of the definition is likely to increase uniformity in the study, as therapy patterns are known to vary across geographic regions. The time between exacerbations was not defined. Ideally, this is specified as at least 7 days to assure that an exacerbation is truly resolved before counting a second event. The definition is similar to that used in the Advair program to form the basis of approval of a COPD exacerbation claim.

COPD symptom scores were recorded by the investigator in four categories: wheezing, shortness of breath, coughing, and tightness of chest. The scores were based on the investigator's assessment of the patient's condition during the week just prior to the visit and were evaluated just prior to PFTs. The severity of symptoms was rated on a four-point scale as follows:

- not present = no symptoms
- mild = awareness of symptom which is easily tolerated
- moderate = discomfort enough to cause interference with usual activity
- severe = incapacitating with inability to do work or usual activity

COPD exacerbations were analyzed per protocol using the Kruskal-Wallis and Wilcoxon-Mann-Whitney tests for differences in location. Since the incidence rates depend on the extent of exposure, the numbers of exacerbations were calculated per day of extent of exposure for each patient in each treatment group. A Poisson regression analysis accounting for overdispersion (increased variance of data compared to the mean) was also used, but was not pre-specified.

6.2.3 Study Design

The study designs are discussed in Section 6.1.3.

6.2.4 Efficacy Findings

6.2.4.1 Study 205.254

At the request of FDA, the Applicant also provided an analysis of COPD exacerbations found in the individual studies, previously provided only as part of the statistical documentation. For Study 205.254, results show a mean exacerbation rate per patient year of 0.72 for tio R5 compared to 0.91 for placebo, with a 95% CI of 0.63-0.99 (p=0.45). The time to first exacerbation for patients in the tio R5 group was 173 days compared to 112 days for placebo (p=0.09). See Table 12. Evaluation of parameters per number of days on therapy was used to correct for the greater number of discontinuations and shorter treatment duration observed in the

placebo group. According to the statistical reviewer, Ruthanna Davi, this is a reasonable correction. Secondary efficacy endpoints were not reported for the individual studies.

Table 12: Protocol 205.254 COPD exacerbation rates and time to first exacerbation (Poisson regression)

	Tio R5	Placebo
Number of patients		
exposed to randomized treatment	332	319
at least one COPD exacerbation	127	131
% of patients with exacerbations	38%	41%
Mean treatment exposure (days)	307	272
Exacerbation rate per patient year		
Mean	0.72	0.91
Rate ratio (RR) versus placebo	0.79	
95% CI for RR	0.63-0.99	
p-value for RR	0.045	
Time to first exacerbation (days)		
Lower quartile	173	112
p-value versus placebo	0.09	

Reviewer comment:

According to the statistical reviewer, Ruthanne Davi, correcting the parameters per number of days of therapy is a reasonable correction. The study reaches statistical significance for the exacerbation rate per patient year but not for time to first exacerbation, although the trend is in the right direction. Only about 1/3 of patients in the study experienced an exacerbation. The difference between tio R5 and placebo was 0.19 events/patient year. In contrast, the exacerbation rate in a study of salmeterol/fluticasone (Advair) that formed the basis of approval for a COPD exacerbation claim for this compound, approximately 70% of patients experienced an exacerbation over 3 years. However, the difference in exacerbation rates per patient year in the Advair program is comparable (0.28 and 0.33). Of note, the Division also requested individual study data for the tio R10 group. This data is still pending from the Applicant as of the finalization of this review.

The analysis provided by the Applicant in response to the FDA request was performed using a Poisson regression model with correction for overdispersion (increased variance in data compared to the mean). While this is a valid method according to the statistical reviewer, it was not prespecified in the protocol. Evaluating the data using the protocol specified Wilcoxin-Mann-Whitney test, which is what was used for the combined analysis, gives a mean COPD exacerbation rate of 0.77 in the tio R5 group, 0.83 in the tio R10 group, and 1.88 in the placebo group. Based on this result, neither tiotropium group had a statistically significant difference from placebo (0.18 and 0.07 for tio R5 and tio R10, respectively).

Although a statistically significant result was obtained for the primary endpoint using the Poisson regression analysis, evaluating the data with a different statistical test suggests that the results are not robust.

6.2.4.2 Study 205.255

In study 205.255, results demonstrated a mean exacerbation rate per patient year of 0.85 for tio R5 compared to 1.10 for placebo, with a 95% CI of 0.62-0.96 (p=0.02). The time to first exacerbation for patients in the tio R5 group was 149 days compared to 74 days for placebo (p <0.0001). See Table 13. Evaluation of parameters per number of days on therapy was used to correct for the greater number of discontinuations and shorter treatment duration observed in the placebo group. According to the statistical reviewer, Ruthanne Davi, this is a reasonable correction.

Table 13: Protocol 205.255 COPD exacerbations rates and time to first exacerbation (Poisson regression)

	Tio R5	Placebo
Number of patients		
exposed to randomized treatment	338	334
at least one COPD exacerbation	122	157
% of patients with exacerbations	36%	47%
Mean treatment exposure (days)	302	259
Exacerbation rate per patient year		
Mean	0.85	1.10
Rate ratio (RR) versus placebo	0.77	
95% CI for RR	0.62-0.96	
p-value for RR	0.02	
Time to first exacerbation (days)		
Lower quartile	149	74
p-value versus placebo	<0.0001	

<u>*Reviewer comment:*</u>

The study reaches statistical significance for both the exacerbation rate as well as time to first exacerbation. Only about 40% of patients in the study experienced an exacerbation. The difference between tio R5 and placebo was 0.25 events/patient year. In contrast, the exacerbation rate in a study of salmeterol/fluticasone (Advair) that formed the basis of approval for a COPD exacerbation claim for this compound, approximately 70% of patients experienced an exacerbation over 3 years. However, the difference in exacerbation rates per patient year in the Advair program is comparable (0.28 and 0.33). Of note, the Division also requested individual study data for the tio R10 group. This data is still pending from the Applicant as of the finalization of this review.

The analysis provided by the Applicant in response to the FDA request was performed using a Poisson regression model with correction for overdispersion (increased variance in data compared to the mean). While this is a valid method according to the statistical reviewer, it was not prespecified in the protocol. Evaluating the data using the protocol specified Wilcoxin-Mann-Whitney test, which is what was used for the combined analysis, gives a mean COPD exacerbation rate of 1.1 in the tio R5 group, 1.21 in the tio R10 group, and 1.95 in the placebo group. Based on this result, both tiotropium groups had a statistically significant difference from placebo (0.0034 and 0.0036 for tio R5 and tio R10, respectively).

In this study, both statistical methodologies give significant results for the tiotropium groups compared to placebo.

6.2.4.3 Combined studies 205.254 and 205.255 (Study report 205.9992)

The protocols and statistical analysis plan for the combined 1-year studies (205.254 and 205.255) prespecified that the combined data set would be utilized for the analysis. Since the incidence rates depend on the extent of exposure, the number of COPD exacerbations was calculated per day of extent of exposure for each patient in each treatment group. This analysis was also performed without any adjustment for the number of days the patient was on randomized treatment.

The mean COPD exacerbation rate per patient year for all patients in the study was 0.93 for the tio R5 group, 1.02 for the tio R10 group, and 1.91 for the placebo group. This result is statistically significant for both tiotropium groups compared to placebo (p=0.002 and p=0.0008, respectively). The effect is smaller when not adjusted for treatment days, but is still present. See Table 14.

The number of exacerbations per patient during the treatment period ranged from 0 to 7 for the tiotropium groups and from 0 to 6 for the placebo group. However, there were fewer patients in the tiotropium groups with any exacerbations compared to the placebo group, with 37.2% of the tio R5 group, 36.9% of the tio R10 group, and 44.1% of the placebo group having at least 1 exacerbation. This difference is statistically significant at p=0.0031 and p=0.0028 for tio R5 and tio R10, respectively. Because the majority of patients had no exacerbations, the median number of exacerbations is zero for all treatment groups.

The distribution of intensity of exacerbations was similar within each of the treatment groups with approximately 60% being classed as moderate, 25% as mild, and 15% as severe. The average number of days of corticosteroids per exacerbation was similar for all three treatment groups, 4.5 days. The two tiotropium groups had on average a numerically greater number of days of antibiotic use per exacerbation compared to placebo (tio R5 = 6.7 days, tio R10 = 6.4 days, and placebo 5.4 days). This difference was not statistically significant. There were no differences between the groups in hospitalizations for COPD exacerbations or all cause hospitalizations.

Table 14: Combined 1-year studies (205.254 and 205.255) COPD exacerbations

	Tio R5 N=670	Tio R10 N=667	Placebo N=653
COPD exacerbation rate			
Mean	0.93	1.02	1.91
p-value vs. placebo	0.0020	0.0008	
Number of COPD exacerbations			
Mean	0.66	0.59	0.73
p-value vs. placebo	0.0002	<.0001	
Time to first COPD exacerbation			
Lower Quartile	160	178	86
p-value vs. placebo	<.0001	<.0001	
Number of patients with at least one COPD exacerbation			
N (%)	249 (37.2%)	246 (36.9%)	288 (44.1%)
p-value vs. placebo	0.0031	0.0028	
% of time in COPD exacerbation			
Mean	4.0	3.9	5.6
p-value vs. placebo	0.0089	0.0027	

Reviewer comment:

In general, the definition of COPD exacerbation is appropriate, taking into consideration both symptoms and treatment. The number of days between exacerbations is not specified, which could be a confounding factor. If a patient "recovers" from an exacerbation then has a second exacerbation within a day or two, this likely represents a continuation of the first event rather than a second, distinct exacerbation.

According to the FDA statistical reviewer, Dr. Ruthanna Davi, there were 17 instances of exacerbations with a start date occurring less than 7 days after the ending date of a previous exacerbation. These instances occurred once in each of 9 placebo patients, 3 tio R5 patients, and 5 tio R10 patients. Given the low incidence of such events, if a 7-day between exacerbation definition were applied, there would likely be little impact on the results, with a slightly greater benefit seen in the tiotropium groups. Therefore, the limitation in definition as a potential confounder does not bias the outcome of this study.

At the request of the Division, the Applicant provided a subgroup analysis of the primary endpoint, COPD exacerbation rate for the combined data sets for studies 205.254 and 205.255 for patients both inside and outside of the United States. See Table 15. *A numerically lower exacerbation rate in the tiotropium groups compared to placebo was shown for both US and non-US sites. This difference did not reach statistical significance in the US sites, as the sample size was not powered to show this effect in subgroups. Of note, the overall exacerbation rate was lower for all treatment groups in the US compared to non-US sites, although the magnitude of change with tiotropium compared to placebo was similar (21% fewer exacerbations in the US versus 22% outside the US).*

Table 15: Combined 1-year studies (205.254 and 205.255) COPD exacerbation rate (per year) and rate ratios for US and non-US sites

Treatment	N	Mean rate [rate ratio]	95% CI	p-value
		US sites		
Tio R5	110	0.62	0.46, 0.84	
Tio R10	107	0.66	0.50, 0.89	
Placebo	99	0.78	0.58, 1.06	
Tio R5 vs. placebo		[0.79]	0.52, 1.21	0.28
Tio R10 vs. placebo		[0.85]	0.56, 1.29	0.44
		Non-US sites		
Tio R5	560	0.81	0.72, 0.92	
Tio R10	560	0.74	0.65, 0.84	
Placebo	554	1.04	0.92, 1.17	
Tio R5 vs. placebo		[0.78]	0.66, 0.93	0.005
Tio R10 vs. placebo		[0.71]	0.60, 0.85	0.0002

6.2.5 Clinical Microbiology

No clinical microbiology data is applicable to this NDA.

6.2.6 Efficacy Conclusions: COPD exacerbation indication

Looking at the two studies individually, one study shows a significant improvement over placebo and one study shows borderline significance. Since reduction of COPD exacerbations is an important claim, the results are not sufficient to demonstrate reproducibility of results in two studies.

Looking at the two studies combined, as they were designed, the efficacy results regarding COPD exacerbations are much more robust, although insufficient to support an efficacy claim as a single study. In combination with a second Respimat study demonstrating efficacy with regards to COPD exacerbations, this combination study would support (b) (4) the claim that Spiriva Respimat "significantly reduced the number of COPD exacerbations compared to placebo" (b) (4) (b) (4).

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety review was generally grouped by study type, with pooling of data from the replicative 4-week crossover (205.249 and 205.250), 12-week (205.251 and 205.252), and 1-year studies (205.254 and 205.255), respectively. In general, additional analyses were only performed on the 1-year trials, as data from these trials represented the greatest safety exposure in the Spiriva Respimat program.

The analysis of deaths included review of study reports, narratives, and case report forms for all patients with adverse events resulting in death. Particular attention was given to the study report for Protocol 205.392, submitted as part of the 4-month safety update. Protocol 205.392 was a retrospective follow up of all patients discontinuing from the two 1-year studies (205.254 and 205.255). The reviewer also performed adjudication of all causes of death occurring in the 1-year studies and follow up (Protocols 205.254, 205.255, and 205.392) as well as an analysis of death by country.

7.1.1 Deaths

An imbalance in deaths in the 1-year studies was noted upon unblinding. The Applicant submitted a summary of mortality data from these trials to the FDA in November 2005. Because there was a marketed product containing the same drug substance (tiotropium HandiHaler), this issue was reviewed by the Drug Safety Oversight Board on June 15, 2006. The committee

recommended additional follow up on the discontinued patients to ascertain if differential discontinuation rates accounted for the mortality imbalance. The Applicant obtained this data as part of Study 205.392, which is reviewed in detail in Section 7.2.2.1. Because the majority of deaths in the Respimat program occurred in the 1-year trials, the focus of this safety discussion will be on data from these trials and the follow up.

7.1.1.1 Number of deaths

Number of deaths in the Spiriva Respimat Phase 3 program overall

In the Integrated Summary of Safety, the applicant reports a total of 40 deaths in the Phase 3 Spiriva Respimat clinical program. Of these, 34 occurred during the 1-year trials (205.254 and 205.255), 3 in 12-week trials (205.251 and 205.252), and 3 in the 4-week crossover trials (205.249 and 205.250). See Table 16 for a summary of deaths by study and treatment group. [Module 2, Volume 1.2, Section 2.7.4. Integrated Summary of Safety, p. 66-67]

Reviewer comment:

The total number of deaths in the study reports of the Phase 2/3 trials differs from the total in the ISS. There were a total of 42 deaths recorded in the primary study reports for the Phase 2/3 Spiriva Respimat program. Thirty-four of them occurred during the 1-year trials (Protocols 205.254 and 205.255), four in the 12-week trials (Protocols 205.251 and 205.252), and four in the 4-week crossover HandiHaler comparison trials (Protocols 205.249 and 205.250). Two of these deaths, both of which occurred more than 30 days after discontinuation of study medication, are not reported by the Applicant in the Integrated Summary of Safety. These patients included one who died of a CVA 8 weeks after starting the washout period following tio HH18 in Trial 205.250, and one who died of lung cancer approximately 4 ½ months after discontinuing tio R5 in Protocol 205.252. The Applicant does not discuss why these two patients were not included in the Integrated Summary of Safety, which reports the number of deaths in the Respimat program as 40, nor is a rationale for excluding these deaths clear to the reviewer. Because these two deaths were not in the 1-year trials, they will not be discussed in the following sections.

Table 16: Spiriva Respimat program deaths by study and treatment group

Protocol	Tio R5	Tio R10	Placebo	Ipratropium	Tio HH18
205.249	1	0	1	not applicable	0
205.250	1	0	0	not applicable	1†
205.251	0	1	0	0	not applicable
205.252	1†	1	0	1	not applicable
205.254	7	8	5	not applicable	not applicable
205.255	5	9	0	not applicable	not applicable
Total	**15**	**19**	**6**	**1**	**1**

†not included in analysis by Applicant

Number of deaths in the 1-year studies (205.254 and 205.255)

An imbalance in the number of deaths occurred in the Respimat program overall, favoring placebo. This was primarily driven by a very low number of deaths observed in the placebo group, particularly in Study 205.255. In the 1-year studies, there was a marked differential discontinuation rate, with increased drop outs in the placebo group, primarily due to COPD exacerbation, with 82.8% of patients in the tio R5 group, 79.6% in the tio R10 group, and only 68.6% of patients in the placebo group completing the trial per protocol. Because a greater number of patients discontinued in the placebo group from the 1-year studies (205.254 and 205.255), the Applicant postulated that the differential drop out may explain the increased mortality observed in the tiotropium groups. Based on the potential mortality signal observed in the Respimat program presented to FDA in November 2005, these data were reviewed by the FDA Drug Safety Oversight Board in June 2006. The Board recommended that all discontinued patients from the 1-year studies be followed up for outcome (vital status).

Follow up of patients who discontinued from the 1-year trials revealed an additional 10 deaths that occurred more than 30 days after discontinuation of study drug but prior to the predicted exit date (follow up Protocol 205.392). These 10 deaths that occurred during the follow-up period are discussed in detail in Section 7.2.9.1 and are not included in Table 14, above. The timing of these 10 deaths ranged from 34 to 309 days from last intake of study drug. An additional 44 deaths that occurred after the predicted exit date were reported as part of the data collection for Study 205.392. In all, vital status was determined for 411 of 456 (90.1%) discontinued patients in the study, and a total of 1945 of 1990 (97.7%) of patients overall.

Counting the number of deaths occurring in Protocols 205.254 and 205.255 depends on the definitions applied regarding date of death. See Section 7.2.9.1 for definitions. In the worst case scenario for the combined 1-year studies and follow up (Protocols 205.254, 205.255, and 205.392), 16 deaths occurred in the tio R5 group, 19 in the tio R10 group, and 9 in the placebo group. The imbalance is most notable in Protocol 205.255, with 7 deaths in the tio R5 group, 11 in the tio R10 group, and 2 in the placebo group. In the best case scenario for the combined studies, 16 deaths occurred in the tio R5 group, 18 in the tio R10 group, and 12 in the placebo group. Even in the best case scenario, an imbalance still exists in favor of placebo in terms of mortality. However, the inclusion of deaths reported in Protocol 205.392 does suggest that a portion of the imbalance found in the original studies may have been due to differential discontinuation as reported by the Applicant. The retrospective collection of data is confounded by the use of Spiriva HandiHaler after discontinuation by 33.3% of patients previously randomized to placebo.

The relative risk of death in the 1-year studies combined with inclusion of the follow up data (205.392) is 1.6 for tio R5 compared to placebo and 1.9 for tio R10 compared to placebo. Neither value reaches statistical significance, although the signal was stronger in the tio R10 group. See Table 17 for a summary of mortality relative risk and excess incidence data from the 1-year studies. Kaplan-Meier curves of time to death are presented in Figure 5 and Figure 6.

Table 17: Studies 205.254, 205.255, and 205.392 relative risk of mortality

Any Fatal Adverse Event	5 mcg Spiriva vs. Placebo		10 mcg Spiriva vs. Placebo	
	Relative Risk (95% C.I.)[2]	Excess Incidence per 1000 pt years (95% C.I.)[3]	Relative Risk (95% C.I.)[2]	Excess Incidence per 1000 pt years (95% C.I.)[3]
Study 254				
Within study	1.2 (0.4, 3.8)	3 (-20, 27)	1.4 (0.4, 4.2)	5 (-19, 28)
Follow-up	1.1 (0.4, 3.0)	2 (-22, 26)	1.1 (0.4, 2.9)	-1 (-24, 21)
Study 255				
Within study	undefined	16 (2, 30)*	undefined	27 (9, 46)*
Follow-up	3.4 (0.7, 16.5)	12 (-5, 28)	5.0 (1.1, 22.9)*	21 (2, 41)*
Studies 254 & 255 combined				
Within study	2.1 (0.7, 5.9)	10 (-4, 23)	2.9 (1.1, 8.0)*	16 (1, 31)*
Follow-up	1.6 (0.7, 3.6)	7 (-7, 21)	1.9 (0.9, 4.3)	10 (-5, 25)

[1]Kaplan-meier estimates at 366 days

[2]As estimated by Cox proportional hazards regression with treatment as independent variable, stratified by study for pooled analysis.

[3]As estimated by the difference in Kaplan-Meier estimates at 366 days, expressed per 1000 person years

* p<0.05

Figure 5: Studies 205.254, 205.255, and 205.392 Kaplan-Meier time to death for tiotropium Respimat 5 mcg versus placebo

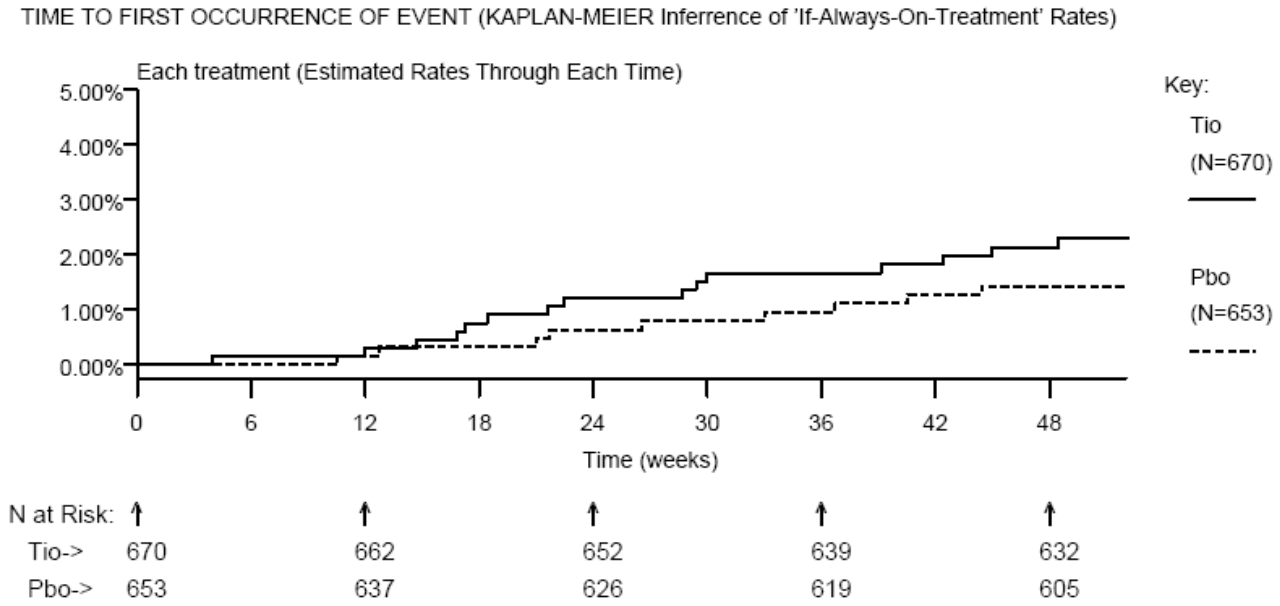
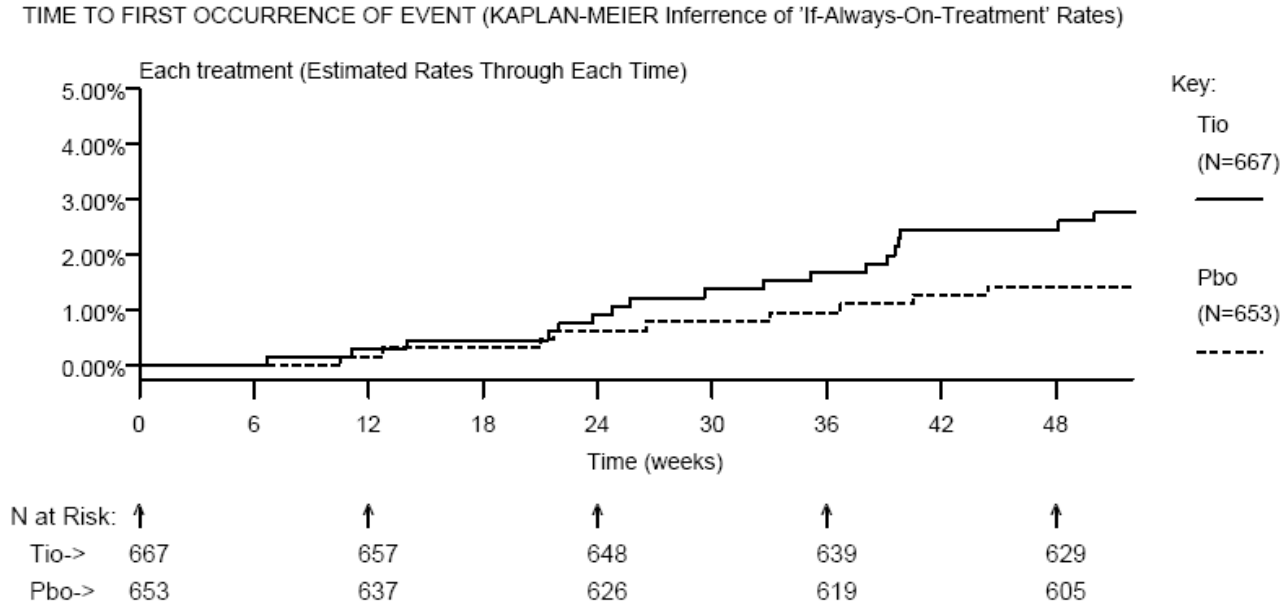


Figure 6: Studies 205.254, 205.255, and 205.392 Kaplan-Meier time to death for tiotropium Respimat 5 mcg versus placebo



7.1.1.2 Cause of death

Cause of death was not adjudicated for the Respimat program, and adverse events leading to death are listed as reported by the investigator. While some AEs were grouped according to BI collapsing rules determined prior to study unblinding, several categories are repetitive or slight variations of similar disorders. The most frequent categories of death as reported by the Applicant are cardiovascular, lower respiratory system, and death of undetermined cause. Deaths of unknown cause were not categorized as sudden deaths, although many of them may have been. See Table 18 for cause of death as reported by the Applicant. Patients in the Respimat program were generally older males with significant smoking histories and multiple co-morbid conditions, particularly cardiovascular. As such, the causes of death in these studies were not unexpected. [Module 2, Volume 1.2, Section 2.7.4. Integrated Summary of Safety, p. 68-69]

<u>*Reviewer comment:*</u>

In order to further evaluate for potential safety signals regarding cause of death, the reviewer grouped and adjudicated all deaths occurring during the 1-year trials (205.255 and 205.254) as well as in the retrospective follow-up of discontinued patients from these trials (205.392) in an unblinded fashion. This is presented in Table 41, *Section 7.2.9.1.*

Based on this review, the most frequent causes of death were undetermined and neoplasms, primarily lung cancer. COPD exacerbations and myocardial infarction were second and third most frequent, respectively. There was an imbalance in deaths due to cardiac causes (7 in the

two tiotropium groups combined compared to none in the placebo group), pneumonia (4 in the two tiotropium groups combined compared to none in the placebo groups), and undetermined causes (6 in the two tiotropium groups combined compared to 3 in the placebo group). Other causes of death were either infrequent or balanced among the treatment groups.

Comparing the causes of death to the overall adverse event database for the 1-year trials does not show a reproducible signal. Myocardial infarction was not increased as an adverse event overall in the studies. No signal regarding tachycardia, congestive heart failure, or arrhythmia is discernable. Centrally read ECGs and Holter monitors performed throughout the 1-year trials on a subset of >300 patients did not show adverse effects in the treatment groups compared to placebo. Pneumonia was only slightly increased in the adverse events (3.3% tio R5, 3.3% tio R10, 1.7% placebo), but the numbers are small thus may represent random chance. Respiratory infections as a whole were not differentially distributed.

The deaths of unknown cause all occurred at home. Attributing all of these to either MI or to CVA does not significantly change the balance, as there were none in the tio R5 group, 6 in the tio R10 group and 3 in the placebo group. In at least one case, the patient was recently discharged from the hospital with a diagnosis of respiratory failure secondary to COPD exacerbation.

Table 18: Respimat program adverse events leading to death

System organ class/ Preferred term	Tio R 5 N (%)	Tio R 10 N (%)	Tio HH 18 N (%)	IB MDI 36 N (%)	Placebo N (%)	Total N (%)
Number of patients	1036	1027	187	178	1016	2899
Total with adverse events leading to death	14 (1.4)	19 (1.9)	0 (0.0)	1 (0.6)	6 (0.6)	40 (1.4)
Cardiac disorders	3 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	6 (0.2)
Cardiac arrest	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Cardiac failure	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Coronary artery insufficiency	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Right ventricular failure	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Gastrointestinal disorders	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.1)
Gastrointestinal hemorrhage	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)
Hernial eventration	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Peritonitis	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
General disorders	1 (0.1)	6 (0.6)	0 (0.0)	0 (0.0)	2 (0.2)	9 (0.3)
Death	1 (0.1)	6 (0.6)	0 (0.0)	0 (0.0)	2 (0.2)	9 (0.3)
Neoplasms benign, malignant and unspecified	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.6)	1 (0.1)	3 (0.1)
Gastrointestinal carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Esophageal cancer metastatic	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Pancreatic carcinoma metastatic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.0)
Nervous system disorders	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.1)
Cerebral infarction	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Psychiatric disorders	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Completed suicide	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Renal and urinary disorders	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Renal failure acute	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

continued

Respimat program adverse events leading to death (continued)

System organ class/ Preferred term	Tio R 5 N (%)	Tio R 10 N (%)	Tio HH 18 N (%)	IB MDI 36 N (%)	Placebo N (%)	Total N (%)
Respiratory system disorders* (Lower)	6 (0.6)	6 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	12 (0.4)
Acute pulmonary edema	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
COPD exacerbation#	2 (0.2)	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.2)
Pneumonia#	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Respiratory failure	2 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Respiratory system disorders* (Other)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Lung neoplasm malignant	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Non-small cell lung cancer, metastatic	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Small cell lung cancer stage undetermined	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)

MedDRA version 8.0 was used for reporting.

Combined data from Phase 3 trials: 205.249, 205.250, 205.251, 205.252, 205.254, and 205.255

Percentages are calculated using total number of patients per treatment as the denominator.

#BI collapsed preferred terms include multiple MedDRA preferred terms.

*Respiratory organ system class was divided into upper, lower, and other.

One patient had 3 listed events (COPD exacerbation, hernial eventration, and pneumonia). Additionally, 2 patients had 2 listed respiratory events each. Therefore, number of patients does not equal number of events.

7.1.1.3 Deaths by country

Evaluation of deaths by country in the combined 1-year studies and follow up (Protocols 205.254, 205.255, and 205.392) demonstrated that the deaths were generally evenly distributed across geographic areas when corrected for volume of enrollment. See Table 19. The highest numbers of deaths occurred in Russia (9 deaths (4.4%) out of 205 patients enrolled), the United States (7 deaths (2.2%) out of 316 patients enrolled) and South Africa (5 deaths out of 94 patients enrolled). Of concern, 6 of the deaths of unknown cause occurred in Russia, comprising the majority of deaths in this country. The other three occurred in the US, France, and Italy.

Reviewer comment:

The largest enrolling Russian site (Moscow) had three deaths of unknown cause. An FDA DSI audit is pending at this site. The analysis presented is per reviewer, with data taken from Study Reports 205.392 and 205.9992, and assumes the worst case scenario for counting deaths.

Other than the deaths of unknown cause, no particular trends are observed in deaths by geographic region, suggesting that mortality was not influenced by site or region.

Table 19: Protocol 205.254, 205.255, and 205.392 deaths by country

Country	Enrollment	Deaths N (%)
Australia	79	1 (1.3)
Austria	60	1 (1.7)
Belgium	68	0
Canada	177	1 (0.6)
Finland	49	1 (2.0)
France	135	3 (2.2)
Germany	102	3 (2.9)
Greece	91	1 (1.1)
Ireland	19	1 (5.3)
Italy	63	1 (1.6)
Netherlands	131	2 (1.5)
New Zealand	25	1 (4.0)
Norway	45	0
Russia	205	9 (4.4)
Spain	66	3 (4.5)
South Africa	94	5 (5.3)
Sweden	29	0
Turkey	43	0
United Kingdom	193	4 (2.1)
United States	316	7 (2.2)
Total	**1990**	**44 (2.2)**

7.1.1.4 Comparison of deaths in the Respimat and HandiHaler programs

A pooled analysis of the 19 tiotropium HandiHaler Phase 3 and 4 trials of at least 4 weeks duration that used a placebo-controlled parallel group design does not demonstrate a mortality signal. The enrollment criteria for the HandiHaler trials were similar to that of the Respimat trials (adult smokers with moderate-severe COPD) and resulted in very similar demographics. All cause mortality is comparable between the HandiHaler and the Respimat, although the mortality rate for the Respimat placebo group is lower. The Respimat studies used for this comparison were the 12-week and 1-year Phase 3 studies (Protocols 205.251, 205.252, 205.254, and 205.255). See Table 20.

The Applicant also notes that there was a substantive increased use of LABAs by patients in the Respimat trials as compared to the HandiHaler trials (6.3% HandiHaler versus 29.5% Respimat). [Module 2, Volume 1.2, Section 2.7.4. Integrated Summary of Safety, p. 24-25] Although these medications were not permitted during the actual treatment period of the clinical trials, they were permitted during the follow up, and a large percentage of patients for whom data were available received LABAs after discontinuation (20.3% LABA alone, 42.9% LABA in combination with

inhaled corticosteroid). Another confounder to comparison of the Respimat versus HandiHaler programs was that 37.3% of patients for whom data were available used Spiriva HandiHaler after discontinuation from the Respimat trials. [March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, pages 47-51]

Table 20: Exposure adjusted death rates in HandiHaler versus Respimat trials

Program	HandiHaler		Respimat		
Treatment Group	Tio HH18	Placebo	Tio R5	Tio R10	Placebo
N	5437	4092	849	846	833
Exposure (pat. years)	2957	2175	669	652	583
N with Event	63	55	12	19	5
Rate/100 pat. years	2.13	2.53	1.79	2.91	0.86
RR Estimate Tio/Pbo	0.89	n/a	2.07	3.36	n/a
95% Conf. Interval	0.61-1.28	n/a	0.73-5.87	1.26-8.92	n/a

n/a=not applicable

Reviewer comment:

In order to further evaluate the potential association between Spiriva Respimat and mortality, the Applicant submitted preliminary data from a recently completed 4-year trial comparing tiotropium HandiHaler 18 mcg once daily to placebo in 5,993 patients with COPD (Study 205.235). Study 205.235 was a randomized, double-blind, placebo-controlled parallel group multi-national trial assessing the rate of decline in lung function with tiotropium in patients with moderate to severe COPD, and is also known as UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium). Enrollment criteria were generally similar to those of the Spiriva Respimat Phase 3 program. Discontinued patients were followed for vital status and the cause of all deaths were adjudicated. Because this preliminary data was submitted on July 18, 2008, less than two weeks prior to the primary review due date, no formal review of the data is presented.

According to the Applicant, the analysis of the UPLIFT data showed no increase in mortality in the tio HH18 group as compared to placebo. See Table 21.

Table 21: Protocol 205.235 (UPLIFT) Spiriva HandiHaler mortality

	Tio HH18 N (%)	Placebo N (%)	Total N (%)
Total treated	2986	3006	5992
Deaths during study	381 (12.8)	410 (13.6)	791 (13.2)
Deaths including discontinued patients	467 (15.6)	514 (17.1)	981 (16.4)

While these data are reassuring, a full review of the complete study report is required to determine if the UPLIFT data can be used to support safety regarding the potential mortality signal observed in the 1-year Spiriva Respimat studies.

7.1.1.5 Mortality conclusions

An increased number of deaths was observed in the tiotropium Respimat treatment groups compared to placebo for the 1-year studies, primarily in Protocol 205.255. Follow up and evaluation of patients who discontinued prematurely demonstrated that a portion of this mortality imbalance can be explained by differential drop outs. The remainder of the signal cannot be explained with available data. The overall percentage of patients in the tiotropium groups who died during the 1-year studies is not unexpected for the patient population, whereas the death rate in the placebo groups is unexpectedly low.

The analysis of drop outs (Protocol 205.392) was potentially confounded by use of anticholinergic medications (primarily Spiriva HandiHaler) and LABAs in a large portion of the treatment group after discontinuation. In addition, vital status could not be collected from approximately 10% of discontinued patients, which may contribute to the remaining imbalance.

Adverse events leading to death in the Respimat program are not unexpected for the patient population. The only potential exception is the large number of deaths of unknown cause. No obvious safety signal can be linked to death. Even attributing all deaths from unknown causes to a particular adverse event (myocardial infarction or stroke) does not lead to a notable imbalance. Deaths were generally distributed evenly across countries when corrected for enrollment with the exception of a large number of deaths of unknown cause in Russia.

Comparison of the Respimat studies to randomized, controlled parallel group studies in the HandiHaler program does not demonstrate a difference in mortality rates other than for the Respimat placebo group, which is lower.

Reviewer comment:

Although a portion of the mortality imbalance observed in the 1-year studies can be explained by the increased discontinuation rate in the placebo group, the remainder of the signal cannot be explained with available data. Complete results are expected in 4Q2008 from a large, 4-year study comparing Spiriva HandiHaler to placebo (UPLIFT—Understanding Potential Long-term Impacts on Function with Tiotropium, Protocol 205.235). This study will more than double the size of the safety database available for the two products. Although UPLIFT was conducted with Spiriva HandiHaler rather than Spiriva Respimat, the study will provide useful information to place the mortality data in the Spiriva Respimat program in perspective. As discussed in Section 5, Spiriva HandiHaler 18 mcg and Spiriva Respimat 5 mcg have similar systemic exposure. If confirmed by additional data, the effect of tiotropium on mortality is likely to be mediated through systemic exposure, suggesting that Spiriva HandiHaler mortality data will be relevant to the Respimat program.

7.1.2 Other Serious Adverse Events

For the combined 1-year studies (205.254 and 205.255), 17.2% of patients overall experienced a serious adverse event, 16.1% in the tio R5 group, 18.7% in the tio R10 group, and 16.8% in the placebo group. The most common serious adverse events were COPD exacerbations, pneumonia,

and cardiac events. COPD exacerbations were balanced among the groups, occurring in 4.9% tio R5, 6.0% tio R10, and 5.7% placebo. Serious adverse events of pneumonia were increased in the tiotropium groups compared to placebo, whereas cardiac events were balanced. See Table 22 for a summary of SAEs occurring in 5 (0.3%) or more patients in the combined 1-year studies.

Table 22: Combined Protocols 205.254 and 205.255 (1-year studies) serious adverse events

MedDRA System Organ Class MedDRA Preferred Term	Treatment Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Total Treated N (%)	670 (100.0)	667 (100.0)	653 (100.0	1990 (100.0)
Total with serious adverse events	108 (16.1)	125 (18.7)	110 (16.8)	343 (17.2)
Cardiac disorders	17 (2.5)	13 (1.9)	16 (2.5)	46 (2.3)
Angina#	3 (0.4)	7 (1.0)	1 (0.2)	11 (0.6)
Atrial fibrillation#	4 (0.6)	2 (0.3)	2 (0.3)	8 (0.4)
Cardiac failure	4 (0.6)	1 (0.1)	3 (0.5)	8 (0.4)
Cardiac failure congestive	2 (0.3)	2 (0.3)	1 (0.2)	5 (0.3)
Myocardial infarction#	2 (0.3)	1 (0.1)	6 (0.9)	9 (0.5)
Gastrointestinal disorders	11 (1.6)	16 (2.4)	7 (1.1)	34 (1.7)
Abdominal pain#	5 (0.7)	0	0	5 (0.3)
General disorders and administration site conditions	6 (0.9)	8 (1.2)	6 (0.9)	20 (1.0)
Chest pain	5 (0.7)	0	1 (0.2)	6 (0.3)
Death	0	6 (0.9)	2 (0.3)	8 (0.4)
Neoplasms	12 (1.8)	12 (1.8)	6 (0.9)	30 (1.5)
Prostate cancer	2 (0.3)	2 (0.3)	3 (0.5)	7 (0.4)
Respiratory system disorders* (Lower)	51 (7.6)	49 (7.3)	51 (7.8)	151 (7.6)
Bronchitis#	0	3 (0.4)	3 (0.5)	6 (0.3)
COPD exacerbation#	33 (4.9)	40 (6.0)	37 (5.7)	110 (5.5)
Hemoptysis	1 (0.1)	1 (0.1)	3 (0.5)	5 (0.3)
Pneumonia#	14 (2.1)	11 (1.6)	6 (0.9)	31 (1.6)
Respiratory system disorders* (Other)	13 (1.9)	8 (1.2)	12 (1.8)	33 (1.7)
Bronchial carcinoma	3 (0.4)	2 (0.3)	2 (0.3)	7 (0.4)
Lung neoplasm malignant	3 (0.4)	2 (0.3)	2 (0.3)	7 (0.4)
Pulmonary embolism	2 (0.3)	1 (0.1)	2 (0.3)	5 (0.3)

Percentages are calculated using total number of patients per treatment as the denominator.

BI Collapsed Preferred Terms include multiple MedDRA Preferred Terms.

All system organ classes are defined by MedDRA with the exception of respiratory, thoracic and mediastinal disorders which have been divided into 3 separate classes of respiratory system disorders lower, upper, and other.

MedDRA version 8.0 was used for reporting.

In the combined 12-week studies (205.251 and 205.252), 5.0% of patients overall experienced a serious adverse event with the highest incidence in the ipratropium group (9.6%), followed by the tio R10 group (5.6%), the placebo group (2.8%), and tio R5 group (2.2%). The most frequent

serious adverse events were COPD exacerbations and pneumonia, which occurred most often in the ipratropium group.

In the combined 4-week crossover studies (205.249 and 205.250), 12.7% of patients overall experienced a serious adverse event, 3.7% in tio R5, 4.4% in tio R10, 2.7% in tio HH18, and 3.8% in placebo. Again, the most common SAEs were COPD exacerbations and pneumonia. These were generally balanced among the groups.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Overall, 25.3% of patients discontinued prematurely from the combined 1-year studies (205.254 and 205.255), 12.1% of patients discontinued prematurely from the combined 12-week studies (205.251 and 205.252), and 42 (20.3%) of patients discontinued prematurely from the combined 4-week crossover studies. The most common reasons for discontinuation from all of the studies were adverse events (primarily COPD exacerbation) and worsening of the disease under study (COPD). In the 1-year studies, there was a marked differential discontinuation rate, with increased drop outs in the placebo group, primarily due to COPD exacerbation, with 82.8% of patients in the tio R5 group, 79.6% in the tio R10 group, and only 68.6% of patients in the placebo group completing the trial per protocol. An increased drop out rate from the placebo group also occurred in the placebo group for the combined 4-week crossover studies, and from the ipratropium group in the 12-week studies. See Table 23 for patient disposition in the combined 1-year studies (205.254 and 205.255) and Table 24 for patient disposition in the combined 12-week studies. [Module 2, Volume 1.2, Section 2.7.4. Integrated Summary of Safety, pages 98-99]

Table 23: Combined 1-year studies (205.254 and 205.255) patient disposition

	Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Enrolled				2544
Not entered				554
Entered	670	667	653	1990
Not treated	0	0	0	0
Treated	670 (100.0)	667 (100.0)	653 (100.0)	1990 (100.0)
Not prematurely discontinued from trial medication	555 (82.8)	531 (79.6)	448 (68.6)	1534 (77.1)
Prematurely discontinued from trial medication	115 (17.2)	136 (20.4)	205 (31.4)	456 (22.9)
Adverse events	67 (10.0)	79 (11.8)	122 (18.7)	268 (13.5)
Worsening of disease under study	31 (4.6)	34 (5.1)	92 (14.1)	157 (7.9)
Worsening of other pre-existing disease	3 (0.4)	4 (0.6)	6 (0.9)	13 (0.7)
Other adverse event	33 (4.9)	41 (6.1)	24 (3.7)	98 (4.9)
Administrative				
Non compliant with protocol	8 (1.2)	13 (1.9)	15 (2.3)	36 (1.8)
Lost to follow-up	9 (1.3)	11 (1.6)	15 (2.3)	35 (1.8)
Consent withdrawn	19 (2.8)	23 (3.4)	38 (5.8)	80 (4.0)
Other	12 (1.8)	10 (1.5)	15 (2.3)	37 (1.9)

Table 24: Combined Protocols 205.251 and 205.252 (12-week studies) patient disposition

	Tio R 5 N (%)	Tio R 10 N (%)	IB MDI 36 N (%)	Placebo N (%)	Total N (%)
Enrolled					920
Not entered					201
Entered	180	180	178	181	719
Not treated	0	0	0	0	0
Treated	180(100.0)	180(100.0)	178(100.0)	181(100.0)	719(100.0)
Not prematurely discontinued from trial medication	164(91.1)	162(90.0)	147(82.6)	159(87.8)	632(87.9)
Prematurely discontinued from trial medication	16(8.9)	18(10.0)	31(17.4)	22(12.2)	87(12.1)
Adverse Events	13(7.2)	12(6.7)	21(11.8)	16(8.8)	62(8.6)
Worsening of disease under study	6(3.3)	3(1.7)	11(6.2)	11(6.1)	31(4.3)
Worsening of other pre-existing disease	2(1.1)	3(1.7)	1(0.6)	0(0.0)	6(0.8)
Other adverse event	5(2.8)	6(3.3)	9(5.1)	5(2.8)	25(3.5)
Administrative	2(1.1)	6(3.3)	8(4.5)	4(2.2)	20(2.8)
Non compliant with protocol	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Lost to follow-up	2(1.1)	3(1.7)	2(1.1)	1(0.6)	8(1.1)
Consent withdrawn	0(0.0)	3(1.7)	6(3.4)	3(1.7)	12(1.7)
Other	1(0.6)	0(0.0)	2(1.1)	2(1.1)	5(0.7)

7.1.3.2 Adverse events associated with dropouts

The most common adverse event associated with discontinuation was COPD exacerbation across all of the studies. Discontinuation due to COPD exacerbation occurred most frequently in the placebo group in the 1-year and 4-week crossover studies and most frequently in the ipratropium group for the 12-week studies. Focusing on the 1-year studies, there were 3.3% of patients in the tio R5 group, 3.9% in the tio R10 group, and 9.6% of patients in the placebo group who discontinued due to the adverse event of COPD exacerbation. Other adverse events leading to discontinuation occurred much less frequently. The next most common of these were dyspnea, cardiac disorders overall, nervous system disorders, neoplasms, and pneumonia. Of these, dyspnea occurred more frequently in the placebo group, pneumonia was slightly increased in the tiotropium groups, and the others were balanced among the groups. [Module 2, Volume 1.2, Section 2.7.4. Integrated Summary of Safety, pages 98-99 and 152-162]

7.1.3.3 Other significant adverse events

No adverse events leading to dose reduction were reported for the Respimat program. COPD exacerbations leading to significant additional concomitant therapy were defined by the 1-year protocols (205.254 and 205.255) as an efficacy endpoint and are discussed under Section 6 (Integrated Summary of Efficacy) and in Section 10.1.6 (Combined data sets from Studies 205.254 and 205.255 reported as Protocol 205.9992).

7.1.4 Other Search Strategies

7.1.4.1 Reviewer determined AE categories

In order to elucidate any potential mechanisms associated with deaths and other SAEs in the 1-year studies (205.254 and 205.255), the reviewer combined a number of adverse events into categories to determine if additional safety signals are present. The categories are as follows:

- arrhythmia: combined events of arrhythmia, atrial fibrillation, atrial tachycardia, extrasystoles, sick sinus syndrome, supraventricular tachycardia, tachycardia, ventricular extrasystoles, ventricular hypertrophy, and ventricular tachycardia
- congestive heart failure: combined events of cardiac failure, cardiac failure congestive, left ventricular failure, and right ventricular failure
- lung cancer: combined events of bronchial carcinoma, bronchial neoplasm, bronchioloalveolar carcinoma, lung neoplasm, lung neoplasm malignant, lung squamous cell carcinoma stage unspecified, non-small cell lung cancer, non-small cell lung cancer metastatic, small cell lung cancer stage unspecified, and tracheal neoplasm
- myocardial infarction: combined events of acute coronary syndrome, coronary artery insufficiency, myocardial infarction, and myocardial ischemia
- stroke: combined events of cerebral infarction, cerebrovascular accident, cerebrovascular insufficiency, and transient ischemic attack

Frequencies of patients with adverse events in these combined categories are presented in Table 25. Based on this combined analysis, no adverse safety signals emerged.

Table 25: Combined Protocols 205.254 and 205.255 (1-year studies) special safety categories

Combined AE term	Treatment			
	Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Total treated	670 (100.0)	667 (100.0)	653 (100.0)	1990 (100.0)
Total with adverse events	505 (75.4)	525 (78.7)	502 (76.9)	1532 (77.0)
Arrhythmia	15 (2.2)	19 (2.8)	12 (1.8)	46 (2.3)
Congestive heart failure	10 (1.5)	8 (1.2)	6 (0.9)	24 (1.2)
Lung cancer	9 (1.3)	8 (1.2)	6 (0.9)	24 (1.2)
Myocardial infarction	3 (0.4)	4 (0.6)	7 (1.1)	14 (0.7)
Stroke	3 (0.4)	6 (0.9)	3 (0.5)	12 (0.6)

Percentages are calculated using total number of patients per treatment as the denominator.

Reviewer comment:

Caution must be used in interpretation of reviewer combined AE categories. Addition of events may result in overestimation of effect if a single patient experienced more than one AE in a category.

7.1.4.2 Aggravated bronchospasm

A specific analysis looking for paradoxical bronchospasm in response to tiotropium was conducted in the 1-year trials (205.254 and 205.255). The term 'aggravated bronchospasm' was used to describe a spontaneously reported AE of 'aggravated' or 'paradoxical bronchospasm' which occurred within 30 minutes of study medication inhalation. The term 'administration related bronchoconstriction' was used to describe occurrence of at least 2 of the following 3 events: 1) use of rescue medication, 2) any potentially bronchospastic AE (cough, wheeze, dyspnea, etc.) and 3) ≥15% fall in FEV_1 below test-day pre-dose FEV_1. To fulfill the definition, each event must have occurred within 30 minutes of study medication inhalation. No patients fulfilled the definition of 'aggravated bronchospasm.' Two patients in the tio R5 group, three patients in the tio R10 group, and one patient in the placebo group had 'administration related bronchoconstriction.' The incidence of asymptomatic falls in FEV_1 of 15% or more occurred in 6.7% of the tio R5 group, 9.6% of the tio R10 group, and 4.5% of the placebo group. [Integrated Summary of Safety, Module 2, Volume 1.2, Section 2.7.4., pages 100-102]

7.1.4.3 Cardiac disorders

The Applicant performed an evaluation of cardiac disorders in the combined 1-year trials (205.254 and 205.255) using special AE groupings. No safety signals regarding tiotropium emerged from this analysis. See Table 26. [Integrated Summary of Safety, Module 2, Volume 1.2, Section 2.7.4, pages 104-109]

Table 26: Number of patients with selected cardiac events with special collapsing in the combined 1-year trials (205.254 and 205.255)

	Tio R5	Tio R10	Placebo
Number of Patients	670	667	653
Total Cardiac Disorders	49 (7.3%)	49 (7.3%)	36 (5.5%)
Ischemic coronary disease	17 (2.5%)	17 (2.5%)	11 (1.7%)
Angina	12 (1.8%)	15 (2.2%)	4 (0.6%)
Coronary artery disease, acute coronary syndrome, coronary artery insufficiency, myocardial ischemia	4 (0.6%)	2 (0.3%)	3 (0.5%)
Myocardial infarction	2 (0.3%)	1 (0.1%)	6 (0.9%)
Atrial fibrillation, atrial tachycardia, supraventricular tachycardia	13 (1.9%)	6 (0.9%)	6 (0.9%)
Palpitations, tachycardia	7 (1.0%)	9 (1.3%)	5 (0.8%)
Ventricular tachycardia	1 (0.1%)	2 (0.3%)	1 (0.2%)
Arrhythmia, extrasystoles, ventricular extrasystoles	2 (0.3%)	5 (0.7%)	1 (0.2%)
Cardiac failure, cardiac failure congestive, right ventricular failure, left ventricular failure	10 (1.5%)	8 (1.2%)	6 (0.9%)

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

No significant AEs were prespecified for this study. All AEs were recorded at each visit after review of the patient's diary card and discussion with the patient. Adverse events were also recorded for an additional 3-4 weeks post-therapy in the Phase 3 program.

COPD exacerbations were reported as AEs. A COPD exacerbation was defined as a complex of respiratory events/symptoms with a duration of three days or more requiring a change in treatment. A complex of respiratory events/symptoms meant two or more 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. The change in or requirement of treatment included the following: prescription of antibiotics, prescription of systemic steroids, or a significant change in prescribed respiratory medication (bronchodilators including theophylline). The onset of an exacerbation was defined by the onset of the first recorded symptom. The end of the exacerbation was defined by the investigator.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were classified according to the MedDRA dictionary version 8.0 for all Phase 3 studies in the Spiriva Respimat development program. Since the development program focused on respiratory outcomes, the Applicant further divided the MedDRA system organ class (SOC) of "respiratory, thoracic, and mediastinal disorders" into three categories: respiratory (lower), respiratory (upper), and respiratory (other). The Applicant classified pneumonia into the "respiratory (lower)" SOC, which groups all pneumonias into a single category. MedDRA also permits classification of pneumonias by organism in the "infections and infestations" SOC. In addition, the Applicant classified neoplasms of the respiratory system into the SOC of "respiratory (other)" rather than under the "neoplasms" SOC.

Reviewer comment:

The Applicant's division of the respiratory category into upper, lower, and other is appropriate for a COPD study. It is also very useful for analysis to have all pneumonias grouped together as the Applicant has done.

7.1.5.3 Incidence of common adverse events

The Applicant groups analysis of common adverse events into 1-year studies (205.254 and 205.255), 12-week studies (205.251 and 205.252), and 4-week crossover studies (205.249 and 205.250). [Module 2, Volume 1.2, Section 2.7.4 Integrated Summary of Safety, pages 62-66] Across the studies as a whole, the most common adverse events were in the respiratory system, including COPD exacerbation, nasopharyngitis, and dry mouth.

Common adverse events in the 1-year studies (205.254 and 205.255)

No new adverse event signals emerge on combination of data from Protocols 205.254 and 205.255. The most common adverse events were COPD exacerbations, nasopharyngitis, upper respiratory tract infection, and dry mouth. Evidence of dose-related increases in dry mouth, dyspepsia, and urinary tract infections occurred. There were small increases in cardiovascular events (angina, arrhythmia, and congestive heart failure), cough, pneumonia, nasopharyngitis, hypertension, and headache in the tiotropium groups compared to placebo. Adverse events of COPD exacerbation and dyspnea occurred more frequently in the placebo group. See also Section 10.1.6 Study 205.9992.

Common adverse events in the 12-week studies (205.251 and 205.252)

In the combined 12-week studies, the most common adverse events were COPD exacerbation, dry mouth, nasopharyngitis, and cough. Dry mouth was increased in the tiotropium groups compared to placebo, occurring in 8.9% of patients in the tio R5 group, 10% in the tio R10 group, 4.5% in the ipratropium group, and 2.2% in the placebo group. Urinary tract infection was also increased in the tiotropium groups compared to placebo, occurring in 5% tio R5, 2.2% tio R10, 1.7% ipratropium, and 2.2% placebo. Other adverse events were generally balanced across the treatment groups.

Common adverse events in the 4-week crossover studies (205.249 and 205.250)

In the combined 4-week crossover studies, the most common adverse events were COPD exacerbation, nasopharyngitis, dyspnea, and dry mouth. The incidences of COPD exacerbations and nasopharyngitis were balanced across the treatment groups. Dyspnea was reported less frequently in the tiotropium groups compared to placebo. There was a dose-related increased incidence of dry mouth, occurring 1.6% of tio R5 and tio HH18, 3.3% of tio R10, and 0.5% of placebo patients.

7.1.5.4 Common adverse event tables

Table 27: Combined Protocols 205.251 and 205.252 (12-week studies) common adverse events (≥3% of patients in any treatment group)

System organ class/ Preferred term	Tio R5 N (%)	Tio R10 N (%)	IB 36 N (%)	Placebo N (%)	Total N (%)
Number of patients	180 (100.0)	180 (100.0)	178 (100.0)	181 (100.0)	719 (100.0)
Total with adverse events	95 (52.8)	108 (60.0)	106 (59.6)	107 (59.1)	416 (57.9)
Gastrointestinal disorders	24 (13.3)	35 (19.4)	24 (13.5)	13 (7.2)	96 (13.4)
Diarrhea	3 (1.7)	4 (2.2)	7 (3.9)	4 (2.2)	18 (2.5)
Mouth dry#	16 (8.9)	18 (10.0)	8 (4.5)	4 (2.2)	46 (6.4)
Nausea	0	3 (1.7)	6 (3.4)	3 (1.7)	12 (1.7)
Infections and infestations	19 (10.6)	15 (8.3)	12 (6.7)	12 (6.6)	58 (8.1)
Urinary tract infection#	9 (5.0)	4 (2.2)	3 (1.7)	4 (2.2)	20 (2.8)
Musculoskeletal and connective tissue disorders	11 (6.1)	15 (8.3)	16 (9.0)	15 (8.3)	57 (7.9)
Back pain	2 (1.1)	4 (2.2)	6 (3.4)	8 (4.4)	20 (2.8)
Nervous system disorders	14 (7.8)	15 (8.3)	14 (7.9)	17 (9.4)	60 (8.3)
Dizziness	3 (1.7)	7 (3.9)	3 (1.7)	1 (0.6)	14 (1.9)
Headache	6 (3.3)	8 (4.4)	7 (3.9)	13 (7.2)	34 (4.7)
Respiratory system disorders* (Lower)	39 (21.7)	41 (22.8)	51 (28.7)	43 (23.8)	174 (24.2)
Bronchitis#	8 (4.4)	3 (1.7)	8 (4.5)	7 (3.9)	24 (3.6)
COPD exacerbation#	17 (9.4)	26 (14.4)	24 (13.5)	21 (11.6)	88 (12.2)
Cough	7 (3.9)	10 (5.6)	10 (5.6)	6 (3.3)	33 (4.6)
Dyspnea#	4 (2.2)	5 (2.8)	9 (5.1)	9 (5.0)	27 (3.8)
Respiratory system disorders* (Upper)	34 (18.9)	34 (18.9)	27 (15.2)	41 (22.7)	136 (18.9)
Nasopharyngitis	11 (6.1)	10 (5.6)	15 (8.4)	20 (11.0)	56 (7.8)
Pharyngolaryngeal pain	5 (2.8)	6 (3.3)	4 (2.2)	6 (3.3)	21 (2.9)
Sinusitis#	6 (3.3)	2 (1.1)	2 (1.1)	3 (1.7)	13 (1.8)
Upper respiratory tract infection#	5 (2.8)	10 (5.6)	1 (0.6)	5 (2.8)	21 (2.9)

Percentages are calculated using total number of patients per treatment as the denominator.

Containing data from trials 0205_0251 and 0205_0252

BI Collapsed Preferred Terms include multiple MedDRA Preferred Terms.

* All system organ class are defined by MedDRA with the exception of Respiratory, thoracic and mediastinal disorders which have been divided into three separate classes of respiratory system disorders lower, upper and other.

MedDRA version 8.0 was used for reporting.

Table 28: Combined Protocols 205.254 and 205.255 (1-year studies) common adverse events (≥ 3% of patients in any treatment group)

System organ class/ Preferred term	Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Number of patients	670 (100.0)	667 (100.0)	653 (100.0)	1990 (100.0)
Total with adverse events	505 (75.4)	525 (78.7)	502 (76.9)	1532 (77.0)
Gastrointestinal disorders	142 (21.2)	193 (28.9)	97 (14.9)	432 (21.7)
Abdominal pain#	24 (3.6)	16 (2.4)	13 (2.0)	53 (2.7)
Mouth dry#	48 (7.2)	97 (14.5)	14 (2.1)	159 (8.0)
General disorders and administration site conditions	92 (13.7)	63 (9.4)	63 (9.6)	218 (11.0)
Chest pain	21 (3.1)	8 (1.2)	12 (1.8)	41 (2.1)
Edema#	24 (3.6)	11 (1.6)	13 (2.0)	48 (2.4)
Infections and infestations	90 (13.4)	95 (14.2)	79 (12.1)	264 (13.3)
Urinary tract infection#	17 (2.5)	28 (4.2)	7 (1.1)	52 (2.6)
Musculoskeletal and connective tissue disorders	94 (14.0)	100 (15.0)	78 (11.9)	272 (13.7)
Back pain	30 (4.5)	27 (4.0)	22 (3.4)	79 (4.0)
Nervous system disorders	75 (11.2)	65 (9.7)	66 (10.1)	206 (10.4)
Headache	31 (4.6)	30 (4.5)	24 (3.7)	85 (4.3)
Respiratory system disorders* (Lower)	304 (45.4)	299 (44.8)	360 (55.1)	963 (48.4)
Bronchitis#	29 (4.3)	35 (5.2)	27 (4.1)	91 (4.6)
COPD exacerbation#	220 (32.8)	216 (32.4)	275 (42.1)	711 (35.7)
Cough	33 (4.9)	41 (6.1)	27 (4.1)	101 (5.1)
Dyspnea#	41 (6.1)	27 (4.0)	51 (7.8)	119 (6.0)
Lower respiratory tract infection	25 (3.7)	24 (3.6)	20 (3.1)	69 (3.5)
Pneumonia#	22 (3.3)	22 (3.3)	11 (1.7)	55 (2.8)
Respiratory system disorders* (Upper)	208 (31.0)	203 (30.4)	171 (26.2)	582 (29.2)
Influenza	27 (4.0)	23 (3.4)	30 (4.6)	80 (4.0)
Nasopharyngitis	94 (14.0)	64 (9.6)	54 (8.3)	212 (10.7)
Pharyngolaryngeal pain	30 (4.5)	27 (4.0)	13 (2.0)	70 (3.5)
Upper respiratory tract infection#	53 (7.9)	49 (7.3)	52 (8.0)	154 (7.7)
Vascular disorders	30 (4.5)	41 (6.1)	35 (5.4)	106 (5.3)
Hypertension	23 (3.4)	26 (3.9)	18 (2.8)	67 (3.4)

Percentages are calculated using total number of patients per treatment as the denominator.

Containing data from trials 0205_0254 and 0205_0255

BI Collapsed Preferred Terms include multiple MedDRA Preferred Terms.

* All system organ class are defined by MedDRA with the exception of Respiratory, thoracic and mediastinal disorders which have been divided into three separate classes of respiratory system disorders lower, upper and other.

MedDRA version 8.0 was used for reporting.

Reviewer comment

Typically, product labels for asthma and COPD trials include an AE table from the combined short-term bronchodilation trials, which form the basis of approval for these compounds. Adverse events from longer-term trials, which may support additional labeling claims, are then mentioned briefly. In this NDA, the Applicant's proposed label includes both data from the 1-year trials and the 12- week trials. Since the Spiriva HandiHaler also includes AE data from long-term trials, inclusion of the 1-year data table in the Respimat label may be appropriate for consistency and also because the majority of potential safety signals (mortality, dry mouth, pneumonia, etc.) were better expressed in the long-term studies.

7.1.5.5 Identifying common and drug-related adverse events

Dry mouth is increased in a dose-related fashion in the tiotropium groups across the Phase 3 program. Dry mouth is an anticholinergic effect that represents a known class effect of this drug. Most patients (41 of 48 in tio R5 group and 81 of 97 in the tio R10 group in the 1-year trials) reported that the intensity of dry mouth was mild. One patient in the tio R5 group and three in the tio R10 group reported a severe intensity, and two patients in each active treatment group discontinued because of dry mouth. Dry mouth had a median onset of 15.5 days in the tio R5 group and 12 days in the tio R10 group. About one third of the patients recovered while still on treatment. [Integrated Summary of Safety, Module 2, Volume 1.2, Section 2.7.4, pages 109-110]

Urinary tract infection is also consistently increased across the Phase 3 program, although the effect size is much smaller than for dry mouth. This may represent a consequence of urinary retention, also a known class effect of the drug.

Reviewer comment:

The proposed Respimat label includes the following statement regarding common adverse events: (b) (4) (b) (4) (b) (4) *The proposed language is acceptable. Very few patients discontinued due to the adverse event of dry mouth.*

7.1.5.6 Additional analyses and explorations

Safety was analyzed in a variety of special groups and situations for the 1-year trials (205.254 and 205.255). These included intrinsic factors of gender, age, race, and disease severity. Extrinsic factors of oral steroid use at baseline, inhaled steroid use at baseline, xanthene use at baseline, and smoking status were also assessed.

Gender analysis

In the 1-year studies, approximately 75% of patients were male. The incidence of adverse events across treatment groups was generally similar across treatment groups for males as compared to females; however, a number of adverse events occurred more frequently in females as compared to males. Adverse events occurring more frequently in females included: abdominal pain, nausea, vomiting, urinary tract infections, and pharyngolaryngeal pain. These adverse events all occurred more frequently in the tiotropium groups compared to placebo in a dose-related fashion. Abdominal pain, nausea, and vomiting are unexpected, as anticholinergics usually decrease these symptoms. Urinary tract infection could be secondary to urinary retention, an anticholinergic side effect. The Applicant reports an association between gender and inhaled steroid use for pharyngolaryngeal pain, with 78% of females reporting this AE using inhaled steroids.

Age analysis

In the 1-year studies (205.254 and 205.255), 55% of patients were 65 years of age or older. As expected, cardiac events occurred more frequently in patients ≥ 65 years. Angina, atrial fibrillation, and palpitations occurred more frequently in the tiotropium groups compared to placebo in those patients ≥ 65 years; in contrast, the incidence of these events was balanced across the treatment groups in younger patients. Eye disorders, primarily cataracts occurred more frequently in older patients and were balanced across treatment groups. Urinary tract infections also occurred more frequently in the older age group. This AE occurred more frequently in the tiotropium groups for both younger and older patients.

Race analysis

Since 98% of patients reporting race in the 1-year studies were white, meaningful subgroup analyses could not be made.

Disease severity analysis

Patients were divided into 3 subgroups to assess interactions with disease severity based on the Global Obstructive Lung Disease (GOLD) criteria for post-bronchodilator FEV_1. Groups included: GOLD Stage I and II ($FEV_1 \geq 50\%$ predicted), GOLD Stage III (FEV_1 30 - <50% predicted), GOLD Stage IV (FEV_1 <30% predicted). The mean baseline FEV_1 for patients in the 1-year studies (205.254 and 205.255) was 1.34, 0.97, and 0.67L for patients categorized as Stage I/II, III, and IV, respectively. As expected, a greater proportion of patients with more severe disease experienced a COPD exacerbation; however, there was no interaction with tiotropium, with a decreased number of exacerbations in the tiotropium groups across all disease severity categories.

Drug interaction analysis

There was no apparent interaction between oral steroid use, xanthene use, or active smoking and tiotropium. Fifty-four percent of patients in the 1-year trials used inhaled steroids throughout the trial. There was an increased incidence of pharyngolaryngeal pain in inhaled steroid users than in non-users. This association was particularly noted in women.

7.1.6 Less Common Adverse Events

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. No particular stroke-related adverse event was definitively increased in the tiotropium groups in the combined 1-year studies (205.254 and 205.255). Combining terms of cerebral infarction, CVA, transient ischemic attack, and cerebrovascular insufficiency gives 3 events in the tio R5 group, 6 in the tio R10 group, and 3 in the placebo group.

Reviewer comment:

In recently completed pooled analyses of tiotropium clinical trial data, the Applicant identified stroke as occurring at higher rates in patients receiving tiotropium compared with patients receiving placebo (RR 1.37, 95% CI 0.73-1.56). This data was submitted to FDA in November 2007 and an Early Communication was issued by FDA for Spiriva HandiHaler on March 18, 2008. This pooled trial population presented information on 13,344 patients from 29 clinical trials, contributing 4,572 person-years of exposure to tiotropium and 3,065 person-years of exposure to placebo. This population included 4 trials from the Spiriva Respimat program (205.251, 205.252, 205.254, and 205.255) and also investigated a large number of other adverse events. The pooled trials in the Respimat program did not demonstrate an increased risk (RR 0.87, 95% CI 0.30-2.56).

In order to further evaluate the potential association between tiotropium and stroke, the Applicant submitted preliminary data from a recently completed 4-year trial comparing tiotropium HandiHaler 18 mcg once daily to placebo in 5,993 patients with COPD (Study 205.235). Study 205.235 was a randomized, double-blind, placebo-controlled parallel group multi-national trial assessing the rate of decline in lung function with tiotropium in patients with moderate to severe COPD, and is also known as UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium). Enrollment criteria were generally similar to those of the Spiriva Respimat Phase 3 program. Because this preliminary data was submitted on July 15, 2008, only two weeks prior to the primary review due date, no formal review of the data is presented.

According to the Applicant, the analysis of the UPLIFT data showed that the rate ratio for stroke (tiotropium/placebo) is 0.95 (95% CI 0.70-1.29). Likewise, there was no evidence of an increased risk for serious stroke or fatal events due to stroke.

Table 29: Protocol 205.235 (UPLIFT) Spiriva HandiHaler stroke events

	Tio HH18 N (%)	Placebo N (%)	Rate Ratio (95% CI)
Number enrolled	2986	3006	
All stroke events	82 (2.7)	80 (2.7)	0.95 (0.70-1.35)
Serious stroke events	67 (2.2)	63 (2.1)	0.98 (0.70-1.39)
On-treatment fatal strokes	12 (0.4)	12 (0.4)	0.92 (0.41-2.05)
On-treatment fatal strokes (adjudicated)	12 (0.4)	13 (0.4)	0.85 (0.39-1.87)

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

For the Phase 3 program, laboratory testing included routine blood chemistry, hematology, and urinalysis. Chemistry included alkaline phosphatase, LDH, SGOT, SGPT, glucose, calcium, inorganic phosphorus, uric acid, urea nitrogen, creatinine, total protein, albumin, and total bilirubin. Hematology included hemoglobin, hematocrit, red blood cell count, white blood cell count including differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) total eosinophil count and platelet count.

Laboratory tests were performed at the start of the run in period and at the end of the treatment period (either 12-weeks or 48 weeks). Follow up laboratories were also completed for all patients discontinuing early. An abnormal laboratory value at the end of treatment was to be recorded as an adverse event if it was not associated with an already reported adverse event symptom or diagnosis. Clinical laboratory values were assessed as individual patient marked changes and as mean changes from baseline.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Laboratory analyses for the ISS were conducted for the combined 12-week studies (205.251 and 205.252) and for the combined 48-week studies (205.254 and 205.255). The dose ranging study (205.127) is discussed as part of the individual study review (Section 10.1.1).

7.1.7.3 Standard analyses and explorations of laboratory data

12-week trials (205.251 and 205.252)

The number of patients with possibly clinically significant abnormalities in hematology and clinical chemistry values was generally small and balanced across the four treatment groups.

There were no clinically important differences between the treatment groups, although there was an increase in glucose noted in the tiotropium groups compared to placebo (6.5% tio R5, 4.8% tio R10, 6.2% ipratropium, and 2.3% placebo patients with a change compared to baseline). LDH also showed a greater percentage of patients in the tiotropium groups with a change compared to baseline, with 4.1% in tio R5, 1.8% in tio R10 and 1.2% ipratropium, compared to no patients in the placebo group.

1-year trials (205.254 and 205.255)

The number of patients with possibly clinically significant abnormalities was generally small and balanced across the three treatment groups. The parameter with the most frequent change from baseline was an increase in uric acid. The two active treatment groups had a greater percentage of patients with an increase than did the placebo group (4.8% in tio R5, 4.1% tio R10, and 3.1% placebo). In contrast to the 12-week studies, glucose showed a lower percentage of tiotropium patients (4.5% tio R5 and 4.3% tio R10) with an increase from baseline compared to patients in the placebo group (6.5%).

7.1.7.4 Additional analyses and explorations

No additional analyses or explorations of laboratory values were conducted.

7.1.7.5 Special assessments

No special laboratory assessments were conducted.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs consisted of pulse rate and blood pressure. Pulse rate and blood pressure were measured and recorded at the same time intervals as pulmonary function testing for the first three hours post-dose. Measurements were obtained immediately before PFTs with the patient seated and rested for a minimum of five minutes. Blood pressure was to be performed by the same person using the same blood pressure instrument on the same arm.

Vital signs were assessed as number of patients with marked changes and mean changes from baseline. Baseline was defined as the value recorded for the pre-dose (-10 minute) Day 1 measurement. Marked changes in vital signs were defined prospectively as presented in Table 30.

Table 30: Definition of marked changes in vital signs

Vital sign parameter	Increase	Decrease
Systolic BP	>150 mmHg and an increase >25 mmHg above baseline	<100 mm Hg and a decrease >10 mmHg below baseline
Diastolic BP	>90 mm Hg and an increase >10 mmHg above baseline	<60 mmHg and a decrease >10 mmHg below baseline
Pulse Rate	>100 bpm and an increase >10 bpm above baseline	<60 bpm and a decrease >10 bpm below baseline

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Vital signs analyses for the ISS were conducted for the combined 12-week studies (205.251 and 205.252) and for the combined 48-week studies (205.254 and 205.255). The dose ranging study (205.127) is discussed as part of the individual study review (Section 10.1.1).

7.1.8.3 Standard analyses and explorations of vital signs data

Overall changes in blood pressure and pulse rate were small without a clinically important difference between treatment groups. Mean decreases in both systolic and diastolic blood pressure in the order of 1-2 bpm were seen following all treatments in both the 1-year and the 12-week trials.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations of vital signs data were conducted.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

A standard 12-lead ECG was to be performed on all patients at the screening visit and repeated at the end of the treatment period for all patients in both the 12-week and 1-year studies. The ECG was to be performed prior to the test-day pre-dose PFT. All ECGs were interpreted by the investigator or other qualified site personnel. ECG equipment and reading were not standardized across sites. Follow up ECGs were also performed on all patients discontinuing early. All abnormal ECG findings at baseline were recorded as concomitant medical diagnoses. Any new

abnormal finding or worsening of a baseline condition detected at a follow up ECG was recorded as an adverse event.

In the 1-year studies (205.254 and 205.255) a subset of 582 patients from this study received additional 12-lead ECG measurements and 364 of these received 24-hour Holter monitoring studies that were reviewed centrally (b) (4) The additional 12-lead ECG monitoring was performed pre-dose and at 5 minutes and 2 hours post-dose at the randomization visit (Visit 2) and at 16 and 40 weeks of treatment (Visits 5 and 8). In these same patients, 24-hour Holter monitoring was performed immediately prior to the randomization visit and at week 16 and 40. Both the ECGs and Holter studies in this subset of patients were centrally read. Measured ECG parameters included heart rate, PR interval, QRS interval, QT interval, QTc. Holter monitoring evaluated heart rate, ectopic activity (supraventricular premature beats and ventricular premature beats), and pauses.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

ECG and Holter analyses for the ISS were conducted for the subset of patients undergoing special testing in the combined 1-year studies (205.254 and 205.255). Analyses of patients undergoing standard ECGs in the Phase 3 program may be found under the individual study reviews (Section 10).

7.1.9.3 Standard analyses and explorations of ECG data

No clinically significant changes in any of the ECG parameters were observed. For heart rate, a small decrease of 2-3 bpm compared to baseline was observed across all treatment groups. Similarly, no clinically significant changes were observed in Holter monitoring data. Evaluation of shift tables for outliers also showed balance between the tiotropium and placebo groups.

Reviewer comment:

Tachycardia is the anticipated anticholinergic side effect. Tachycardia was not observed with either tio R5 or tio R10 doses. This is consistent with ECG data across the studies, vital sign data, and adverse event data.

7.1.9.4 Additional analyses and explorations

The Applicant conducted a “thorough QT study” using tiotropium HandiHaler 18 mcg, tiotropium HandiHaler 54 mcg (3 times the approved dose), and moxifloxicin as a positive control. The study was submitted under NDA 21,395 (Spiriva HandiHaler) on May 21, 2007.

The study was a single-center, randomized, placebo controlled, double-blind, three period crossover study in 54 healthy male and female subjects, with dosing of study medication once daily for 12 days. No significant effect of tiotropium was detected. The largest upper limit of the two-sided 90% CI for the mean difference between tio HH18 and tio HH54 compared to placebo

was below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline. [FDA Interdisciplinary Review Team for QT Studies Consultation, January 22, 2008].

7.1.10 Immunogenicity

Since tiotropium is a small molecule, immunogenicity is not a concern; thus, it was not evaluated as part of the Respimat program.

7.1.11 Human Carcinogenicity

Inhalational carcinogenicity studies in animals did not suggest carcinogenic potential for tiotropium. In the 1-year human studies, a total of 57 patients overall had adverse events of neoplasm including benign, malignant, and unspecified as well as cysts and polyps. Events excluded neoplasms of the respiratory system. These included 20 patients in the tio R5 group, 21 in the tio R10 group, and 16 patients in the placebo group. The most common neoplasm reported overall was basal cell carcinoma in 14 patients followed by prostate cancer in 7 patients, which were both balanced among the groups. Given the older male population enrolled in these studies, the neoplasms observed are not unexpected.

In addition to the neoplasm system organ class, tumors of the lung were categorized under the system organ class of respiratory, other. There were 25 patients reported with neoplasms of the respiratory system, 9 in the tio R5 group, 8 in the tio R10 group, and 8 in the placebo group. Given the heavy smoking history of the patient population enrolled in these studies, the neoplasms observed are not unexpected.

Reviewer comment:

The reviewer added AEs of neoplasms in the respiratory (other category) to determine total events. Since this category contained AEs other than neoplasms, addition of events may result in overestimation of effect if a single patient experienced more than one AE in this category.

7.1.12 Special Safety Studies

Ocular toxicity

Study 205.138 was conducted to determine the effect of inadvertent exposure of the eye to tiotropium from the Respimat inhaler. The trial was conducted in 48 healthy male volunteers using the instillation of "eye drops" of tiotropium. The dose range of tiotropium used in this trial as administered to one eye (0.02-0.40 mcg) was based on a previous trial to determine the maximum dose that might inadvertently reach the eye. The study was a randomized, placebo-controlled, double-blind, parallel group, rising dose study. Eight subjects, six on tiotropium and two on placebo, were enrolled in each of 6 dose levels. Each subjects received a single dose of two drops to one eye. Adverse effects were limited to the treated eye and consisted of a mild and transient burning sensation in both the tiotropium and placebo groups, suggesting that this was due to the excipients. The burning sensation lasted up to five minutes and did not require any

form of treatment of follow up. A dose-relationship was not observed. No changes in pupil diameter, papillary reflex, intraocular pressure, or accommodation were seen. [Module 5, Volume 1.1, Study Report 205.138, pages 1-51]

Local tolerability of placebo solution

Study 205.248 was conducted to evaluate the local tolerability of Respimat placebo solution with (b) (4) (more acidic than Spiriva Respimat solution (b) (4)) in 32 hypersensitive asthmatic patients. The study was a single-dose, randomized, double-blind (within device) four way cross-over trial evaluating Respimat placebo solution matching Atrovent (b) (4) Respimat placebo neutral solution (pH= 7.0), CFC-MDI placebo solution, and Respimat placebo solution matching tiotropium ((b) (4)). Subjects were monitored for spirometry, cough, physical examination, vital signs, and adverse events for 30 minutes following administration of the test drug. Each subject received one of the 4 treatments (a single dose of 4 puffs) on each of 4 consecutive days, with a 12 hour washout between treatments. The CFC-MDI caused significantly more cough episodes than the Respimat inhaler. The Respimat (b) (4) 7 solution was well tolerated compared to the other solutions. [Module 5, Volume 1.2, Study Report 205.248, pages 1-50]

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The Phase 3 12-week and 1-year trials (205.251, 205.252, 205.254 and 205.255) all included a 3-week follow-up period off drug to evaluate for possible withdrawal-induced rebound. Peak flow, use of rescue medication, and Physician's Global Evaluation data were recorded. These studies did not show a sudden worsening of COPD following withdrawal of treatment (rebound effect). Data from each study are presented in Section 10, and an integrated summary is presented in Section 6, Integrated Review of Efficacy.

Spiriva Respimat is not a controlled substance and has no known abuse potential.

7.1.14 Human Reproduction and Pregnancy Data

No clinical data are available for pregnancies exposed to tiotropium or for nursing females. Because COPD is a disease that generally occurs only in older patients with a significant smoking history, clinical trials only enrolled patients greater than 40 years of age. Studies in animals have shown evidence of reproductive toxicity.

7.1.15 Assessment of Effect on Growth

COPD is a disease that occurs only in the adult population. No data are available regarding the use of tiotropium in the pediatric population. Therefore, an assessment of effect on growth does not apply to this application. A pediatric waiver was granted for this application.

7.1.16 Overdose Experience

In the Spiriva HandiHaler development program, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 340 mcg in healthy volunteers. In a dose ranging study of tiotropium bromide administered via nebulizer to healthy volunteers once daily for 14 days, doses of 10, 20, and 40 mcg were evaluated. A dose dependent increase in mild-moderate dry nose and dry mouth was observed in addition to a pronounced reduction in salivary flow from day 7 on in the 40 mcg dose group (Protocol 205.112).

A dose ranging study was conducted using doses of up to 20 mcg/day Spiriva Respimat for three weeks in patients with moderate-severe COPD (Protocol 205.127). In this study, there was only one serious adverse event (chest pain secondary to hiatal hernia) and no discontinuations due to adverse events in the tio R20 group. The only anticholinergic side effect reported was dry mouth.

Reviewer comment:

The Applicant proposes adding the following new language to the overdose section of the label:

(b) (4)

The first statement is supported by the results of Protocol 205.112; however, the statement should be modified (b) (4)*. The second statement will require modification or deletion, as the increased incidence of dry mouth in the 10 mcg group (14.5% tio R10 versus 7.2% tio R5 in the combined 1-year studies, 205.254 and 205.255) was the primary reason that the Applicant chose the 5 mcg dose going forward for approval.*

7.1.17 Postmarketing Experience

At the time of the NDA, post-marketing experience was not available with Spiriva Respimat. Post-marketing data for Spiriva HandiHaler was submitted in the NDA covering the period of April 10, 2002 to June 1, 2005.

Spiriva Respimat has been available in 5 European countries starting in October 2007. Post-marketing safety reports from the period of October 1, 2007 to January 20, 2008 were included in the 4-month safety update. These data are reviewed in Section 7.2.9.2.

In the Spiriva HandiHaler report provided in the NDA, market exposure as of June 1, 2005 was estimated to be in excess of 2.0 million patient-years. Post-marketing experience includes a prescription-event monitoring study (PEM) of tio HH18 in 13,891 patients from the United Kingdom. In the PEM study, exposure data were comprised of prescriptions collected by the Prescription Pricing Authority in England for tiotropium over the period September 2002 to August 2003. The outcome data are event reports obtained by sending questionnaires to the

doctors who issued prescriptions for the monitored drug. Of the 13,891 patients followed, there were 1017 deaths (7%). COPD was the most frequent cause of death. [Integrated Analysis of Spiriva HandiHaler Post-marketing Safety Report U05-3295; IND 46,687, S-242, December 21, 2005; Medical Officer Review IND 65,127 April 11, 2006]

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Safety data was drawn primarily from four Phase 3 studies: two 12-week studies (205.251 and 205.252) and two 1-year studies (205.254 and 205.255). See Table 31. Emphasis was placed on the 1-year trials. Additional safety data from other studies were summarized as appropriate. See Section 7.2.2.1.

Table 31: Spiriva Respimat Program Phase 3 pivotal studies used to support safety

ID #	Study type	Study duration	Patient age	Treatment groups	N (ITT)	Study Year†	Countries
205.251	Efficacy and safety COPD	12 wks	≥40 yrs	tio R5 QD tio R 10 QD ipratr 36 mcg QID placebo	88 93 89 91	2003	Germany Italy Switzerland S Africa
205.252	Efficacy and safety COPD	12 wks	≥40 yrs	tio R5 QD tio R10 QD ipratr 36 mcg QID placebo	92 87 89 90	2003	US Canada
205.254	Efficacy and safety COPD	48 wks	≥40 yrs	tio R5 QD tio R10 QD placebo	332 332 319	2005	EU N America
205.255	Efficacy and safety COPD	48 wks	≥40 yrs	tio R5 QD tio R10 QD placebo	338 335 334	2005	EU N America Africa Australia

†Year patient enrollment ended

Disposition of patients in the 12-week studies (205.251 and 205.252)

A total of 719 male and female patients with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 180 in the tio R5 group, 180 in the tio R10 group, 178 in the ipratropium group, and 181 in the placebo group. Of these, 632 (87.9%) completed the study. A summary of patient disposition for the trial is presented in Table 24. See also Section 7.1.3.1. [Module 5, Volume 1.21, Study report 205.9994, page 34]

Disposition of patients in the 1-year studies (205.254 and 205.255)

A total of 1990 male and female patients with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were randomized; 670 in the tio R5 group, 667 in the tio R10 group, and 653 in the placebo group. Of these, 1534 (77.1%) completed the study. A summary of patient disposition for the trial is presented in Table 23. See also Section 7.1.3.1. [Module 5, Volume 1.22, Study report 205.9992, page 73]

Reviewer comment:

A greater percentage of patients discontinued from the placebo group, primarily due to adverse events and worsening of COPD. The adverse event accounting for this difference was COPD exacerbation. Comparing the two studies, disposition of patients was generally similar.

7.2.1.2 Demographics

Demographics and baseline characteristics for the combined 12-week trials (205.251 and 205.252)

The mean age of the patients was 64.0 years (range 40-87 years); 69.4% of the trial population was male and 97.4% were white. The mean duration of COPD was 9.7 years. All patients were current (39.1%) or ex-smokers (60.9%), with a mean smoking history of 51.0 pack years. The mean pre-bronchodilator FEV_1 was 1.15L with a mean percent predicted of 40.7%. The mean pre-bronchodilator FEV_1/FVC was 47.5%. The mean post-bronchodilator FEV_1 was 1.35L with a mean percent predicted of 47.8%. The overall demographic profile was generally balanced across the four treatment groups. Pulmonary function data at baseline were generally comparable. Any differences in PFT data were dealt with in the analysis by including baseline as a covariate in the model. Demographic characteristics are provided in Table 32, and baseline PFT variables are provided in Table 33. [Module 5, Volume 1.21, Study report 205.9994, pages 46-61]

Table 32: Combined studies 205.251 and 205.252 patient demographic and disease characteristics

	Tio R 5	Tio R 10	IB MDI 36	Placebo	Total
Number of patients[1]	180	180	178	181	719
Gender [N(%)]					
Male	125(69.4)	129(71.7)	120(67.4)	125(69.1)	499(69.4)
Female	55(30.6)	51(28.3)	58(32.6)	56(30.9)	220(30.6)
Race					
White	176(97.8)	171(95.0)	177(99.4)	176(97.2)	700(97.4)
Black	3(1.7)	8(4.4)	0(0.0)	5(2.8)	16(2.2)
Asian	1(0.6)	1(0.6)	1(0.6)	0(0.0)	3(0.4)
Age [years][2]					
Mean	64.4	63.6	64.7	63.4	64.0
Median	64.0	64.0	64.0	64.0	64.0
SD	8.9	9.0	8.4	8.9	8.8
Min	41.0	40.0	42.0	40.0	40.0
Max	84.0	87.0	84.0	87.0	87.0
Smoking history [N(%)]					
Never smoked	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Ex smoker	114(63.3)	113(62.8)	107(60.1)	104(57.5)	438(60.9)
Smoker	66(36.7)	67(37.2)	71(39.9)	77(42.5)	281(39.1)
Smoking history [pack years]					
Mean	51.9	53.1	48.4	50.8	51.0
Median	42.5	45.0	42.5	44.0	44.0
SD	30.3	31.2	24.7	30.0	29.2
Min	10.0	10.0	11.0	10.0	10.0
Max	171.0	168.0	195.0	200.0	200.0
Duration of COPD [years][3]					
Mean	10.4	9.6	9.8	9.1	9.7
Median	9.0	7.0	8.0	7.2	8.0
SD	7.5	8.5	6.6	7.1	7.5
Min	0.4	0.8	0.3	0.3	0.3
Max	46.0	50.0	30.0	42.0	50.0

1 The percentages may not add up to 100% due to missing data.
2 Calculated from date of birth and date screened.
3 Regardless of when COPD diagnosis was made.

Table 33: Combined studies 205.251 and 205.252 screening PFT data

	Tio R 5	Tio R 10	IB MDI 36	Placebo	Total
Number of patients	180	180	178	181	719
Pre-bronchodilator FEV1 [L]					
Mean	1.103	1.135	1.157	1.198	1.148
Min	0.35	0.4	0.31	0.41	0.31
Max	2.42	2.15	2.17	2.28	2.42
Pre-bronchodilator % predicted normal FEV1 - ECCS					
Mean	39.7	39.4	41.4	42.1	40.7
Min	10	15	12.7	12.6	10
Max	66.8	60.3	64.3	64.2	66.8
Pre-bronchodilator FVC [L]					
Mean	2.401	2.461	2.432	2.531	2.457
Min	0.71	1.07	0.55	0.89	0.55
Max	4.32	4.73	4.94	5.61	5.61
Pre-bronchodilator FEV1/FVC [%]					
Mean	46.7	46.9	48.3	48	47.5
Min	19.8	15.3	15.4	20.5	15.3
Max	70.7	88.9	72.1	81.3	88.9
Post-bronchodilator FEV1 [L]					
Mean	1.301	1.345	1.345	1.404	1.349
Min	0.48	0.44	0.49	0.49	0.44
Max	2.71	2.56	2.7	2.76	2.76
Post-bronchodilator[2] % predicted normal FEV1 - ECCS					
Mean	47.1	46.6	48.2	49.5	47.8
Min	14.1	18.3	16	14.8	14.1
Max	81.4	74.5	76.2	103	103
Post-bronchodilator[2] FEV1 [L] change from pre-dose[1]					
Mean	0.198	0.207	0.188	0.208	0.2
Min	-0.13	-0.27	-0.12	-0.12	-0.27
Max	0.66	0.79	0.84	0.87	0.87
Post-bronchodilator[2] % change from pre-dose[1]					
Mean	19.9	19.6	18.5	18.1	19
Min	-9.1	-19	-12	-9.7	-19
Max	85.7	103	67.2	60.4	103
Post-bronchodilator[2] FVC [L]					
Mean	2.722	2.799	2.749	2.838	2.777
Min	1.1	1.01	1.08	1.04	1.01
Max	6.05	5.31	5.48	6.41	6.41

[1] Obtained from Visit 1, Screening Visit
[2] 30 minutes after 400 µg of albuterol

Demographics and baseline characteristics for the combined 1-year trials (205.254 and 205.255)

The mean age of the patients was 65.0 years (range 38-90 years); 74.2% of the trial population were male and 91.4% were white. The mean duration of COPD was 8.9 years. All patients were current (36.3%) or ex-smokers (63.7%), with a mean smoking history of 47.8 pack years. The mean pre-bronchodilator FEV1 was 1.09L with a mean percent predicted of 38.5%. The mean pre-bronchodilator FEV1/FVC was 42.8%. The mean post-bronchodilator FEV1 was 1.28L with a mean percent predicted of 45.3%. The overall demographic profile was generally balanced across the treatment groups. Pulmonary function data at baseline were generally comparable. Any differences in PFT data were dealt with in the analysis by including baseline as a covariate in the model. Demographic characteristics are provided in Table 34, and baseline PFT variables are provided in Table 35. [Module 5, Volume 1.22, Study report 205.9992, pages 80-88]

Table 34: Combined studies 205.254 and 205.255 patient demographic and disease characteristics

	Tio R5	Tio R10	Placebo	Total
Number of patients[1]	670	667	653	1990
Gender [N (%)]				
Male	491 (73.3)	498 (74.7)	487 (74.6)	1476 (74.2)
Female	179 (26.7)	169 (25.3)	166 (25.4)	514 (25.8)
Race [N (%)]				
Missing	46 (6.9)	44 (6.6)	45 (6.9)	135 (6.8)
White	611 (91.2)	613 (91.9)	594 (91.0)	1818 (91.4)
Black	7 (1.0)	8 (1.2)	14 (2.1)	29 (1.5)
Asian	6 (0.9)	2 (0.3)	0 (0.0)	8 (0.4)
Age [years][2]				
Mean	64.7	65.1	65.2	65.0
Median	65.0	65.0	66.0	65.0
SD	8.6	8.5	8.7	8.6
Min	38.0	41.0	40.0	38.0
Max	90.0	88.0	87.0	90.0
Smoking history [N (%)]				
Ex smoker	416 (62.1)	435 (65.2)	417 (63.9)	1268 (63.7)
Smoker	254 (37.9)	232 (34.8)	236 (36.1)	722 (36.3)
Smoking history [pack years]				
Mean	47.1	48.6	47.6	47.8
Median	42.0	41.5	42.0	42.0
SD	26.9	26.9	26.1	26.6
Min	10.0	10.0	10.0	10.0
Max	250.0	208.0	180.0	250.0
Duration of COPD [years][3]				
Mean	8.3	9.0	9.5	8.9
Median	6.5	7.0	8.0	7.0
SD	6.4	7.4	7.5	7.1
Min	0.0	0.0	0.0	0.0
Max	35.8	48.0	44.0	48.0

1 The percentages may not add up to 100% due to missing data.
2 Calculated from date of birth and date screened
3 Regardless of when COPD diagnosis was made
Obtained from Visit 1, screening visit

Table 35: Combined studies 205.254 and 205.255 screening PFT data

	Tio R5	Tio R10	Placebo	Total
Number of patients	670	667	653	1990
Pre-bronchodilator FEV_1 [L]				
Mean	1.088	1.088	1.083	1.086
Min	0.25	0.28	0.16	0.16
Max	2.78	3.88	2.44	3.88
Pre-bronchodilator % predicted normal FEV_1 – ECCS				
Mean	38.7	38.5	38.3	38.5
Min	9.6	11.5	11.6	11.5
Max	83.5	91.4	84.5	91.4
Pre-bronchodilator FVC [L]				
Mean	2.589	2.613	2.579	2.594
Min	0.56	0.47	0.19	0.19
Max	5.57	6.28	5.67	6.28
Pre-bronchodilator FEV_1 / FVC [%]				
Mean	43.0	42.6	42.7	42.8
Min	41.7	41.9	42.1	41.9
Max	82.7	85.1	84.2	85.1
Post-bronchodilator FEV_1 [L]				
Mean	1.280	1.278	1.273	1.277
Min	0.20	0.32	0.24	0.20
Max	3.14	4.08	2.80	4.08
Post-bronchodilator[2] % predicted normal FEV_1 – ECCS				
Mean	45.6	45.2	45.2	45.3
Min	11.5	11.9	8.4	8.4
Max	85.1	96.1	101.5	101.5
Post-bronchodilator[2] FEV_1 [L] change from pre-dose[1]				
Mean	0.192	0.189	0.190	0.190
Min	-0.38	-0.71	-0.69	-0.71
Max	1.19	1.34	1.36	1.36
Post-bronchodilator[2] FEV1 % change from pre-dose[1]				
Mean	19.9	19.4	20.8	20.0
Min	-65.5	-48.3	-42.9	-65.5
Max	293.3	158.6	850.0	850.0
Post-bronchodilator[2] FVC [L]				
Mean	2.959	2.960	2.963	2.961
Min	0.98	0.82	1.06	0.82
Max	5.88	6.71	7.83	7.83

1 Obtained from Visit 1, Screening Visit
2 30 minutes after 400µg of albuterol

7.2.1.3 Extent of exposure (dose/duration)

Extent of exposure for the combined 12-week studies (205.251 and 205.252)

A total of 719 COPD patients were randomized and received at least one dose of study medication. The planned exposure for each patient was 12 weeks (85 days). Overall, the mean exposure was 81 days. Patients randomized to the IB MDI 36 group had a slightly shorter exposure duration (79 days) than those in the other three groups, consistent with a larger number of discontinuations in this group. See Table 36. [Integrated Summary of Safety, Module 2, Volume 1.2, Section 2.7.4., page 26]

Table 36: Combined 12-week studies (205.251 and 205.252) summary of treatment exposure

	Tio R5	Tio R10	IB MDI 36	Placebo	Total
Total Treated N	180	180	**178**	181	719
Maximum Exposure n (%)					
1 day	0	2 (1.1)	2 (1.1)	3 (1.7)	7 (1.0)
2 – 8 days	2 (1.1)	2 (1.1)	4 (2.2)	6 (3.3)	14 (1.9)
9 – 50 days	10 (5.6)	9 (5.0)	11 (6.2)	8 (4.4)	38 (5.3)
51 – 80 days	6 (3.3)	5 (2.8)	11 (6.2)	9 (5.0)	31 (4.3)
>80 days	162 (90.0)	162 (90.0)	150 (84.3)	155 (85.6)	629 (87.5)
Treatment Exposure (days)					
N	180	180	178	181	719
Mean	82.7	82.2	79.0	80.1	81.0
SD	16.8	19.0	22.1	22.5	20.2
Median	85.0	85.0	85.0	85.0	85.0
Min	4	1	1	1	1
Max	120	111	119	131	131

Extent of exposure for the combined 1-year studies (205.254 and 205.255)

A total of 1990 COPD patients were randomized and received at least one dose of study medication. The planned exposure for each patient was 48 weeks (337 days). Overall, the mean exposure was 289.4 days. Patients randomized to the tio R5 group had the longest mean duration of 304.7 days. The tio R10 group was exposed for 297.2 days, and the placebo group for 265.6 days, consistent with a larger number of discontinuations in the placebo group. See Table 37. [Integrated Summary of Safety, Module 2, Volume 1.2, Section 2.7.4., page 25]

Table 37: Combined studies 205.254 and 205.255 summary of treatment exposure

	Tio R5	Tio R10	Placebo	Total
Total Treated N	670	667	653	1990
Maximum Exposure n (%)				
1 day	2 (0.3)	1 (0.1)	6 (0.9)	9 (0.5)
2 – 7 days	3 (0.4)	3 (0.4)	14 (2.1)	20 (1.0)
8 – 60 days	33 (4.9)	41 (6.1)	85 (13.0)	159 (8.0)
61 – 100 days	14 (2.1)	19 (2.8)	13 (2.0)	46 (2.3)
101 – 200 days	27 (4.0)	36 (5.4)	44 (6.7)	107 (5.4)
201 – 330 days	72 (10.7)	74 (11.1)	67 (10.3)	213 (10.7)
>330 days	519 (77.5)	493 (73.9)	424 (64.9)	1436 (72.2)
Treatment Exposure (days)				
N	670	667	653	1990
Mean	304.7	297.2	265.6	289.4
SD	87.9	96.4	123.5	104.9
Median	337.0	337.0	337.0	337.0
Min	1	1	1	1
Max	412	450	414	450

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Two 4-week crossover studies comparing Respimat to HandiHaler were also considered by the Applicant to be pivotal. Safety data was also drawn from these studies, in addition to the 3-week parallel group Phase 2 dose-ranging study. See Table 38. Finally, retrospective follow up data from the two 1-year pivotal trials (205.254 and 205.255) are described as Protocol 205.392 in Section 7.2.9.1.

Table 38: Spiriva Respimat program additional studies used to support safety

ID	Study type	Study duration	Patient age	Treatment groups†	N (ITT)	Study Year#	Countries
205.249	cross over comparison, COPD	4 wks	≥40 yrs	tio R5 QD tio R10 QD tio HH18 QD placebo	131 131 131 131	2004	US Canada
205.250	cross over comparison, COPD	4 wks	≥40 yrs	tio R5 QD tio R10 QD tio HH18 QD placebo	76 76 76 76	2003	Belgium Netherlands
205.127	Dose ranging	3 wk	≥40 yrs	tio R1.25, R2.5, R5, R10, R20 QD tio HH 18 QD Placebo R, HH	202	1999	France

† tio R5 = tiotropium Respimat 5mcg total daily dose (2.5 mcg/spray); tio R10 = tiotropium Respimat 10 mcg total daily dose (5 mcg/spray); ipratr = ipratropium bromide 36 mcg (2 inhalations of 18 mcg) four times a day; tio HH18 = tiotropium HandiHaler 18 mcg one inhalation daily

Year study subject enrollment ended

7.2.2.2 Postmarketing experience

Spiriva Respimat 5mcg has been commercially available in five European countries (Germany, Denmark, Ireland, Netherlands, and United Kingdom) starting in October 2007. Cases were included in the post-marketing safety report for the period October 1, 2007 to January 20, 2008. Post-marketing experience with Spiriva Respimat is described under Section 7.2.9.2.

7.2.2.3 Literature

In response to an FDA request in the 72-day letter, the Applicant submitted a literature review of all clinical trials involving tiotropium over the period December 2001 to April 2008. Literature prior to this date was reviewed as part of the Spiriva HandiHaler application (NDA 21,395). The Applicant performed a literature review of all original clinical and pre-clinical articles referencing tiotropium from Medline, Embase, and current contents plus supplemental manual journal scanning. The clinical papers include both those with major mentions of tiotropium and those with minor mentions. In addition to the search for articles mentioning tiotropium, the Applicant conducted an additional Medline search for anticholinergic-antimuscarinic antagonist clinical citations. [NDA 21,936 submission dated April 11, 2008]

The tiotropium pre-clinical citations and the citations with minor mention of tiotropium do not contain any pertinent information relating to safety or efficacy. There are 109 citations with major clinical mentions of tiotropium. The Applicant divided the citations into the following groups:

- Publications with mention of AEs or discontinuations for AEs (15)
- Publications with no mention of AEs (27)

- Publications of individual case reports (10)
- Publications based on BI trials for which a full study report was submitted to FDA (47)
- Publications of health economic studies (10)

Of the 15 publications with mention of safety data, 4 were meta-analyses or database studies, 6 were open-label, and 1 was retrospective. Three studies were randomized, double-blind, prospective, controlled trials. These included:

- A 12-week cross over study comparing salmeterol/fluticasone propionate (50/500) twice daily with tio HH18 once daily to both together in 90 patients with COPD. The most common AEs in the tio HH18 group were dry mouth, headache, and cough. No SAEs were reported.[1]
- A single dose crossover study comparing tio HH18 to placebo in 11 healthy volunteers. No effect of tio HH18 on heart rate variability was observed with tiotropium.[2]
- The INSPIRE study, sponsored by Glaxo Smith Kline. It is a 2-year parallel group study comparing salmeterol/fluticasone propionate 50/500 (SFC) twice daily to tio HH18 once daily in 1323 patients with COPD.[3]

The INSPIRE study demonstrated a similar number of COPD exacerbations between the groups and similar improvements in FEV_1 which were maintained throughout the study. Patients in the tio HH18 had significantly more discontinuations (35.3% SFC versus 42.0% tio HH18), and a lower number of days of exposure (561 days SFC versus 519 days tio HH18). All cause mortality was significantly lower in the SFC group compared to the tio HH18 group; 21 (3%) of SFC patients and 38 (6%) of tio HH18 patients died (p=0.032) during the study period. The most frequent event associated with death in the tio HH18 group was cardiac disorders. Adverse events overall were generally similar in the two groups, except for an increased incidence of pneumonia in the SFC group, occurring in 50 patients (8%) versus 24 (4%) in the tio HH18 group.

<u>*Reviewer comment:*</u>

Discontinued patients in the INSPIRE study were not followed up for vital status; therefore, any potential effect of differential discontinuation on mortality is unknown. In addition, INSPIRE was not a placebo-controlled study; therefore, whether the mortality difference observed between treatment groups could be secondary to a reduction in mortality in the SFC (Advair) group as opposed to an increase in the tiotropium group. In the TORCH study[4], Advair showed a numerical but not a statistically significant improvement in 3-year all-cause mortality over placebo (12.6% SFC versus 15.2% placebo, p=0.052). A survival indication was not granted for Advair. [NDA 21,077; Medical Officer Review June 5, 2007]

7.2.3 Adequacy of Overall Clinical Experience

Overall, 3173 patients, 3103 of whom had COPD, participated in the Spiriva Respimat clinical trials, and 2077 were exposed to at least one dose of Spiriva Respimat. Of these, 1061 were exposed to the 5 mcg dose. The total number of patients exposed to any dose of Spiriva Respimat included 519 patients for more than 330 days, and 591 were exposed for more than 200 days. Similar exposure times were seen for the 10 mcg dose. The overall exposure is adequate to meet the ICH guidelines for new drug products. In addition, a large safety database is available with Spiriva HandiHaler, a product that contains the same chemical entity with a different delivery mechanism.

Although the overall clinical experience for Spiriva Respimat is numerically adequate, a potential mortality signal in favor of placebo was observed in the 1-year trials. A portion of this imbalance can be explained by differential discontinuation from the placebo group, but the remainder cannot be explained with currently available data. Therefore, additional data are required to determine the nature of this mortality imbalance.

The Applicant submitted partial preliminary data from a 6000 patient 4-year placebo-controlled trial of Spiriva HandiHaler (UPLIFT) that does not demonstrate increased mortality in the tiotropium group. See Section 7.1.1.4. While these data are reassuring, full review of a complete study report is needed to determine safety for Spiriva Respimat.

Reviewer comment:

If the potential mortality signal is real, it is most likely to be associated with systemic exposure of tiotropium rather than a local effect. Therefore, application of Spiriva HandiHaler safety data to the Respimat program is supported.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal or in vitro testing was submitted as part of this application.

7.2.5 Adequacy of Routine Clinical Testing

For the majority of patients in the Phase 3 program, monitoring of physical exam, vital signs, ECGs, and clinical laboratory variables occurred only at baseline and at the end of the study. A subset of over 300 patients in the 1-year trials had additional ECGs as well as Holter monitoring performed. This is consistent with the Division's request for Holter monitoring in a subset of patients. In addition, tiotropium bromide is already available on the market as Spiriva HandiHaler, with a large safety database.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

A workup for metabolic, clearance, and interactions was not completed as part of this application since the same chemical entity (tiotropium bromide) is already marketed as Spiriva HandiHaler.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adverse events, with the exception of mortality, have been adequately assessed as part of the Spiriva Respimat development program. See Section 7.2.3 for a discussion of additional data required to assess mortality.

7.2.8 Assessment of Quality and Completeness of Data

The clinical follow up was adequate and protocol violations were infrequent in all of the studies. No concerns regarding data quality were identified during the review. A final assessment of quality will await the DSI audit.

7.2.9 Additional Submissions, Including Safety Update

The 4-month safety update included: 1) the final report from Protocol 205.392, a retrospective follow up of patients discontinuing from the 1-year pivotal trials (205.254 and 205.255); 2) post-marketing safety data for Spiriva Respimat; and 3) a summary of safety data from completed and ongoing clinical trials, including new trials not submitted in the original NDA. Because the final report of Protocol 205.392 is reviewed in detail, the interim report of this study provided in the original NDA submission was not reviewed.

7.2.9.1 Protocol 205.392

Study title

A retrospective collection of vital status and pulmonary medication usage data for patients with chronic obstructive pulmonary disease (COPD) who withdrew prematurely from either of two one-year trials (205.254, 205.255) of tiotropium inhalation solution delivered by the Respimat inhaler [March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, page 1]

Design

This study was undertaken to collect vital status data for all of the 456 patients who withdrew prematurely from Protocols 205.254 and 205.255. Regulatory Agency and Ethics/Investigational Review Committee approvals were sought as appropriate along with written informed consent for medical record review from patients or next of kin. Source data verification was performed by the clinical research organization (b) (4) that undertook the conduct of the study on behalf of the applicant. Previously, available vital status data were collected by fax inquiry to the sites without source data verification. [March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, page 22]

Duration

The two original trials were conducted from February 2003 through June 2005 and were unblinded in July 2005. This study was initiated March 11, 2007 and completed January 25, 2008. An interim report dated October 26, 2007 was submitted to FDA as part of the NDA. The final study report dated March 5, 2008 was submitted to FDA with the 4-month safety update. [March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, page 1]

Objectives

The primary objective was to ascertain the vital status (dead or alive) of patients who participated in two one-year trials (205.254 and 205.255) and withdrew prematurely prior to their predicted exit date (i.e. withdrew sometime between the first intake of randomized treatment to 48 weeks + 30 days after).

The secondary objective was to collect information on pulmonary medications and other pulmonary interventions used by the patients at the time of their predicted exit date.

[March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, page 148 (Protocol 205.392, page 18)]

Endpoints

The primary endpoint for this study was the number of patients alive, dead or lost to follow up at their predicted exit date, defined as 48 weeks after first intake of randomized treatment plus 30 days follow-up. The secondary endpoint was information on patients' pulmonary medication use at the predicted exit date or at date of death if before the predicted exit date. [March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, page 148 (Protocol 205.392, page 18)]

Study procedures

This study was a retrospective data collection on patients who withdrew from Protocols 205.254 and 205.255. When not apparent from direct contact with the patient or next of kin, information on vital status was sought from public registries, databases and any other accessible means. Information on pulmonary medications was obtained from review of medical records. For patients who died, information on cause of death was sought from patients' medical records, autopsy reports, and death certificates. [March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, page 149 (Protocol 205.392, page 149)]

A number of regulatory issues were encountered which delayed data retrieval or made it impossible. These included: 1) some countries have additional regulatory agencies and Ethics Committees required to release such a study, 2) some countries required regulatory approval before Ethics Committee review, 3) prolonged review time at several Ethics Committees, 4) some investigators refused to participate, and 4) two Ethics Committees disbanded and there were delays in setting up new committees.

All deaths occurring and date of death were reported, irrespective of the time interval between the event and the last intake of trial medication. The collected data allow evaluation up to the predicted exit date and additional sensitivity analysis using a different cut-off date.

[March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, pages 25-28]

Statistical plan

The summary of all data was based on all patients that received at least one dose of study medication in the 205.254 or 205.255 trials and withdrew prematurely; this set of patients was defined as the Treated Set. The predicted exit date was calculated as 48 weeks from first intake of randomized treatment + 30 days (366 days).

The primary analysis compared treatment groups with respect to the number of patients dead or alive at their predicted exit dates. Summary statistics were presented by treatment group. The secondary analysis compared treatment groups with respect to the number of patients taking pulmonary medication (yes or no) after their withdrawal from the 205.254 or 205.255 trials at their predicted exit dates or at date of death if before predicted exit date. Pulmonary medications were summarized by class of drug: short acting beta adrenergics, long acting beta adrenergics, short acting anticholinergics, long acting anticholinergics, inhaled corticosteroids, oral corticosteroids, LABA/ICS combinations, theophyllines, oxygen therapy, and other pulmonary interventions. Pulmonary medications were also summarized by treatment group.

Vital status at the predicted exit date was determined with the following assumptions:

- If a patient has died and the predicted exit date was before the date of death, the patient is considered to be alive.
- If a patient refused consent but the last contact date is after the predicted exit date, the patient is considered to be alive.
- If a patient is lost to follow up and the last contact date a patient was known to be alive is after the predicted exit date, the patient is considered to be alive.

[March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, page 35]

Results

Vital status

Of the 1990 patients randomized into Studies 205.254 and 205.255, 456 patients discontinued prior to completing the study. Of the 456 patients in the study population, 201 (44%) were participants in Study 205.254 and 255 (56%) were participants in Study 205.255. Vital status was obtained on a total of 411 of 456 discontinued patients (90.1%). See

Figure 7 for a graphical representation of patient disposition.

Thirty-two of the 456 discontinued patients died during the trials and were reported in the original study reports. An additional two deaths were also reported in the original study reports from Trials 205.254 and 205.255. These two patients were reported as dead in the original study reports because death occurred due to serious adverse events that began during the study period. Ten patients were found to have died after discontinuation but prior to the predicted exit date, for a total of 44 deaths during the two studies. The timing of these 10 deaths ranged from 34 to 309 days from last intake of study drug. An additional 44 deaths that occurred after the predicted exit date were reported as part of the data collection for Study 205.392.

Of the 45 patients for whom vital status was not available, 24 were reported as lost to follow up. One patient refused consent for the study, and the last contact was prior to the predicted exit date; therefore, vital status could not be determined. Vital status could not be collected for an additional 20 patients, primarily due to prolonged regulatory approval times in 14 patients. These data are listed as missing. Vital status on 6 patients is reported as not available. Five of these patients were invited to consent on two occasions but did not respond; legislation in Finland requires informed consent for vital status retrieval. One patient in Norway withdrew consent in the original study; legislation in that country requires exclusion from follow up. The number of patients with missing vital status was similar among the treatment groups. Vital status at the predicted exit date by the previous study treatment is provided in Table 39. [March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, pages 37-47]

Figure 7: Disposition and vital status for patients originally enrolled in Studies 205.254 and 205.255, as determined in Study 205.394

Table 39: Protocol 205.392 vital status at predicted exit date by previous study treatment

Patient vital status	Tio R5 N=103	Tio R10 N=121	Placebo N=200	Total N=424†
Alive	85	106	178	369
Dead	4	2	4	10
No data	14	13	18	45
Lost to follow up	8	5	11	24
Refused consent	0	0	1	1
Not available	3	2	1	6
Missing	3	6	5	14

†not including 32 patients reported in 205.254/205.255 whose vital status was already known (dead)

Number of deaths

Counting the number of deaths occurring in Protocols 205.254 and 205.255 depends on the definitions applied regarding date of death. The "worst case" scenario counts all deaths reported in the study reports for Protocols 205.254 and 205.255 in addition to the 10 deaths found in follow up which occurred prior to the predicted exit date (366 day cut off). The "best case" scenario determined by the reviewer makes the following changes to the "worst case" scenario:

- excludes two patients originally counted in the study reports for Protocols 205.254 and 205.255 because they occurred after the cut off date (Patient 6833 tio R10 and Patient 4778 tio R5)
- includes two patients who died on day 667 (Patient 6601 placebo and Patient 3822 tio R5)
- includes two patients who had an unknown date of death (Patient 6370 placebo and Patient 8032 placebo) counted by the applicant as 'alive'

The applicant justifies a cut off date of 369 days as an alternative to 366 days because 369 days was the mean exposure time for patients who completed study medication. See Table 40 for a summary of numbers of deaths in the trials. [March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, pages 37-47]

Table 40: Protocol 205.392 number of deaths by study treatment

	205.254			205.255			Combined			
	tio R5	tio R10	plac	tio R5	tio R10	plac	tio R5	tio R10	plac	total
Original study reports	7	8	5	5	9	0	12	17	5	34
Worse case	9	8	7	7	11	2	16	19	9	44
Censored at 369 days	9	8	7	7	10	3	16	18	10	44
Best case	9	8	7	7	10	5	16	18	12	46

Reviewer comment:

Follow up of patients discontinuing shows that although a portion of the imbalance in deaths found in Protocols 205.254 and 205.255 may be due to differential discontinuation from the placebo group, the tiotropium groups still show an increase in mortality compared to placebo. The difference is particularly apparent in Protocol 205.255. Protocol 205.255 did show an unusually good outcome in patients in the placebo group; however, baseline characteristics do not suggest obvious fundamental differences between the treatment groups.

Cause of death

The most frequent causes of death were undetermined and neoplasms, primarily lung cancer. COPD exacerbations and myocardial infarction were third and fourth most frequent, respectively. There was an imbalance in deaths due to cardiac causes (7 in the tiotropium groups compared to none in the placebo group) and pneumonia (4 in the tiotropium groups compared to none in the placebo groups). Other causes of death were either infrequent or balanced among the treatment groups. The causes of death were generally conditions that are anticipated in the patient population chosen for the studies, older adult smokers, and former smokers with moderate to severe COPD. See Table 41 for a summary of causes of death. [March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, pages 53-58, 123]

Reviewer comment:

Causes of death for the studies were adjudicated by the reviewer in an unblinded fashion from data provided in the narratives. Causes are grouped by preferred term.

Table 41: Protocol 205.255, 205.255 and 205.392 fatal events by treatment group (reviewer adjudication)

Events leading to death	Tio R-5 [n=670]	Tio R-10 [n=667]	Placebo [n=653]
Total deaths	**16**	**19**	**9**
Cardiac failure	1		
Myocardial infarction/coronary insufficiency	5	1	
Gastrointestinal hemorrhage		1	1
Death (cause undetermined)		6	3
Neoplasms†	4	3	2
Motor vehicle accident		1	
Suicide	1		
Sepsis		1	
CVA		1	1
COPD exacerbated	3	3	2
Pneumonia	2	2	

†7 patients with lung, one esophageal, and one colon cancer

Pulmonary medication use

Medical records were only available for 226 (53.9%) of patients. A contributing factor to this low percentage was that if patients did not provide informed consent and medication data was available, the data were not used. As expected, the majority of patients for whom records were available used pulmonary medications at the predicted exit date (217, 96.0%). Of the patients who used pulmonary medications, 77.9% used short acting beta agonists, 20.3% used long acting beta agonists (LABA), 31.3% used inhaled corticosteroids (ICS), 42.9% used LABA/ICH combinations, 17.1% used theophyllines, 40.6% used short acting anticholinergics, and 37.3% used long acting anticholinergics (Spiriva HandiHaler). Among those patients for whom data were available, use of long acting anticholinergics after discontinuation from the study was generally consistent across the treatment groups, with 33.3% of the tio R5 group, 47.5% of the tio R10 group, and 33.3% of the placebo group using Spiriva at the predicted exit date. [March 18, 2008 Safety Update Report, Module 5, Volume 1, Study report 205.392, pages 47-51]

Reviewer comment:

Use of Spiriva after discontinuation from the study is a confounding factor for interpreting retrospectively collected mortality data. Unfortunately, none of the 4 discontinued patients originally randomized to the placebo group who died prior to the predicted exit date had medical records available, so it is not known whether or not these patients were using Spiriva prior to death.

Summary and conclusions

Of the 1990 patients randomized into Studies 205.254 and 205.255, 456 patients discontinued prior to completing the study. Vital status was obtained on a total of 411 of 456 discontinued patients (90.1%). Thirty-two of the 456 discontinued patients died during the trials and were reported in the original study reports. An additional two deaths were also reported in the original study reports from Trials 205.254 and 205.255. Ten patients were found to have died after discontinuation but prior to the predicted exit date, for a total of 44 deaths during the two studies.

In the worst case scenario for the combined studies, 16 deaths occurred in the tio R5 group, 19 in the tio R10 group, and 9 in the placebo group. The imbalance is most notable in Protocol 205.255, with 7 deaths in the tio R5 group, 11 in the tio R10 group, and 2 in the placebo group. In the best case scenario for the combined studies, 16 deaths occurred in the tio R5 group, 18 in the tio R10 group, and 12 in the placebo group. Even in the best case scenario, an imbalance still exists in favor of placebo in terms of mortality. However, the inclusion of deaths reported in Protocol 205.392 does suggest that a portion of the imbalance found in the original studies may have been due to differential discontinuation as reported by the applicant. The retrospective collection of data is confounded by the use of Spiriva HandiHaler after discontinuation by 33.3% of patients previously randomized to placebo.

The most frequent causes of death were undetermined and neoplasms, primarily lung cancer. COPD exacerbations and myocardial infarction were second and third most frequent, respectively. There was an imbalance in deaths due to cardiac causes (7 in the tiotropium groups compared to none in the placebo group) and pneumonia (4 in the tiotropium groups compared to none in the placebo groups). Other causes of death were either infrequent or balanced among the treatment groups.

7.2.9.2 Post-marketing safety data

Spiriva Respimat 5mcg has been commercially available in five European countries (Germany, Denmark, Ireland, Netherlands, and United Kingdom) starting in October 2007. Cases were included in the post-marketing safety report for the period October 1, 2007 to January 20, 2008. During the reporting period, it is estimated that approximately (b) (4) inhalers were sold or provided as samples, with a cumulative patient exposure of approximately 20,000 patient-years. During this same time period, there were a total of nine SAE events (among 3 patients) and 34 AE events (among 17 patients). Of these, all SAE events and 20 AE events were reported by healthcare practitioners and 14 AE events were reported by consumers.

The SAEs included the following single events: COPD, pulmonary hypertension, bronchopneumonia, chlostridial infection, diarrhea, megacolon, ileus, gastric cancer, and anaphylactic shock. The AE reports did not suggest any unusual events other than what is anticipated in a COPD population.

The case of anaphylactic shock was also reported to the IND (February 6, 2008). The patient was a 67 year old male who had been on Spiriva Respimat for one month. Directly after an inhalation, he "passed out" and experienced urticaria. He was diagnosed with anaphylactic shock in the hospital, from which he recovered. Later on the patient had a small amount of Spiriva in his mouth and complained of swelling and redness of his mouth.

[Four-month safety update report, March 18, 2008, Module 5, Volume 2, pages 72-78]

Reviewer comment:

The reported case of anaphylactic shock provides convincing evidence that anaphylaxis can occur with Spiriva Respimat. This adverse event will be added to the product label.

7.2.9.3 Additional studies described in the 4-month safety update

A total of nine additional studies are described in the 4-month safety update report. Of these, 3 are completed and 6 are ongoing. The following clinical trials were completed during safety update period (07 June 2005 to 01 November 2007):

- Trial 1205.4 (23 July 2005 to 09 May 2006): a Phase IIb, dose ranging trial of BEA 2180, with Spiriva Respimat 5 µg as the active comparator, in COPD patients. [4 week parallel group]
- Trial 1205.6 (18 August 2005 to 22 September 2006): a Phase IIb, dose-ranging trial of BEA 2180, with Spiriva Respimat 5 µg as the active comparator, in COPD patients. [4-week crossover]
- Trial 205.291 (10 February 2006 to 07 March 2007): a Phase II crossover trial of the efficacy and safety of Spiriva Respimat 5 µg in comparison to Spiriva HandiHaler 18µg in Japanese COPD patients.

The following clinical trials were ongoing as of 01 November 2007:

- Trial 205.372 (06 October 2006 to ongoing): a Phase IIIb one-year, randomized, placebo-controlled trial of Spiriva Respimat 5 µg compared with placebo to evaluate reductions in exacerbations in COPD patients.
- Trial 205.341 (07 August 2006 to ongoing): a Phase II trial to demonstrate the superiority of Spiriva Respimat (5 and 10 µg) compared with placebo in severe asthmatic patients (added on to standard care with high dose inhaled steroids plus long-acting beta-agonist).

- Trial 205.342 (06 July 2006 to ongoing): a Phase II genotype trial to compare the efficacy and safety of Spiriva Respimat 5 µg and salmeterol hydrofluoroalkane (HFA) MDI in moderate persistent asthmatic patients homozygous for B16-Arg/Arg.
- Trial 1205.14 (06 September 2007 to ongoing): a Phase IIb trial of the efficacy and safety of BEA 2180 in COPD patients with Spiriva Respimat 5 µg as the comparator.
- Trial 205.338 (12 September 2006 to ongoing): a Phase II exploratory trial to evaluate pharmacokinetics and safety in adult and pediatric patients with cystic fibrosis treated with 2.5 µg, 5 µg and 10 µg of Spiriva Respimat in a single and multiple dose setting.

The three completed trials for which unblinded data are available were all 4 week trials enrolling relatively few patients receiving Spiriva Respimat. The patient population for the three trials included a total of 271 COPD patients with a mean FEV_1 of 44% predicted, and a mean smoking history of 56 pack years. Patients were exposed to tio R5 for a mean of 29 days.

The overall safety profile in these trials is presented in Table 42. Approximately 1/3 of patients experienced any AE, 1.4-3.8% of patients experienced a serious AE, and no deaths were reported. The most common AEs were nasopharyngitis and COPD exacerbation.

Table 42: Adverse event profile of Spiriva Respimat studies completed during the 4-month safety update period

	Trial Number		
	1205.4	**1205.6**	**205.291**
	Number (%)		
Treated patients	53 (100.0)	71 (100.0)	147 (100.0)
Patients with any AEs	20 (37.7)	25 (35.2)	45 (30.6)
Patients with severe AEs	2 (3.8)	1 (1.4)	3 (2.0)
Patients with drug-related AEs	0	1 (1.4)	4 (2.7)
Patients with AEs leading to discontinuation	0	3 (4.2)	1 (0.7)
Patients with serious AEs	2 (3.8)	1 (1.4)	4 (2.7)
Fatal	0	0	0
Requiring hospitalization	2 (3.8)	1 (1.4)	4 (2.7)
Prolonged hospitalization	1 (1.9)	0	0
Other	0	0	0

In the six ongoing trials, 25 deaths have been reported, all of which occurred in Study 205.372, a 1-year placebo-controlled study to evaluate the effect of tio R5 on COPD exacerbations. All of the deaths are attributable to causes which are not unusual for the patient population. Because the study is ongoing, the data currently remain blinded.

Reviewer comment:

While the data presented in the 4-month safety update add to the overall safety database for Spiriva Respimat, the completed trials are all short-term comparison studies enrolling a relatively small number of patients. None of these studies show any new or unexpected findings with regards to safety. The ongoing 1-year COPD exacerbation trial (205.372) will be important in further elucidating the safety profile of Spiriva Respimat, particularly mortality.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

An increased number of deaths was observed in the tiotropium Respimat treatment groups compared to placebo for the 1 year studies, primarily in Protocol 205.255. Follow up and evaluation of patients who discontinued prematurely demonstrated that a portion of this mortality imbalance can be explained by differential drop outs. The remainder of the signal cannot be explained with available data. The overall percentage of patients in the tiotropium groups who died during the 1-year studies is not unexpected for the patient population, whereas the death rate in the placebo groups is unexpectedly low. However, additional data are required to determine the nature of this mortality imbalance.

The Applicant submitted partial preliminary data from a 6000 patient 4-year placebo-controlled trial of Spiriva HandiHaler (UPLIFT) that does not demonstrate increased mortality in the tiotropium group. While these data are reassuring, full review of the complete study report is needed to determine safety for Spiriva Respimat.

Other adverse events were not unexpected for the patient population. Across the studies as a whole, the most common adverse events were in the respiratory system, including COPD exacerbation, nasopharyngitis, and dry mouth. Dry mouth was the most common drug-related AE, occurring in a dose-related fashion in the 1-year studies. This is a known anticholinergic effect and is reported in the Spiriva HandiHaler label.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The Applicant pooled data from the two 4-week crossover studies (205.249 and 205.250), the two 12-week studies (205.251 and 205.252), and the two 1-year studies (205.254 and 205.255). Each set of studies was designed to be pooled for both efficacy and safety with an identical protocol and enrollment criteria. Each set also utilized a separate set of investigators and patients, which is important for pooling.

7.4.1.1 Pooled data vs. individual study data

In general, data analyses from the individual studies closely approximated that seen in the pooled data sets. The one notable exception is the mortality data observed in the two 1-year studies. Only a small imbalance is observed in study 205.254, which can be completely explained by differential discontinuation of placebo patients. In study 205.255, a much larger imbalance is observed that can only partially be explained by differential drop outs. While it is reassuring that the mortality imbalance is notable only in one study, from a statistical perspective the two studies show similar results as the 95% CI for the relative risk ratios are overlapping (Study 205.254 after retrospective follow up, tio R5 versus placebo mortality RR 1.1, 95% CI 0.4-3.0; Study 205.255 after retrospective follow up, tio R10 versus placebo mortality RR 3.4, 95% CI 0.7-16.5).

7.4.1.2 Combining data

As noted above, studies were designed prospectively to be pooled. Review of patient demographic and baseline characteristics further support demonstrate that the studies designed to be combined are, in fact, appropriate for pooling of data.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

Dry mouth is increased in a dose-related fashion in the tiotropium groups across the Phase 3 program. Dry mouth is an anticholinergic effect that represents a known class effect of this drug. Urinary tract infection is also consistently increased across the Phase 3 program in a dose-related fashion, although the effect size is much smaller than for dry mouth. This may represent a consequence of urinary retention, also a known class effect of the drug.

7.4.2.2 Explorations for time dependency for adverse findings

The effect of time dependency on mortality was investigated using Kaplan-Meier curves. See Section 7.1.1.1. In general, deaths accumulated gradually over the course of the study, suggesting that mortality was not a time-dependent effect.

7.4.2.3 Explorations for drug-demographic interactions

Safety was analyzed in a variety of special groups and situations for the 1-year trials (205.254 and 205.255). These included intrinsic factors of gender, age, race, and disease severity. See Section 7.1.5.6 for a complete discussion.

7.4.2.4 Explorations for drug-disease interactions

Safety was analyzed by disease severity according to the GOLD criteria for COPD. See Section 7.1.5.6 for a complete discussion.

7.4.2.5 Explorations for drug-drug interactions

Safety was analyzed for drug-drug interactions in the combined 1-year trials (205.254 and 205.255). These included oral steroid use at baseline, inhaled steroid use at baseline, xanthene use at baseline, and smoking status. See Section 7.1.5.6 for a complete discussion.

7.4.3 Causality Determination

No plausible explanation for the increase in mortality observed in the 1-year studies is supported by the available data. Additional data are required to determine if this potential signal represents a true safety risk for Spiriva Respimat, and if so, what the mechanism might be.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen is "5 mcg once daily administered as two inhalations of 2.5 mcg once daily." This regimen and choice of doses is supported by Phase 3 data. See Section 5.3 for a complete discussion. The primary endpoint in the six Spiriva Respimat Phase 3 trials, trough FEV_1 response, confirmed that an improvement of lung function was maintained for 24 hours at steady state for both tio R5 and tio R10.

In all four primary pivotal studies (205.251, 205.252, 205.254, and 205.255) a small, clinically insignificant efficacy advantage of tio R10 was demonstrated over tio R5, suggesting that tio R5 is at the plateau of the dosing curve. In the 1-year studies, a clear dose-effect was demonstrated for anticholinergic adverse effects of dry mouth and urinary tract infection. The most sensitive of these measures, dry mouth, was doubled in the tio R10 group as opposed to the tio R5 group (14.5% versus 7.2%). On the basis of this aggregate safety data in conjunction with comparable efficacy between the groups, the Applicant selected the 5 mcg dose (2 actuations, 2.5 mcg per actuation) for marketing.

8.2 Drug-Drug Interactions

Patients in the Spiriva Respimat Phase 3 studies were permitted to be on regularly scheduled doses of inhaled corticosteroids, xanthenes, low dose oral corticosteroids, and as needed albuterol. No interactions were observed between these drugs and tiotropium Respimat with

regards to either efficacy or safety. No formal drug-drug interaction studies were submitted with this program.

See Sections 6.1.4.4 and 7.4.2.5 for a complete discussion of drug-drug interactions. Long-acting beta-agonists were prohibited during the treatment period in the pivotal Phase 3 trials, as were anticholinergics. The proposed label contains the following statements regarding drug interactions: (b) (4) (b) (4) (b) (4) The label also contains a description of an interaction study with IV tiotropium and cimetidine or ranitidine. This was taken directly from the approved Spiriva HandiHaler label.

Reviewer comment:

The proposed labeling statements are supported by Phase 3 clinical data. The label is silent with regards to long acting beta-agonists. Literature review reveals a pilot 12-week cross over study comparing salmeterol/fluticasone propionate (50/500) twice daily with tio HH18 once daily to both together in 90 patients with severe COPD. Although no significant benefit was observed from combining therapy (although a small numerical increase was noted), no serious adverse events were observed in the combination therapy group. See Section 7.2.2.3. Clinically, combining a LABA or LABA/corticosteroid combination with tiotropium is often used in patients with severe disease, and the combination short-acting beta-agonist (albuterol) and short-acting anticholinergic (ipratropium)(Atrovent and others) is approved for the treatment of COPD. The GOLD (Global initiative for chronic Obstructive Lung Disease)[5] guidelines have the following statement regarding combining bronchodilators: "combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects."

8.3 Special Populations

Language regarding pregnancy, labor and delivery, and nursing mothers has been taken directly from the approved Spiriva HandiHaler label for the Spiriva Respimat label.

The following statement is proposed in the Spiriva Respimat label regarding geriatric use: (b) (4) (b) (4)

(b) (4)
(b) (4) Based on available data, no adjustment of SPIRIVA RESPIMAT dosage in geriatric patients is warranted."

Data regarding Spiriva Respimat in geriatric patients are reviewed in Sections 6.1.4.4 and 7.4.2.3. The proposed labeling statements are supported based on data from the combined 1-year studies. The proposed statement should be modified to mention that it is based on data from the 1-year studies.

8.4 Pediatrics

COPD is a disease which occurs only in adults; as such, this condition qualifies for a PREA waiver because studies in children would be impossible or highly impractical.

On December 4, 2007, the Division denied a submission by the sponsor to issue a pediatric Written Request for tiotropium Respimat (b) (4) .

8.5 Advisory Committee Meeting

An Advisory Committee Meeting was not held for this NDA. An internal FDA Regulatory Briefing was held on July 18, 2008. The opinions of the Board are in concurrence with the regulatory action being taken on this application by the Division of Pulmonary and Allergy Products.

8.6 Literature Review

See Section 7.2.2.3.

8.7 Postmarketing Risk Management Plan

The Applicant did not submit a post-marketing risk management plan.

8.8 Other Relevant Materials

No other relevant materials were used in this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

9.1.1 Efficacy conclusions

9.1.1.1 Bronchodilator effect

The results of the Phase 3 clinical trials including the primary endpoint trough FEV_1 are sufficient to form the basis of approval for Spiriva Respimat 5mcg once daily for the indication maintenance treatment of bronchospasm associated with COPD. In all four primary pivotal studies (205.251, 205.252, 205.254, and 205.255) a small, clinically insignificant efficacy advantage of tio R10 was demonstrated over tio R5, suggesting that tio R5 is at the plateau of the dosing curve.

In each of the four pivotal studies (205.251, 205.252, 205.254, and 205.255), both tiotropium 5 mcg (tio R5) and tiotropium 10 mcg (tio R10) were superior to placebo for the primary endpoint, trough FEV_1 response at the end of treatment. In addition, in the 12-week studies (205.251 and 205.252) both tiotropium groups were superior to ipratropium for trough FEV_1 at the end of treatment. While tio R10 was generally numerically superior to tio R5, the differences were generally small and not statistically significant. Overall, these data are sufficient to support an efficacy claim for the maintenance treatment of bronchospasm associated with COPD. Because the primary endpoint was evaluated at the end of the 24-hour dosing interval and the active pharmaceutical ingredient, tiotropium bromide, is currently approved for once daily dosing, a once daily dosing regimen for tiotropium Respimat is supported.

For the 1-year studies (205.254 and 205.255), the differences between the tiotropium groups and placebo were also highly statistically significant ($p<0.0001$) for mean FEV_1 $AUC_{(0\text{-}3h)}$ response and mean FEV_1 $peak_{(0\text{-}3h)}$ response throughout the treatment period. A similar treatment difference was observed by Day 85 in the 12-week trials (205.251 and 205.252). Based on the 1-year studies (205.254 and 205.255), the effects of tiotropium on FEV_1 appeared to reach steady state after 15 days of dosing.

In the 1-year studies (205.254 and 205.255), the forced vital capacity (FVC) results generally paralleled the FEV_1 results. The difference in FVC between the tiotropium groups and placebo were statistically significant ($p<0.0001$) at all time points post-dose on all test days. In general, the tio R10 group showed some improvement over the tio R5 group, but the differences were small and not significant. In the 12-week studies, results were more variable, but a significant difference from placebo was demonstrated for most time points.

Other secondary efficacy variables including peak expiratory flow rate (PEFR), St. George Respiratory Questionnaire (SGRQ), and Mahler Transitional Dyspnea Index (TDI) were generally supportive of efficacy of Spiriva Respimat.

In the 1-year studies for all treatment groups combined, albuterol was used an average of 2.5-2.7 occasions/day at baseline. Compared to placebo, both tiotropium groups showed a significant decrease in the use of albuterol rescue throughout the study, ranging from 0.3-1.0 fewer rescue uses per day.

9.1.1.2 COPD exacerbations

Efficacy was assessed with respect to COPD exacerbations with two replicative 1-year double-blind, placebo-controlled clinical trials (205.254 and 205.255). These trials had identical protocols and a pre-specified combined analysis for the fourth primary endpoint, number of COPD exacerbations occurring in a year. Secondary endpoints related to COPD exacerbations were also combined.

As a second study in support of the COPD exacerbation indication, the application included Protocol 205.392, a 6-month double-blind trial in a US Veterans Affairs population comparing Spiriva HandiHaler (tio HH18) to placebo (Protocol 205.266). Similar but not identical endpoints to the Respimat 1-year trials (Protocols 205.254 and 205.255) were included. Because Spiriva Respimat and Spiriva HandiHaler are different drug products, the HandiHaler data cannot be used to support the Spiriva Respimat efficacy claim. Thus, the VA clinical trial (Protocol 205.266) was not reviewed for this application.

Looking at the two studies individually, one study shows a significant improvement over placebo and one study shows borderline significance. Since reduction of COPD exacerbations is an important claim, the results are not sufficient to demonstrate reproducibility of results in two studies.

Looking at the two studies combined, as they were designed, the efficacy results regarding COPD exacerbations are much more robust, although insufficient to support an efficacy claim as a single study. In combination with a second Respimat study demonstrating efficacy with regards to COPD exacerbations, this combination study would support (b) (4) the claim that Spiriva Respimat "significantly reduced the number of COPD exacerbations compared to placebo" (b) (4) (b) (4).

9.1.2 Safety conclusions

The safety data submitted in the Spiriva Respimat clinical program are not sufficient to support approval. A potential mortality signal was noted in the one year clinical trials. While the remainder of the safety data, including adverse events, laboratory, and ECG data, are generally supportive of the safety of Spiriva Respimat, the potential mortality signal cannot be completely explained. Therefore, additional long term safety data with tiotropium will be necessary to resolve this safety issue.

Overall, 3173 patients, 3103 of whom had COPD, participated in the Spiriva Respimat clinical trials, and 2077 were exposed to at least one dose of Spiriva Respimat. Of these, 1061 were exposed to the 5 mcg dose. The total number of patients exposed to any dose of Spiriva Respimat

included 519 patients for more than 330 days, and 591 were exposed for more than 200 days. Similar exposure times were seen for the 10 mcg dose. The overall exposure is adequate to meet the ICH guidelines for new drug products. In addition, a large safety database is available with Spiriva HandiHaler, a product that contains the same chemical entity with a different delivery mechanism.

9.1.2.1 Mortality

An increased number of deaths was observed in the tiotropium Respimat treatment groups compared to placebo for the 1-year studies, primarily in Protocol 205.255. For the studies combined, a total of 12 deaths in the tio R5 group, 17 in the tio R10 group, and 5 in the placebo group were reported during the study. In 205.255, there were no deaths in the placebo group during the treatment period. The fatal adverse events were reviewed in detail and no pattern or potential mechanism of action of these events could be identified. The overall percentage of patients in the tiotropium groups who died during the 1-year studies is not unexpected for the patient population, whereas the death rate in the placebo groups is unexpectedly low.

Follow up and evaluation of patients who discontinued prematurely demonstrated that a portion of this mortality imbalance can be explained by differential drop outs. For Protocols 205.254 and 205.255 combined, the relative risk of death for the tio R5 group compared to placebo was 2.1 (95% CI 0.7-5.9) during the study; relative risk decreased to 1.6 (0.7-3.6) when deaths identified in the retrospective follow up are included. The relative risk of death for the tio R10 group compared to placebo was 2.9 (95% CI 0.7-5.9) during the study; relative risk decreased to 1.9 (0.7-3.6) when deaths identified in the retrospective follow up are included. Thus, even with the follow up vital status data, the remainder of the signal cannot be explained with available data.

The analysis of drop outs (Protocol 205.392) was potentially confounded by use of anticholinergic medications (primarily Spiriva HandiHaler) and LABAs in a large portion of the treatment group after discontinuation. In addition, vital status could not be collected from approximately 10% of discontinued patients, which may contribute to the remaining imbalance.

Adverse events leading to death in the Respimat program are not unexpected for the patient population. The only potential exception is the large number of deaths of unknown cause. No obvious safety signal can be linked to death. Even attributing all deaths from unknown causes to a particular adverse event (myocardial infarction or stroke) does not lead to a notable imbalance. Deaths were generally distributed evenly across countries when corrected for enrollment with the exception of a large number of deaths of unknown cause in Russia.

Comparison of the Spiriva Respimat trials to randomized, placebo-controlled parallel group trials in the HandiHaler program demonstrates a similar fatal adverse event rate for the tiotropium treatment groups; however, the placebo group in the Spiriva Respimat program, particularly in Study 205.255, has a lower fatal adverse event rate. The clinical trial database for Spiriva HandiHaler does not suggest a mortality signal.

The Applicant has recently completed a large, 4-year clinical trial comparing Spiriva HandiHaler to placebo (UPLIFT—Understanding Potential Long-term Impacts on Function with Tiotropium,

Protocol 205.235). This study will provide long-term safety data with Spiriva HandiHaler. Although UPLIFT was conducted with Spiriva HandiHaler rather than Spiriva Respimat, the study will provide useful information to place the mortality data in the Spiriva Respimat program in perspective. The results of UPLIFT with Spiriva HandiHaler are applicable to the Spiriva Respimat program because the products contain the same active pharmaceutical ingredient, tiotropium bromide, and Spiriva HandiHaler 18 mcg and Spiriva Respimat 5 mcg have similar systemic exposure. The study report for UPLIFT is expected in the fourth quarter of 2008.

9.1.2.2 Other safety data

For the combined 1-year studies (205.254 and 205.255), 17.2% of patients overall experienced a serious adverse event, 16.1% in the tio R5 group, 18.7% in the tio R10 group, and 16.8% in the placebo group. The most common serious adverse events were COPD exacerbations, pneumonia, and cardiac events. COPD exacerbations were balanced among the groups, occurring in 4.9% tio R5, 6.0% tio R10, and 5.7% placebo. Serious adverse events of pneumonia were increased in the tiotropium groups compared to placebo, whereas cardiac events were balanced

The most common adverse event associated with discontinuation was COPD exacerbation across all of the studies. Discontinuation due to COPD exacerbation occurred most frequently in the placebo group in the 1-year and most frequently in the ipratropium group for the 12-week studies. Focusing on the 1-year studies, there were 3.3% of patients in the tio R5 group, 3.9% in the tio R10 group, and 9.6% of patients in the placebo group who discontinued due to the adverse event of COPD exacerbation. Other adverse events leading to discontinuation occurred much less frequently. The next most common of these were dyspnea, cardiac disorders overall, nervous system disorders, neoplasms, and pneumonia. Of these, dyspnea occurred more frequently in the placebo group, pneumonia was slightly increased in the tiotropium groups, and the others were balanced among the groups.

Other adverse events were not unexpected for the patient population. Across the studies as a whole, the most common adverse events were in the respiratory system, including COPD exacerbation, nasopharyngitis, and dry mouth. Dry mouth was the most common drug-related AE, occurring in a dose-related fashion in the 1-year studies. This is a known anticholinergic effect and is reported in the Spiriva HandiHaler label.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. No particular stroke-related adverse event was definitively increased in the tiotropium groups in the combined 1-year studies (205.254 and 205.255). Combining terms of cerebral infarction, CVA, transient ischemic attack, and cerebrovascular insufficiency gives 3 events in the tio R5 group, 6 in the tio R10 group, and 3 in the placebo group.

In the 1-year studies (205.254 and 205.255) a subset of 582 patients from this study received additional 12-lead ECG measurements and 364 of these received 24-hour Holter monitoring studies that were reviewed centrally. No clinically significant changes in any of the ECG parameters were observed. For heart rate, a small decrease of 2-3 bpm compared to baseline was observed across all treatment groups. Similarly, no clinically significant changes were observed

in Holter monitoring data. Evaluation of shift tables for outliers also showed balance between the tiotropium and placebo groups.

9.2 Recommendation on Regulatory Action

This is a 505(b)(1) application for Spiriva Respimat Inhalation Spray for the long term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. In this application, Boehringer Ingelheim (BI) proposes a novel inhalation device, the Respimat inhaler, to deliver tiotropium bromide of oral inhalation. Tiotropium bromide is an anticholinergic/antimuscarinic that is currently approved as a dry powder inhaler - Spiriva HandiHaler Inhalation Powder (NDA# 21-395) – for the same indication at a dose of 18mcg once daily. The Spiriva Respimat product proposed for registration delivers 2.5mcg tiotropium bromide per actuation. The proposed dose is 5mcg (two actuations) once daily.

To support this application, BI submitted an extensive clinical development program. Sufficient data to support approval is provided from an efficacy perspective; however, a potential adverse mortality signal was demonstrated in the 1-year Phase 3 trials. Additional safety data from a long-term placebo-controlled clinical trial are required to support approval. From a clinical perspective, the recommended regulatory action is "**complete response**," i.e. non-approval.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

This section does not apply as the recommended regulatory action is complete response.

9.3.2 Required Phase 4 Commitments

This section does not apply as the recommended regulatory action is complete response.

9.3.3 Other Phase 4 Requests

This section does not apply as the recommended regulatory action is complete response.

9.4 Labeling Review

A full labeling review was conducted and the following issues regarding labeling were identified.

- Because of the complex nature of the Respimat device, patient assembly and use instructions will be important.

- Although both Spiriva Respimat and Spiriva HandiHaler contain the same drug substance, the Division of Pulmonary and Allergy Products considers them to be different products from an efficacy standpoint because they use a different delivery device and formulation. [redacted] (b) (4).

- One issue with the clinical pharmacology information submitted in this application is the two early studies that included clinical pharmacology assessments (Protocols 205.112 and 205.127) were conducted with an earlier version of Spiriva Respimat, version A3. Version [redacted] (b) (4). Because of the differences in device, the clinical pharmacology data obtained using the A3 device is not suitable for labeling purposes.

- A cautionary statement regarding renal impairment is appropriately included in the label.

- The Applicant proposes the following statement regarding pharmacodynamics in the label: [redacted] (b) (4) This statement is not supported by available data. The data support a steady state claim of 15 days based on the 1-year trials.

- No evidence of tolerance to tiotropium Respimat occurred. The slight decline in FEV_1 observed across all groups over the course of the study is expected because COPD is a progressive disease. The proposed Respimat label contains the following statement regarding the 1-year trials: [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4)" Based on presented data, this statement is supported.

- The sponsor evaluated rebound only with PEFR. PEFR is generally regarded as a secondary, supportive endpoint; therefore, data provided are not sufficiently robust to support a claim regarding rebound. The Applicant has not proposed any labeling statements regarding rebound effects.

- The results of the Phase 3 studies including the primary endpoint trough FEV_1 are sufficient to form the basis of approval for Spiriva Respimat 5mcg once daily for the indication maintenance treatment of bronchospasm associated with COPD.

- The Applicant proposes [redacted] (b) (4) Since the studies are evaluated as stand alone efficacy trials with respect to FEV_1, [redacted] (b) (4). In general, the Division prefers to include figures from one representative trial.

- The Applicant proposes [redacted] (b) (4) this figure will be removed.

- Looking at the two 1-year studies both individually and in combination, the Applicant has not demonstrated sufficient basis of approval for the claim "Spiriva Respimat significantly reduced the number of COPD exacerbations compared to placebo" [redacted] (b) (4)

[redacted] (b) (4) An additional study comparing Spiriva Respimat to placebo is required to support these claims.

- Typically, product labels for asthma and COPD trials include an AE table from the combined short-term bronchodilation trials, which form the basis of approval for these compounds. Adverse events from longer-term trials, which may support additional labeling claims, are then mentioned briefly. In this NDA, the Applicant's proposed label includes both data from the 1-year trials and the 12- week trials. Since the Spiriva HandiHaler also includes AE data from long-term trials, inclusion of the 1-year data table in the Respimat label may be appropriate for consistency and also because the majority of potential safety signals (mortality, dry mouth, pneumonia, etc.) were better expressed in the long-term studies.

- The proposed Respimat label includes the following statement regarding common adverse events: [redacted] (b) (4) (b) (4) [redacted] (b) (4) The proposed language is acceptable. Very few patients discontinued due to the adverse event of dry mouth.

- Labeling language regarding the "thorough QT study" is currently under negotiation for the Spiriva HandiHaler label. Once this language is finalized for the HandiHaler label, it will also be added to the Spiriva Respimat label.

- The Applicant proposes adding the following new language to the overdose section of the label: [redacted] (b) (4) (b) (4) [redacted] (b) (4) The first statement is supported by the results of Protocol 205.112; however, the statement should be modified [redacted] (b) (4). The second statement will require modification or deletion, as the increased incidence of dry mouth in the 10 mcg group (14.5% tio R10 versus 7.2% tio R5 in the combined 1-year studies, 205.254 and 205.255) was the primary reason that the Applicant chose the 5 mcg dose going forward for approval.

- The reported case of anaphylactic shock reported in the 4-month Safety Update provides convincing evidence that anaphylaxis can occur with Spiriva Respimat. This adverse event supports the statement in the label "Immediate hypersensitivity reactions including angioedema, may occur after administration of Spiriva Respimat. If such a reaction occurs, therapy with Spiriva Respimat should be stopped at once and alternative treatments should be considered." The same statement is also included in the Spiriva HandiHaler label.

- A number of phrases are included in the Patient's Instructions for Use, (b) (4) that may be considered promotional. Such terminology will be removed or changed.

Reviewer comment:

At the time of finalization of this review, the Division does not plan to conduct labeling negotiations due to the complete response action.

9.5 Comments to Applicant

- The submitted data do not provide substantial evidence that Spiriva Respimat is sufficiently safe for the proposed indication of the long-term, once daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. An increased number of deaths was observed in the Spiriva Respimat treatment groups compared to placebo for the 1 year studies, primarily in Protocol 205.255. Differential drop outs among the treatment groups do not completely explain the mortality imbalance. In addition, in a pooled analysis of tiotropium clinical trial data, you identified an increase in stroke events in patients receiving tiotropium compared with patients receiving placebo; this potential safety signal was reported publically by FDA as an Early Communication on March 18, 2008.

- To support approval of Spiriva Respimat for the proposed indication, provide data in the form of a complete, finalized clinical study report from an adequate and well-controlled clinical trial to demonstrate the safety of Spiriva Respimat with regards to mortality and stroke. The clinical trial should be of adequate duration and power to evaluate fatal and stroke adverse events. If you intend to use the recently completed 4-year placebo-controlled trial with Spiriva HandiHaler (UPLIFT; Protocol 205.235) to fulfill this requirement, provide justification for use of safety data from Spiriva HandiHaler to support safety of Spiriva Respimat.

- The submitted data do not provide substantial evidence that Spiriva Respimat is sufficiently effective for the proposed claim that "Spiriva Respimat significantly reduced the number of COPD exacerbations compared to placebo (b) (4) " While the pre-specified combined analysis of the two 1 year clinical trials (205.254 and 205.255) demonstrated a significant decrease in COPD exacerbations compared to placebo, replication of the findings is necessary to support the labeling claim. Evaluation of the individual clinical trials did not demonstrate robust results that are sufficient for replication, since only one study showed a statistically significant improvement from placebo. The VA clinical trial (205.266) is not acceptable for replication of findings since this trial was conducted with Spiriva HandiHaler, which is a distinct product in terms of efficacy.

- To support approval of Spiriva Respimat for the proposed indication of reduction in COPD exacerbations, provide data from an adequate and well-controlled clinical trial comparing

Spiriva Respimat to placebo to replicate the efficacy findings with regards to the proposed indication.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Study 205.127

10.1.1.1 Protocol

Study Title

Pharmacodynamic and pharmacokinetic dose ranging study of tiotropium bromide administered via Respimat device in patients with chronic obstructive pulmonary disease (COPD): a randomized, 3-week multiple-dose, placebo controlled, intraformulation double-blind, parallel group study [Module 5, Volume 1.2, Study Report 205.127, page 1]

Design

This was a randomized, intraformulation double-blind, placebo controlled parallel group dose ranging study in patients with COPD. A total of five dosage groups of tiotropium solution using the Respimat device (1.25, 2.5, 5, 10, and 20 mcg) were evaluated compared to a Respimat placebo. In addition, one dosage group of tiotropium dry powder (18 mcg) using the HandiHaler device was evaluated compared to a HandiHaler placebo. Treatments were not blinded regarding device (Respimat or HandiHaler). All treatments were given once daily. [Module 5, Volume 1.2, Study report 205.127, page 8]

Duration

The duration of active treatment was 3 weeks. Prior to active treatment, patients participated in a 1 week screening period. The treatment period was followed by an additional one week safety visit. The study was performed during the period of March 16, 1998 to April 2, 1999. The final study report is dated December 21, 1999. An amended study report, containing revised Appendices I.2 and PK II (pharmacokinetic evaluation), is dated July 12, 2000. [Module 5, Volume 1.2, Study report 205.127, page 1]

Investigators and centers

The study was conducted in 15 different centers in France. [Module 5, Volume 1.2, Study report 205.127, pages 20-21]

Materials

The study treatments were:

- tio R1.25: tiotropium Respimat 1.25 mcg (2 inhalations 0.625 mcg) once daily in the morning
- tio R2.5: tiotropium Respimat 2.5 mcg (2 inhalations 1.25 mcg) once daily in the morning
- tio R5: tiotropium Respimat 5 mcg (2 inhalations 2.5 mcg) once daily in the morning
- tio R10: tiotropium Respimat 10 mcg (2 inhalations 5 mcg) once daily in the morning
- tio R20: tiotropium Respimat 20 mcg (2 inhalations 10 mcg) once daily in the morning
- Respimat placebo: Respimat placebo (2 inhalations) once daily in the morning
- tio HH18: tiotropium HandiHaler 18 mcg (1 capsule of 18 mcg inhaled) once daily in the morning
- HandiHaler placebo: HandiHaler placebo (1 capsule inhaled) once daily in the morning

All clinical drug supplies were packaged by Boehringer Ingelheim (BI) GmbH. Batch numbers and expiration dates are provided in Table 43. [Module 5, Volume 1.2, Study report 205.127, pages 28-30]

This study utilized the A3 Respimat device. The proposed device for marketing is the A5 Respimat device, while the A4 Respimat device was used in Phase 3 clinical trials. According to the Applicant, all three versions of the inhaler have the same nozzle type and are identical in terms of aerodynamic performance of the emitted aerosol sprays. (b) (4) [redacted] The A5 device differs from the A4 device only by the addition of a locking mechanism after 60 actuations (30 days of dosing). [Module 2, Volume 1.1, Clinical Overview, p. 8]

Table 43: Protocol 205.127 identity of investigational product

Substance/Device	Form	Unit strength	Lot Number	Expiry date
tiotropium	solution	0.625	9707206	July 1999
tiotropium	solution	1.25	9707207	July 1999
tiotropium	solution	2.5	9708201	July 1999
tiotropium	solution	5	9708202	July 1999
tiotropium	solution	10	9708203	July 1999
tiotropium	lactose powder (capsule)	18	9706007	August 1999
placebo	solution	not applicable	9707202	July 1999
placebo	lactose powder (capsule)	not applicable	9611002	January 2000
Respimat A3		not applicable	97080202	not provided
HandiHaler	DPI	not applicable	96070235 96070239	not provided

Reviewer comment:

According to Dr. Alan Schroeder, the CMC reviewer, the drug product used for Protocol 205.127 used a slightly higher (b) (4) *and higher* (b) (4) *than the drug product used in other pivotal clinical batches. There are limited data comparing the performance of the Respimat A3 device with the Respimat A4 device. Based on these limited data, the A3 inhaler appears to be similar in delivered dose to A4 and A5 and appears to have a generally similar in aerodynamic particle size distribution (APSD) profile. Although there are small differences, the data from this dose ranging trial can be relied upon to support dose selection for tiotropium Respimat. In addition, the applicant also explored two different doses (tio R5 and tio R10) in Phase 3 clinical trials, lessening potential concern regarding device differences in the dose ranging study.*

Objectives

The objective of this study was to determine pharmacodynamic and pharmacokinetic profiles of a range of doses of tiotropium in order to determine the optimal dose inhaled as a solution from a Respimat device once a day for three weeks in patients with COPD. [Module 5, Volume 1.2, Study report 205.127, p. 125]

Population

A total of 202 male and female patients with moderate to severe COPD (FEV_1 30-65% predicted) were enrolled. Patients were evenly divided among the 8 treatment groups, with 23-28 patients per group. Of these, 191 (94.6%) completed the study. [Module 5, Volume 1.2, Study report 205.127, page 43]

Inclusion criteria

Notable inclusion criteria included: [Module 5, Volume 1.2, Study report 205.127, page 26]

- diagnosis of COPD and with the following spirometric criteria:
  - 30% ≤ FEV_1 ≤ 65% of predicted normal
  - FEV_1 ≤ 70% of FVC
- male or female patients 40 years of age or older
- current or ex-smokers with a smoking history of more than 10 pack-years

Exclusion criteria

Notable exclusion criteria included: [Module 5, Volume 1.2, Study report 205.127, pages 27-28]

- history of asthma, allergic rhinitis or atopy, or blood eosinophil count >600 mm^3
- change in therapeutic (pulmonary) plan < 6 weeks prior to Visit 1
- cromolyn/nedocromil
- antihistamines
- lower respiratory infection or COPD exacerbation <6 weeks prior to Visit 1
- daytime oxygen use
- oral corticosteroids <6 weeks prior to Visit 1 or daily dose of prednisone >10 mg
- life threatening pulmonary obstruction, cystic fibrosis or bronchiectasis
- thoracotomy with pulmonary resection
- significant other disease
- history of myocardial infarction, heart failure, or arrhythmia within 1 year
- tuberculosis
- cancer within last 5 years
- psychiatric disorder
- known symptomatic prostatic hypertrophy or bladder neck obstruction
- history or glaucoma or increased intra-ocular pressure
- SGOT/PT>2X ULN, bilirubin >1.5X ULN, creatinine >1.25X ULN
- beta-blocker medication

- pregnant or nursing women and women of childbearing potential not using contraception

Procedures

Following an initial one-week screening phase, patients were randomized to one of 8 different treatment groups (tio R1.25, tio R2.5, tio R5, tio R10, tio R20, Respimat placebo, tio HH18, or HandiHaler placebo. All treatments were double-blind within the formulation group (Respimat or HandiHaler). Patients in the Respimat groups were to self-administer two inhalations from the Respimat inhaler (tiotropium or placebo) once daily in the morning between 8 and 10 am for three weeks (21 ±2 days). Patients in the HandiHaler groups were to self-administer one inhalation (one capsule) from the HandiHaler (tiotropium or placebo) once daily in the morning between 8 and 10 am for three weeks (21 ±2 days). On-treatment visits were scheduled on a weekly basis. Patients were evaluated for an additional week following completion of the randomized treatment period. Compliance with study medication was encouraged by the investigators but was not specifically was assessed as part of the protocol. [Module 5, Volume 1.2, Study report 205.127, p. 51]

The protocol and protocol amendments were approved by a central IRB (b) (4) . The Applicant states that the study was conducted according to GCP principals and guidelines defined in the "Bulletin Officiel" published by the Ministry of Social Affairs and Employment in France and ICH guidelines. Written informed consent was obtained from each patient prior to participation in the study. [Module 5, Volume 1.2, Study report 205.251, page 26]

The study flow chart is presented in Table 44.

Table 44: Protocol 205.126 study flow chart

Trial periods	Screening	Treatment period				Follow-up
Day	-7 ± 2	0	7 ± 2	14 ± 2	21 ± 2	24 to 28
Visit	1 Screening	2 Test Day 1	3 Test Day 2	4 Test Day 3	5 Test Day 4	6 Final
Administration of investigational drug		x	x	x	x	
Informed consent	x					
Demographics	x					
Medical history	x					
Physical examination	x					x
Laboratory tests	x					x
Inclusion/exclusion criteria	x	x				
Randomization		x				
Theophylline levels		x	x	x	x	
COPD symptoms		x	x	x	x	
Physician's global evaluation		x	x	x	x	
Pharmacokinetics study			x	x	x	
12-lead resting ECG	x	x	x	x	x	x
Vital signs (seated)	x	x	x	x	x	x
FEV_1, FVC	x	x	x	x	x	x
Concomitant therapy	x	x	x	x	x	x
Adverse events		x	x	x	x	x
Conclusion of participation						x
PEFR measurements	x	x	x	x	x	x
Diary recordings	x	x	x	x	x	x

Efficacy endpoints

Primary

- Trough FEV_1 response after 3 weeks of treatment

Trough FEV_1 was defined as the FEV_1 measured in the last two hours of the 24 hour dosing interval. Trough FEV_1 was calculated as the mean of the three FEV_1 readings measured at the end of the dosing interval (22, 23, and 24 hours after previous day's dose). Trough FEV_1 response was defined as change from baseline in trough FEV_1. Baseline FEV_1 was calculated as the mean of the three FEV_1 readings measuring in the morning of the randomization visit (Visit 2) prior to the first administration of trial drug. [Module 5, Volume 1.2, Study report 205.127, p. 40]

Pulmonary function testing was to occur hourly for 2 hours prior to and 4 hours following test-drug administration on Visits 2-5. At Visit 2, patients used a newly primed Respimat inhaler or HandiHaler. Patients used the same inhaler for the entire three week dosing period. Spirometry was performed according to ATS criteria. The highest FEV_1 and FVC of three maneuvers were recorded regardless of whether they came from the same or different maneuvers. For each patient, PFTs started at approximately 8 am in the morning ± 1 hour.

A number of medications were appropriately restricted prior to PFT testing:

- short-acting theophylline (at least 24 hour washout)
- long-acting theophylline (at least 48 hour washout)
- inhaled corticosteroids (not to be taken 1 hour prior)
- study medications (not to be taken prior to test-day pre-dose PFTs)
- short-acting beta-adrenergic bronchodilators (at least 8 hour washout)

In addition, long-acting beta-adrenergics, both long- and short-acting anticholinergics, oral beta-adrenergics, and antihistamines were not permitted at any time during the study. Patients who required rescue medication on a test day did not complete pulmonary function testing for that day. Patients were also instructed to avoid food or drink containing caffeine, heavy exercise, cold environments, and environmental smoke, dust, or smells in the 12 hours prior to testing.

Secondary

- FEV_1 during the first four hours post-dose on each test day
- FVC (same times as FEV_1)
- daily PEFR measurements
- PK evaluation
- COPD symptom scores
- sleep questionnaire (not protocol defined as a secondary endpoint)
- use of rescue medication (not protocol defined as a secondary endpoint)
- physician's global evaluation

[Module 5, Volume 1.2, Study report 205.127, page 37-42 and 125]

The patients had to record peak flow measurements three times daily in a daily diary. Morning measurements had to be done immediately upon arising after the patient cleared out mucus and before administration of the test drug. Midday measurements had to be done at noon and the evening measurements at bedtime. The best of three peak-flow meter readings on each occasion were recorded in the diary.

For 10 patients in each treatment group, at Visit 3 (day 7), Visit 4 (day 14), and Visit 5 (day 21), urine samples were performed two hours before and two hours after dosing of study drug. Diuresis was supported by intake of 100 mL of water in both periods. Tiotropium levels were measured in samples by (b) (4) using a validated high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS). The lower limit of quantification (LOQ) of the assay was 10 pg/ml.

COPD symptom scores were recorded by the investigator in four categories: wheezing, shortness of breath, coughing, and tightness of chest. The scores were based on the investigator's assessment of the patient's condition during the week just prior to the visit and were evaluated just prior to PFTs. Patients were also asked if they were awakened during the night by coughing or shortness of breath. The severity of symptoms was rated on a four-point scale as follows:

- not present = no symptoms
- mild = awareness of symptom which is easily tolerated
- moderate = discomfort enough to cause interference with usual activity
- severe = incapacitating with inability to do work or usual activity

The Physician's Global Evaluation was made prior to pulmonary function testing at each visit to reflect the investigator's opinion of the patient's overall clinical condition. The Physician's Global Evaluation was reported on an 8 point scale, ranging from 1-2=poor to 7-8=excellent. The evaluation was based on the need for concomitant therapy, number, and severity of exacerbations, severity of cough, ability to exercise, amount of wheezing and other relevant clinical observations since the patient's last visit.

Safety endpoints

- adverse events
- pulse rate and blood pressure
- routine blood chemistry, hematology and urinalysis
- 12-lead ECG
- physical examination

[Module 5, Volume 1.2, Study report 205.127, page 38-39]

No significant AEs were prespecified for this study. All AEs were recorded at each visit after review of the patient's diary card and discussion with the patient.

Pulse rate and blood pressure were measured and recorded at the same time intervals as pulmonary function testing for the first three hours post-dose. Measurements were obtained immediately before PFTs on Visits 1 and 6. On test days (during active treatment, Visits 2-5), they were measured at the same intervals as pulmonary function testing (t-120 minutes, T-60 minutes, T-5 minutes, T60 minutes, T120 minutes, and T240 minutes). Blood pressure was to be performed by the same person using the same blood pressure instrument on the same arm.

A standard 12-lead ECG was to be performed on all patients at each visit. The ECG was to be performed prior to the test-day pre-dose PFT. All ECGs were interpreted by the investigator or other qualified site personnel. ECG equipment and reading were not standardized across sites.

Laboratory tests consisting of hematology, blood chemistry and urinalysis were carried out by one central laboratory. These tests were performed at Visit 1 (screening) and at the end of the trial (3-7 days after the last dose of test drug). A serum pregnancy test was conducted on all women of childbearing potential. For all patients taking concomitant theophylline, theophylline blood level was measured at each test day (visits 2-5) just before the pulmonary function test.

Concomitant therapy

The protocol included a number of restrictions regarding concomitant therapy during the course of the study. The following medications were not allowed throughout the study period and withdrawal was required a pre-determined period of time prior to the initial screening visit (Visit 1):

- long-acting inhaled beta-agonists (48 hours)
- short-acting anticholinergics (8 hours)
- long-acting anticholinergics (12 hours)
- short-acting oral beta-agonists (18 hours)
- long-acting oral beta-agonists (36 hours)
- oral anticholinergics (7 days)
- antihistamines (48 hours)
- hydroxyzine (96 hours)
- astemizole (3 months)

The following medications were allowed throughout the study period but must be held prior to study visits for a pre-determined period of time:

- inhaled-short acting beta-agonists (8 hours)
- short-acting theophylline (24 hours)
- slow release theophylline (48 hours)
- inhaled corticosteroids (1-2 hours)

Oral corticosteroids were permitted during the study up to a daily dose of <10 mg. A constant dose was required for at least 6 weeks prior to screening (Visit 1) and throughout the study period. Inhaled short-acting beta-agonists were permitted as needed throughout the study (except

in the 8 hours preceding visits) and were to be recorded on the patient's daily diary. [Module 5, Volume 1.2, Study report 205.127, pages 131-133.]

Statistical plan

Sample size

Based on a multiple dose parallel group study, the standard deviation for average FEV_1 at 22-24 hours post drug administration corrected for baseline was assumed to be 0.17L. Therefore, a random sample of 24 patients per treatment group was chosen to detect a 150 mL difference in mean FEV_1 response between Respimat tiotropium doses and placebo at a 5% level of significance with at least 80% power using a two-tailed t-test. A difference of 150 mL was chosen to account for a 15% improvement over baseline FEV_1, as the average baseline was assumed to be about 1.0L. [Module 5, Volume 1.2, Study report 205.127, page 145]

Statistical model and analysis

The statistical model used for this study was analysis of covariance with baseline data measured on Test day 1 used as a covariate. The null hypothesis was that there is no difference in response among the six Respimat treatment groups. The alternative hypothesis was that each tiotropium Respimat dose is more effective than placebo. Tiotropium HandiHaler was also compared to HandiHaler placebo. The optimum Respimat dose chosen was then to be compared with HandiHaler.

The trough FEV_1 response at Visit 5 (day 21) was used as the primary efficacy endpoint for determining the bronchodilatory efficacy of tiotropium. Trough FEV_1 was calculated as the mean of the three readings measured at the end of the dosing interval (22-24 hours after previous dose). The FEV_1 response of the five Respimat doses was compared to Respimat placebo using ANCOVA with treatment effect as the one factor.

[Module 5, Volume 1.2, Study report 205.127, pages 40-41, 142-145]

Missing data

Missing values for spirometry endpoints were estimated using other values recorded for the patient on that test day. Linear interpolation was used to estimate missing data. The minimum spirometry value observed on that test day (even if it was the pre-dose value) was used as the estimate for missing values at the end of profiles if rescue medication was taken. [Module 5, Volume 1.2, Study report 205.127, pages 41, 144-145]

Data sets

All treated patients were included in the safety analysis. All randomized patients with baseline and data at Visit 5 (Day 21) were included in the efficacy analysis. [Module 5, Volume 1.2, Study report 205.127, page 45]

10.1.1.2 Results

Population characteristics

Disposition of patients

A total of 202 male and female patients with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 25 in the tio R1.25 group, 28 in the tio R2.5 group, 25 in the tio R5 group, 26 in the tio R10 group, 26 in the tio R20 group, 24 in the Respimat placebo group, 25 in the tio HH18 group, and 23 in the HandiHaler placebo group. Of these, 191 (94.6%) completed the study and 11 patients (5.4%) discontinued prematurely. Due to the low number of patients per group, four of the discontinued patients were replaced by patients receiving the same treatment. This was done by a third party not involved with evaluating the patients or the data. All patients were included in the safety analysis (intent-to-treat, ITT). Four patients from the ITT group were excluded from the efficacy analysis because they did not have valid pulmonary function tests; two of these patients were withdrawn due to worsening of COPD, one withdrew due to an AE, and one withdrew consent.

A summary of patient disposition for the trial is presented in Table 45. [Module 5, Volume 1.2, Study report 205.127, page 43-44]

Table 45: Protocol 205.127 patient disposition

Device	**Respimat**						**HandiHaler**		
Dose	**1.25**	**2.5**	**5**	**10**	**20**	**Plac R**	**18**	**Plac HH**	**Total**
Number of patients	**N (%)**						**N (%)**		**N (%)**
Randomized	25	28	25	26	26	24	25	23	202
Not prematurely discontinued from trial medication	23 (92.0)	25 (89.3)	25 (100)	25 (96.2)	24 (92.3)	23 (95.8)	24 (96.0)	22 (95.7)	191 (94.6)
Prematurely discontinued from trial medication	2 (8.0)	3 (10.7)	0	1 (3.8)	2 (7.7)	1 (4.2)	1 (4.0)	1 (4.3)	11 (5.4)
Worsening of disease under study	0	1 (3.6)	0	1 (3.8)	0	1 (4.2)	0	0	3 (1.5)
Worsening pre-existing disease	0	2 (7.1)	0	0	0	0	0	0	2 (1.0)
Other adverse event	1 (4.0)	0	0	0	0	0	1 (4.0)	1 (4.0)	3 (1.5)
Non compliant with protocol	0	0	0	0	1 (3.8)	0	0	0	1 (0.5)
Consent withdrawn	1 (4.0)	0	0	0	0	1 (3.8)	0	0	2 (1.0)

Demographics and baseline characteristics

The mean age of the patients was 60.2 years (range 38-83 years); 85.6% of the trial population was male. Ethnic and racial origin was not collected. The mean duration of COPD was 10.5 years. All patients were current (44.6%) or ex-smokers (55.4%), with a mean smoking history of 44.7 pack years. The overall demographic profile was balanced across the treatment groups. Pulmonary function data were generally comparable, although the HandiHaler placebo group was higher the other groups (FEV_1=1.457 compared to an overall average FEV_1 for all groups combined of 1.310). Any differences in PFT data were dealt with in the analysis by including baseline as a covariate in the model. Demographic characteristics are provided in Table 46, and baseline PFTs are provided in Table 47.

Table 46: Protocol 205.127 patient demographic and disease characteristics

Device	Respimat						HandiHaler		
Dose	1.25	2.5	5	10	20	Plac R	18	Plac HH	Total
Randomized	25	28	25	26	26	24	25	23	202
Gender N (%)									
male	24 (96.0)	25 (89.3)	18 (72.0)	23(88.5)	24 (92.3)	22 (91.7)	19 (76.0)	18 (78.3)	173 (85.6)
female	1 (4.0)	3 (10.7)	7 (28.0)	3 (11.5)	2 (7.7)	2 (8.3)	6 (24.0)	5 (21.7)	29 (14.4)
Age									
mean [years]	60.0	63.4	61.4	59.8	58.4	61.0	59.7	57.6	60.2
SD	8.0	8.6	10.3	11.1	9.5	9.0	10.8	9.6	9.6
range	43-73	52-83	38-76	40-83	44-77	40-76	41-77	41-76	38-83
Smoking history									
ex-smoker	13 (52.0)	12 (42.9)	16 (64.0)	14 (53.8)	16 (61.5)	17 (70.8)	13 (52.0)	11 (47.8)	112 (55.4)
current smoker	12 (48.0)	16 (57.1)	9 (36.0)	12 (46.5)	10 (38.5)	7 (29.2)	12 (48.0)	12 (52.2)	90 (44.6)
Smoking pack years									
mean [N]	42.3	50.1	40.6	44.4	43.8	45.1	45.2	45.2	44.7
SD	16.4	19.3	15.6	19.8	19.3	21.2	13.7	17.3	17.9
range	10-80	20-100	20-78	10-90	14-100	10-80	20-70	20-99	10-100
COPD duration									
mean [years]	11.6	10.7	11.4	9.1	9.2	8.8	13.3	9.5	10.5
SD	7.4	7.2	8.9	6.7	7.1	8.0	9.7	8.1	7.9
range	1.4-30	1.5-30	3.0-41	1.4-30	2.0-29	0.9-30	0.2-40	0.2-30	0.2-41

Table 47: Protocol 205.127 screening PFT data

Device	Respimat						HandiHaler		
Dose	1.25	2.5	5	10	20	Plac R	18	Plac HH	Total
Randomized	25	28	25	26	26	24	25	23	202
Baseline FEV_1									
mean (L)	1.256	1.230	1.212	1.416	1.318	1.332	1.277	1.457	1.310
min	0.867	0.667	0.617	0.693	0.820	0.777	0.643	0.673	0.617
max	1.883	2.107	2.260	2.250	2.000	2.143	2.103	2.667	2.667
%predicted FEV_1									
mean (%)	41.7	42.1	43.0	45.7	41.8	43.9	44.1	46.7	43.6
min	28.2	25.2	28.8	28.8	31.0	30.3	28.8	26.9	25.2
max	64.1	68.1	63.3	70.0	54.0	65.8	67.8	65.8	70.0
Baseline FVC									
mean (L)	2.549	2.570	2.553	2.686	2.781	2.677	2.492	2.794	2.636
min	1.470	1.237	1.483	1.510	1.710	1.370	1.093	1.500	1.093
max	3.557	3.907	4.130	4.190	3.987	3.817	4.120	4.310	4.310

Protocol violations

No patients were excluded from the analysis due to protocol violations. There were 37 patients who were determined retrospectively not to have met entry criteria, and 10 patients were found to have taken prohibited medications. [Module 5, Volume 1.2, Study report 205.127, p. 48]

Concomitant respiratory medications

The Applicant states that concomitant medication use during the treatment period was comparable among the groups. During the treatment period, 79.7% used beta-agonists, 62.0% of patients overall were taking inhaled steroids, and 27.2% were taking theophylline preparations. [Module 5, Volume 1.2, Study report 205.127, page 51]

Pharmacokinetic outcomes

Urinary excretion of tiotropium was above the LOQ except for those patients who received placebo. Six samples in the placebo group had very low but detectable levels of tiotropium. The highest level in the placebo group was approximately 60-fold less than trough levels in any tiotropium group. The Applicant considered these samples as slightly contaminated rather than interchanged.

Urinary excretion of tiotropium was dose dependent, and increased with increasing dose across the Respimat groups. Dose dependency was apparent for both trough and peak values. The urinary excretion of tio HH18 fell between tio R5 and tio R10, and appears most comparable to excretion in the tio R5 group. The applicant notes that scatter between patients was fairly high for all doses, and there were several values that appeared to be interchanged between pre-dose and post-dose samples.

There was an increase in drug excretion from Day 7 to Day 14 and again from Day 14 to Day 21 for the pre-dose values. In contrast, excretion in the post-dose interval appeared to be fairly constant from Day 7 to 21. See Table 48 for a comparison of geometric mean values of tiotropium cumulative urinary excretion (Aes) and coefficient of variation (% gCV) of patients within a group.

Table 48: Protocol 205.127 geometric mean tiotropium urinary excretion (Ae) values [ng/fraction]

	Day 7		Day 14		Day 21	
Dose (mcg)	2 h predose g mean (% gCV)	2 h postdose g mean (% gCV)	2 h predose g mean (% gCV)	2 h postdose g mean (% gCV)	2 h predose g mean (% gCV)	2 h postdose g mean (% gCV)
R1.25 N=10	7.38 (50.4)	29.4 (64.9)	10.2 (82.1)	28.2 (88.1)	13.2 (79.8)	31.1 (106)
R2.5 N=9	11.5 (43.3)[‖]	47.4 (100)	27.6 (118)	53.2 (82.8)	23.4 (62.0)	50.9 (107)
R5 N=10	29.9 (51.2)	170 (60.1)	35.4 (144)	167 (66.3)	48.0 (66.6)	185 (50.3)
R10 N=12	45.8 (97.9)	273 (59.5)	62.3 (54.1)[†]	241 (90.0)[‡]	74.1 (68.4)[†]	283 (54.7)[†]
R20 N=11	87.5 (88.4)	759 (75.0)	164 (144)	690 (98.4)[‡]	117 (135)	706 (104)
HH18 N=9	28.2 (83.4)	251 (63.2)	46.2 (58.5)[‖]	124 (121)[‖]	45.9 (86.6)[‖]	192 (140)[‖]

[†]N=11, [‡]N=10, [‖]N=8

<u>*Reviewer comment:*</u>

Although the data are quite variable from patient to patient, peak Ae values do show an increase with increasing dose in a roughly linear fashion. Dose accumulation at trough is apparent out to Day 21, which fits with improving trough FEV_1 levels over the first month of treatment observed in Phase 3 studies. The urinary excretion after drug administration is roughly the same for a given dose across time.

Given the sensitivity of the assay, very low levels of drug found in urine samples from a few placebo patients is consistent with contamination during handling. Additional handling difficulties and variability are more likely with urine rather than blood sampling.

A total of eleven samples were found to have higher levels before dosing than after dosing in the 14 day and 21 day time points. These instances were distributed evenly across the treatment groups. Reversing the order of these samples decreases the variability of the data somewhat and results in small changes to some levels, but does not change the overall pharmacokinetic conclusions.

Pharmacokinetic conclusions

Urinary excretion of tiotropium was dose dependent, and increased with increasing dose across the Respimat groups. Dose dependency was apparent for both trough and peak values. The urinary excretion of tio HH18 fell between tio R5 and tio R10, and appears most comparable to excretion in the tio R5 group. Drug accumulation at trough is apparent out to Day 21, while Ae after drug administration is roughly the same for a given dose across time.

Device performance characteristics

Device performance characteristics were not evaluated as part of this study.

Efficacy outcomes

Efficacy analyses were performed on an "intent to treat" population. The Applicant defined this as randomized patients who received at least one dose of study drug and had at least a valid baseline and one post-treatment PFT measurement. Four patients without adequate post-treatment data were excluded from the ITT population.

Primary endpoint

The primary efficacy measurement was change from baseline of trough FEV_1 (mean pre-dose FEV_1 at Visit 2). There was a numerical increase in trough FEV_1 in all treatment groups relative to placebo. The HandiHaler placebo group had a markedly lower response compared to the Respimat placebo group, resulting in a higher than expected improvement in tio HH18 relative to the placebo HH. The rank order of response among the Respimat groups was tio R5, tio R20, and tio R10. The difference from placebo R was only significant in the tio R5 and tio R20 groups. However, the difference in the tio R10 group was comparable to the tio R5 and tio R20 groups with a p=0.06. The tio R2.5 and tio R1.25 groups did not demonstrate a clinically important response, with a difference of <150 mL. See Table 49 for a summary of mean change in trough FEV_1.

Table 49: Protocol 205.127 FEV_1 trough response [L] treatment differences

Device	Respimat						HandiHaler	
Dose	1.25	2.5	5	10	20	Plac R	18	Plac HH
Randomized	25	28	25	26	26	24	25	23
Day 7 trough								
mean [L]	0.13*	0.10	0.16*	0.08	0.12	0.03	0.22**	-0.08
SEM	0.03	0.03	0.03	0.03	0.03	0.03	0.05	0.05
Day 14 trough								
mean [L]	0.13	0.08	0.17*	0.12	0.17*	0.02	0.22**	-0.04
SEM	0.04	0.04	0.04	0.04	0.04	0.04	0.05	0.05
Day 21 trough								
mean [L]	0.10	0.05	0.15*	0.13	0.15*	0.20	0.23**	-0.09
SEM	0.04	0.03	0.04	0.03	0.04	0.04	0.05	0.05

significantly different from placebo *p<0.05, **p≤ 0.001
SEM=standard error of the mean
adjusted mean change from baseline, imputed data, ITT population

Reviewer comment:

The response for Spiriva HandiHaler in this trial is markedly higher than expected, driven by a lower than expected placebo response. The HandiHaler placebo group had a higher baseline FEV_1, suggesting that regression towards the mean may have contributed to the decrease in FEV_1 observed across the time points for this group.

The mean difference in trough FEV_1 response at the end of 13 weeks of treatment for Spiriva HandiHaler (18 mcg) found in pivotal trials was 0.110 and 0.130. The differences in the tio R5, tio R10, and tio R20 groups found in this study are comparable to these historic values. Based on these findings, the Applicant chose to take two doses, tio R5 and tio R10, forward into Phase 3 studies.

Secondary endpoints

Post-dose FEV_1

All tiotropium groups (Respimat and HandiHaler) demonstrated an increase in FEV_1 response significantly greater than placebo. The bronchodilation generally peaked at approximately 3 hours. Responses ranged from 0.150 to 0.300L over the doses tested. No clear dose separation was observed. The Respimat placebo showed a greater response than the HandiHaler placebo.

FVC

Trough and peak FVC generally showed similar responses to FEV_1. A dose response relationship was not observed for the Respimat groups, although the response was generally numerically greater than placebo. Adjusted mean change from baseline in trough FVC ranged from 0.09 to

0.25L for the Respimat groups and 0.31-0.34L for the tio HH18 group. Only the tio HH18 group showed a consistently significant difference from placebo in trough FVC. Again, the Respimat placebo group showed a greater response than the HandiHaler placebo group.

PEFR

Peak expiratory flow rate was measured in the morning, noon, and evening. Baseline mean morning (pre-dose) PEFR for all treatment groups was 259 L/min, noon was 274 L/min, and evening was 261 L/min. All doses of tiotropium showed a numerical increase in PEFR compared to placebo at all time points on all weeks, which was generally statistically significant. As expected, noon and evening PEFR were consistently higher than the pre-dose morning values. A top down dose-ordered trend was generally observed at Week 1, with the tio R20 group showing a decreased response in subsequent weeks.

Rescue medication use

Baseline mean rescue medication use was 1.42 albuterol doses per day overall, ranging from 1.03 to 1.74 doses/day. Over the total treatment period, all tiotropium groups except for the tio R2.5 group showed a statistically significant decrease in rescue medication use compared to placebo (-0.54 to -0.872 doses/day). Dose ordering was not apparent, with the tio R1.25 group showing the largest difference.

Other secondary endpoints

Overall treatment differences for COPD symptoms scores, physician global evaluation, and nocturnal awakenings were generally small and were not statistically significant for any treatment groups.

Efficacy conclusions

There was a numerical increase in trough FEV_1 at Week 3 in all tiotropium groups (Respimat and HandiHaler) relative to placebo. The rank order of response among the Respimat groups was tio R5, tio R20, and tio R10. The difference from placebo R was only significant in the tio R5 and tio R20 groups. However, the difference in the tio R10 group was comparable to the tio R5 and tio R20 groups with a p=0.06. The tio R2.5 and tio R1.25 groups did not demonstrate a clinically important response, with a difference of <150 mL. All tiotropium groups demonstrated an increase in post-dose FEV_1 response significantly greater than placebo. Trough and peak FVC generally showed similar responses to FEV_1. A dose response relationship was not observed for the Respimat groups, although the response was generally numerically greater than placebo. Based on these findings, the Applicant chose to take two doses, tio R5 and tio R10, forward into Phase 3 studies.

Safety outcomes

Safety outcomes for Study 205.127 included adverse events, laboratory findings (hematology, blood chemistry, and urinalysis at screening and at the end of treatment), ECGs (performed and interpreted by the investigator at each visit), vital signs (pulse rate and blood pressure measured at the same time intervals as PFTs for the first 3 hours post-dose), and physical examinations (screening and at the end of treatment). All patients who were randomized and received at least one dose of trial medication were included in the safety analysis.

Extent of exposure

A total of 202 patients were randomized and received at least one dose of study medication. The planned exposure was 21 days. Overall, the mean treatment exposure was 21.6 days, ranging from 20.2 to 22.5 days. Mean exposure was comparable among the treatment groups, with no evidence of differential drop out.

Adverse events

Deaths

There were no deaths during the study.

Serious adverse events

Six patients had SAEs during the trial. These events included two in the tio R1.25 group (Achilles tendon rupture and pneumonia), two in the tio R2.5 group (hematuria and COPD exacerbation), one in the tio R20 group (chest pain secondary to hiatal hernia), and one in the placebo HH group (COPD exacerbation).

Adverse events leading to discontinuation

Eight patients discontinued from the study due to an AE. These included one patient in the tio R1.25 group (pneumonia), three in the tio R2.5 group (AV block, COPD exacerbation and hematuria), one in the tio R10 group (COPD exacerbation), one in the placebo R group (COPD exacerbation), one in the tio HH18 group (dyspnea), and one in the placebo HH group (COPD exacerbation). Overall, the most common AE leading to discontinuation was COPD exacerbation, occurring in 4 patients.

Overall adverse events

Adverse events (AEs) were reported in 27.7% of the patients. Treatment emergent adverse events and were generally balanced among the groups with the exception of dry mouth, which occurred only in the tiotropium groups. The most common AEs across all treatment groups were COPD exacerbation and dry mouth. See Table 50 for a summary.

Three cardiovascular heart rate and rhythm AEs occurred during the study: tachycardia, AV block, and extrasystoles, which occurred in the tio R5, tio R2.5, and tio R10 groups, respectively. None of these AEs were reported as serious. The patient with AV block was discontinued from the study.

Table 50: Protocol 205.127 adverse events

Device	Respimat						HandiHaler	
Dose	1.25	2.5	5	10	20	Plac R	18	Plac HH
Randomized	25	28	25	26	26	24	25	23
Any AE	6	9	7	8	6	5	9	6
Serious AE	2	2	0	0	1	0	1	0
AE leading to discontinuation	1	3	0	1	0	1	1	1
AEs by body system								
General	2	2	1	0	1	1	2	1
Cardiovascular	1	0	0	0	0	0	0	1
Central and peripheral nervous	0	1	0	0	0	0	2	0
Gastrointestinal	1	0	2	3	4	0	3	0
Heart rate and rhythm	0	1	1	1	0	0	0	0
Musculoskeletal	0	0	0	1	0	0	0	0
Respiratory	3	6	3	3	5	5	6	3
Urinary	0	1	1	0	0	0	0	0
Vision	0	0	0	1	0	0	0	1
Common AEs (>3%)								
COPD exacerbation	0	4	2	2	3	3	5	1
Dry mouth	1	0	1	3	2	0	2	0

Reported as number of patients with event

Laboratory findings

There were no significant or clinically important changes from baseline in the mean or median values of any laboratory parameter. Overall, the changes in laboratory values throughout the study were small. The largest change from baseline was for mean SGPT and SGOT, which increased from baseline by 15.45 and 22.87 U/L, respectively, in the tio R5 group compared to a change of 3.61 and 3.11 U/L in the placebo R group. All of the other tio R groups showed a reduction in SGPT and SGOT compared to baseline values.

No patient in any group was discontinued due to a laboratory abnormality, and no patient reported an AE associated with changes in laboratory values.

Reviewer comment:

The increase in SGPT and SGOT in the tio R5 group was driven by a single patient (Pt no. 168), who had baseline SGPT/SGOT of 26.76 and 24.59 U/L that increased to 542.71 and 408.69 U/L, respectively, during the study. During the time of the elevation, which occurred during the

follow-up period after conclusion of study drug administration, the patient also had an adverse event of acute alcoholic intoxication, which likely accounted for the elevation. Transaminases reportedly returned to normal nine days later.

ECG findings

ECG parameters evaluated included heart rate and QTc. No clinically important changes were observed in either of these parameters with any treatment group.

Physical examination

Significant changes in blood pressure and pulse were defined as follows:

- SBP decrease: below 100 mm Hg if not at that level at baseline and a decrease of greater than 10 mmHg below baseline
- SBP increase: an increase of 25 mmHg or more above baseline
- DBP decrease: below 60 mmHg if not at that level at baseline and a decrease of greater than 10 mmHg below baseline
- DBP increase: above 90 mm Hg and an increase of greater than 10 mmHg above baseline
- PR decrease: below 60 bpm if not at that level at baseline and a decrease of greater than 10 bpm below baseline
- PR increase: greater than 100 bpm if not at that level at baseline and an increase greater than 10% above baseline

In general, significant changes in vital signs occurring in only a few patients who were evenly distributed among the treatment groups. The possible exception was significant pulse rate increase, which occurred in 1 patient in the tio R5 group, 1 in the tio HH18 group, and 3 in the tio R20 group. New or worsened findings on physical examination were recorded as adverse events. These occurred in 2 patients in the tio R5 group, one in the tio R10 group, and one in the placebo R group.

Safety conclusions

No specific safety concerns are raised from the data set for this study, considered in isolation. There were no deaths in the study, and only six patients had SAEs, two of which were COPD exacerbations. The most common AEs were COPD exacerbation and dry mouth. Of note, dry mouth occurred only in the tiotropium groups, although the sample size was too small to permit determination of a dose relationship.

10.1.1.3 Summary and conclusions

There was a numerical increase in trough FEV_1 at Week 3 in all tiotropium groups (Respimat and HandiHaler) relative to placebo. The rank order of response among the Respimat groups was tio R5, tio R20, and tio R10. The difference from placebo R was only significant in the tio R5

and tio R20 groups. However, the difference in the tio R10 group was comparable to the tio R5 and tio R20 groups with a p=0.06. The tio R2.5 and tio R1.25 groups did not demonstrate a clinically important response, with a difference of <150 mL. All tiotropium groups demonstrated an increase in post-dose FEV_1 response significantly greater than placebo. Trough and peak FVC generally showed similar responses to FEV_1. A dose response relationship was not observed for the Respimat groups, although the response was generally numerically greater than placebo. Based on these findings, the Applicant chose to take two doses, tio R5 and tio R10, forward into Phase 3 studies.

No specific safety concerns are raised from the data set for this study, considered in isolation. There were no deaths in the study, and only six patients had SAEs, two of which were COPD exacerbations. The most common AEs were COPD exacerbation and dry mouth. Of note, dry mouth occurred only in the tiotropium groups, although the sample size was too small to permit determination of a dose relationship.

10.1.2 Study 205.251

10.1.2.1 Protocol

Study Title

A randomized, double-blind, double-dummy, placebo- and active-controlled, parallel group efficacy and safety comparison of 12-week treatment of two doses [5 mcg (2 actuations of 2.5 mcg) and 10 mcg (2 actuations of 5 mcg)] of tiotropium inhalation solution delivered by the Respimat inhaler, placebo and ipratropium bromide inhalation aerosol (MDI) in patients with chronic obstructive pulmonary disease (COPD) [Module 5, Volume 1.6, Study report 205.251, page 1]

Design

This was a randomized, double-blind, placebo and active controlled parallel group efficacy and safety comparison of two doses (5 mcg and 10 mcg) of tiotropium Respimat (tio R) in patients with COPD. The active control group received ipratropium bromide via metered dose inhaler (HFA) device at a dose of 36 mcg four times daily (total daily dose 144 mcg). The single placebo group received both Respimat and MDI placebo products. Active treatment and active control groups also received the alternative active treatment (Respimat or MDI) placebo in a double-dummy fashion. [Module 5, Volume 1.6, Study report 205.251, page 3]

Duration

The duration of active treatment was 12 weeks. Prior to active treatment, patients participated in a 2-week run-in period. The study was performed during the period of November 26, 2002 to December 17, 2003. The final study report is dated September 16, 2004. [Module 5, Volume 1.6, Study report 205.251, page 1, 40]

Investigators and Centers

The study was conducted in 39 different centers in 4 countries (Germany, Italy, Switzerland, and South Africa). [Module 5, Volume 1.6, Study report 205.251, page 5-9]

Materials

The study treatments were:

- tio R5: tiotropium Respimat 5 mcg (2 inhalations of 2.5 mcg) once daily in the morning and MDI placebo four times daily
- tio R10: tiotropium Respimat 10 mcg (2 inhalations of 5 mcg) once daily in the morning and MDI placebo four times daily
- ipratropium: ipratropium bromide HFA inhalation aerosol (MDI) 36 mcg (2 inhalations of 18 mcg) four times daily and Respimat placebo once daily in the morning
- placebo: Respimat placebo once daily in the morning and MDI placebo four times daily

The tiotropium bromide inhalation solution, placebo inhalation solution and Respimat inhalers were manufactured at Boehringer Ingelheim Pharma KG (Ingelheim, Germany). Batch numbers and expiration dates of investigational product are provided in Table 51. This study utilized the A4 Respimat device. The proposed device for marketing is the A5 Respimat device, which differs from the A4 by the inclusion of a locking mechanism to lock the Respimat A5 after 30 doses (60 actuations).

Table 51: Protocol 205.251 identity of investigational product

Investigational Product	Expiration Date	Ingelheim Batch No.
Tiotropium Bromide Inhalation Solution, 2.5 µg Tiotropium PA	04/2004	202948
Respimat Inhaler (A4)		WE01070187
Tiotropium Bromide Inhalation Solution, 5 µg Tiotropium PA	08/2004	202821
Respimat Inhaler (A4)		WE01080199
Placebo Inhalation Solution (for Tiotropium Bromide)	08/2004	202942
Respimat Inhaler (A4)		WE02050101
Ipratropium Bromide Inhalation Aerosol 0.021 mg TTV, 10 mL	02/2005	202261
Placebo Inhalation Aerosol, 10 mL (0.1% Soya, for Ipratropium Bromide)	07/2005	205392

Reviewer comment:

Typically we recommend that the Applicant conduct pivotal studies with the to be marketed product. The addition of a locking mechanism to the A5 model is unlikely to have a significant impact on device performance. The CMC reviewer, Alan Schroeder, indicates that the in vitro data shows that the two models perform similarly. Thus, the data from clinical trials utilizing the A4 Respimat model can be relied upon to support the safety and efficacy of tiotropium Respimat.

Objectives

The primary objective of this study was to compare the bronchodilator efficacy of two doses (5 mcg and 10 mcg) of tiotropium inhalation solution delivered by the Respimat inhaler once daily to placebo and to ipratropium bromide inhalation aerosol delivered by MDI four times daily in patients with chronic obstructive pulmonary disease (COPD). The secondary objective was to compare the safety of tiotropium inhalation solution delivered by Respimat inhaler to placebo and ipratropium bromide inhalation aerosol. [Module 5, Volume 1.6, Study report 205.251, page 3]

Population

A total of 361 male and female patients with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 88 in the tio R5 group, 93 in the tio R10 group, 89 in the ipratropium group, and 91 in the placebo group. Of these, 320 (88.6%) completed the study. [Module 5, Volume 1.6, Study report 205.251, page 3]

Inclusion criteria

Notable inclusion criteria included: [Module 5, Volume 1.6, Study report 205.251, page 41]

- Diagnosis of COPD and with the following spirometric criteria:
  - $FEV_1 \leq 60\%$ of predicted normal and $FEV_1 \leq 70\%$ of FVC
- Male or female patients 40 years of age or older
- Current or ex-smokers with a smoking history of more than 10 pack-years

Exclusion criteria

Notable exclusion criteria included: [Module 5, Volume 1.6, Study report 205.251, page 42-45]

- History (6 months or less) of myocardial infarction
- Unstable/life-threatening arrhythmia or hospitalized for heart failure within the past year
- Malignancy within the last 5 years
- Narrow-angle glaucoma
- History of asthma, allergic rhinitis or total blood eosinophil count $\geq 600/mm^3$
- History of life-threatening pulmonary obstruction, cystic fibrosis or bronchiectasis
- Active tuberculosis

- Thoracotomy with pulmonary resection
- Pulmonary rehabilitation program within 6 weeks
- Daytime oxygen use
- Oral beta-adrenergics
- Cromolyn sodium or nedocromil sodium
- Antihistamines, antileukotrienes or leukotriene receptor antagonists
- Oral corticosteroids > 10 mg prednisone/day

Reviewer comment:

Protocol amendment 2 permitted inclusion of patients with prostatic hyperplasia, bladder neck obstruction and those receiving systemic beta-blocker medications. The following precautions from the Spiriva HandiHaler product label were added:

- *As with other anticholinergic drugs, tiotropium should be used with caution in patients with prostatic hyperplasia or bladder neck obstruction*
- *As with all predominantly renally excreted drugs, tiotropium use should be monitored closely in patients with moderate to severe renal impairment (creatinine clearance of ≤ 50 mL/min.)*

These modifications allow for inclusion of a broader patient population that more closely represents those patients who are likely to receive the product if approved.

Procedures

Following an initial screening visit and a 2-week run-in period, patients were randomized to 1 of 4 treatment groups: tio R5, tio R10, ipratropium, or placebo. All treatments were double-blind and double-dummy so that the four treatments were indistinguishable. Each patient was to self-administer two inhalations from the Respimat inhaler (tiotropium or placebo) once daily in the morning and two inhalations from the MDI (ipratropium or placebo) 4 times daily at appropriately spaced intervals (morning, mid-day, early evening and prior to bed) for 12 weeks. On-treatment visits were scheduled at the end of the first week, and every 3-4 weeks thereafter. Patients were evaluated for an additional 3 weeks following completion of the randomized treatment period. Patients completed a daily Diary Card indicating each dose of study medication taken and the number of occasions of rescue albuterol use. Compliance with study medication, based on the patient's daily Diary Card, was assessed at each study visit.

The protocol and protocol amendments were approved by the appropriate IRBs or IECs prior to shipment of study drug or enrollment of patients. The Applicant states that the study was conducted according to FDA regulations and guidelines and that written informed consent was obtained from each patient prior to participation in the study. [Module 5, Volume 1.6, Study report 205.251, page 26]

The study flow chart as revised by Protocol Amendment 2 is presented in Table 52. Protocol Amendment 2 was enacted prior to enrollment of the first patient.

Table 52: Protocol 205.251 study flow chart

Trial Periods	**Screening**	**Treatment**					**Follow -up**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7[1]**
Week	**-2**	**0**	**1**	**4**	**8**	**12**	**+3**
Day	**-14**	**1**	**8**	**29**	**57**	**85**	**+21[1]**
Informed consent[2]	X						
Demographics	X						
Medical history	X						
Smoking status	X					X[6]	
Inclusion/exclusion criteria	X	X					
Physical examination	X					X[6]	
Vital signs (seated)	X	X[3]	X[3]	X[3]	X[3]	X[6]	
Laboratory tests (fasting)	X					X[6]	
12-lead ECG	X					X[6]	
Medication washout compliance assessment	X	X	X	X	X	X	
Training in Respimat and MDI use	X	X					
Screening PFT with reversibility assessment	X						
Issue diary cards	X	X	X	X	X	X	
Issue peak flow meter	X						
Dispense rescue medication	X	X[7]	X[7]	X[7]	X[7]	X[7]	
Conclusion of screening		X					
Randomization		X					
COPD symptom scores		X	X	X	X	X	X
Global evaluations		X	X	X	X	X	X
Collect and review diary cards		X	X	X	X	X	X
Administration of test drugs in clinic		X	X	X	X	X	
Pulmonary function tests (FEV1/FVC)		X[4]	X[5]	X[5]	X[5]	X[4]	
Dispense Respimat test drugs		X			X		
Dispense MDI test drugs		X	X	X	X		
Collect test drugs				X	X	X	
Adverse events	X	X	X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X
Termination of trial medication						X[6]	

1 Post-treatment period.
2 All subjects must sign an informed consent consistent with ICH-GCP guidelines before participating in the trial, which includes medication washout and restrictions.
3 In conjunction with pulmonary function testing.
4 Before drug administration and 5, 15, 30, and 60 minutes and 2, 3, 4, 5 and 6 hours afterwards.
5 Before drug administration and 30 and 60 minutes and 2, 3, 4, 5 and 6 hours afterwards.
6 To be completed by all subjects, including those who discontinued early.
7 As needed.

Efficacy endpoints

Primary

- Trough FEV_1 response after 12 weeks of treatment

Trough FEV_1 was defined as the FEV_1 measured at the -10 minute time point at the end of the dosing interval 24 hours post drug administration. Trough FEV_1 response was defined as the change from baseline in trough FEV_1. Baseline FEV_1 was the pre-treatment FEV_1 value measured at Visit 2 in the morning 10 minutes prior to administration of the first dose of study medication.

Pulmonary function testing was to occur both prior to and following test-drug administration on Visits 2-6. At Visit 2, patients used a newly primed Respimat inhaler and MDI. At subsequent visits the Respimat inhaler and MDI in current use by the patient were to be used to administer the test-dose. Spirometry was performed according to ATS criteria. The highest FEV_1 and FVC of three maneuvers were recorded regardless of whether they came from the same or different maneuvers. For each patient, PFTs started at approximately the same time of day ±30 minutes in the morning between 7 and 10 am. Although not an enrollment criteria, reversibility was tested at baseline after administration of 400 mcg albuterol aerosol.

A number of medications were appropriately restricted prior to PFT testing:

- short-acting theophylline (at least 24 hour washout)
- long-acting theophylline (at least 48 hour washout)
- short-acting anticholinergic bronchodilators (at least 8 hour washout)
- short-acting beta-adrenergic bronchodilators (at least 8 hour washout)
- long-acting beta-adrenergics (at least 48 hour washout)
- inhaled corticosteroids (not to be taken 1 hour prior)
- study medications (not to be taken prior to test-day pre-dose PFTs)

In addition, patients were to refrain from strenuous exercise, smoking, caffeinated or ice-cold beverages, cold temperatures, dust, and environmental smoke the morning prior to spirometry.

Secondary

- Trough FEV_1 response after 1, 4, and 8 weeks
- Trough FVC response after 1, 4, 8, and 12 weeks
- FEV_1 and FVC area under the curve $(AUC)_{0\text{-}6h}$ and peak response after 0, 1, 4, 8 and 12 weeks
- Individual FEV_1 and FVC measurements at each time point
- Onset and duration of therapeutic response and percentage of responders after 0 and 12 weeks

- Weekly mean pre-dose morning and evening PEFR
- Weekly mean number of occasions of rescue therapy (albuterol) used per day
- COPD symptom scores (wheezing, shortness of breath, coughing and tightness of chest)
- Physicians Global Evaluation

[Module 5, Volume 1.6, Study report 205.251, page 38-39]

The patient received a diary card at each visit. This card was used to record twice daily PEFR, test medication use, and rescue albuterol use. An additional card was given to record health-related comments. The card was returned and reviewed with the patient at each visit. The best of three PEFR measurements at each time point was to be recorded. Baseline PEFR and rescue therapy use were defined the average during the last week of the run-in (Week -1).

Therapeutic response was determined based on FEV_1. A response was considered to have been achieved if an FEV_1 measurement of at least 1.15 times the Test Day 1 baseline value was recorded at any time during the first 2 hours of observation (15% increase). The onset of the therapeutic response was defined as the linear interpolation of the time of the first therapeutic response and the time of the observation just prior to the first therapeutic response (even if that was the baseline observation). If no therapeutic response was achieved within the first 2 hours following dosing, then the onset was flagged with the value 361 minutes. Termination of the therapeutic response was identified by the first fall below 1.15 times baseline FEV_1 on two consecutive measurements following a therapeutic response. Alternatively, response termination was identified by a single point if the initial measured value falling below 1.15 times pre-dose FEV_1 occurred at the 6-hour observation. If a response had been observed and was still present at the 6-hour time point, the termination of therapeutic response was flagged with the value of 361 minutes. Duration of the therapeutic response was defined as termination of response minus onset of response.

COPD symptom scores were recorded by the investigator in four categories: wheezing, shortness of breath, coughing, and tightness of chest. The scores were based on the investigator's assessment of the patient's condition during the week just prior to the visit and were evaluated just prior to PFTs. The severity of symptoms was rated on a four-point scale as follows:

- not present = no symptoms
- mild = awareness of symptom which is easily tolerated
- moderate = discomfort enough to cause interference with usual activity
- severe = incapacitating with inability to do work or usual activity

The Physician's Global Evaluation was made prior to PFTs and was to reflect the investigator's opinion of the patient's overall clinical condition. The Physician's Global Evaluation was reported on an 8 point scale, ranging from 1-2=poor to 7-8=excellent. The evaluation was based on the need for concomitant therapy, number and severity of exacerbations, severity of cough,

ability to exercise, amount of wheezing and other relevant clinical observations since the patient's last visit.

Safety endpoints

- Adverse events
- Pulse rate and blood pressure
- Routine blood chemistry, hematology and urinalysis
- 12-lead ECG
- Physical examination

[Module 5, Volume 1.6, Study report 205.251, page 39]

No significant AEs were prespecified for this study. All AEs were recorded at each visit after review of the patient's diary card and discussion with the patient.

COPD exacerbations were reported as AEs. A COPD exacerbation was defined as a complex of respiratory events/symptoms with a duration of three days or more requiring a change in treatment. A complex of respiratory events/symptoms meant two or more 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. The change in or requirement of treatment included the following: prescription of antibiotics, prescription of systemic steroids, or a significant change in prescribed respiratory medication (bronchodilators including theophylline). The onset of an exacerbation was defined by the onset of the first recorded symptom. The end of the exacerbation was defined by the investigator.

Pulse rate and blood pressure were measured and recorded at the same time intervals as pulmonary function testing for the first three hours post-dose. Measurements were obtained immediately before PFTs with the patient seated and rested for a minimum of five minutes. Blood pressure was to be performed by the same person using the same blood pressure instrument on the same arm.

A standard 12-lead ECG was to be performed on all patients at the screening visit and repeated at the end of the treatment period. The ECG was to be performed prior to the test-day pre-dose PFT. All ECGs were interpreted by the investigator or other qualified site personnel. ECG equipment and reading were not standardized across sites.

A complete physical examination was to be performed on all patients at the screening visit and repeated at the end of the treatment period. New abnormal findings or worsening of baseline conditions detected at follow-up physical examination were recorded as AEs.

[Module 5, Volume 1.8, Study report 205.251, pages 791-793]

Concomitant therapy

The protocol included the following restrictions regarding concomitant therapy during the course of the study:

- Minimal doses of oral corticosteroids (10 mg or less of prednisone daily), orally inhaled corticosteroids, theophylline preparations, mucolytic agents, antileukotrienes, and leukotriene receptor antagonists were permitted if stabilized for at least 6 weeks prior to the study.
- Anticholinergic drugs including Atrovent Inhalation Aerosol, Atrovent Nasal Spray, and Spiriva HandiHaler were allowed during the baseline and follow up periods but not during the treatment period.
- Orally inhaled long-acting beta adrenergics were allowed during the baseline and follow-up periods but not during the treatment period.
- Patients using fixed combinations inhaled corticosteroids/long-acting beta adrenergics were to be switched to the inhaled corticosteroid monoproduct prior to randomization without a change in corticosteroid dose.
- Patients using fixed dose combination anticholinergic/short-acting beta adrenergic medications were to be switched to Atrovent prior to the baseline period without a change in the anticholinergic dose. Atrovent was to be discontinued during the active treatment period.
- PRN albuterol was allowed throughout the study.
- All other investigational drugs and oral beta agonists were not allowed for at least one month prior to the baseline period. Cromolyn sodium and nedocromil sodium were not allowed for at least 3 months prior to the baseline period.

In addition, the following medications were restricted prior to PFTs:

- short-acting theophylline preparations (24 hours)
- long-acting theophylline preparations (48 hours)
- short-acting anticholinergic bronchodilators (8 hours; Visits 1 and 2 only)
- long-acting beta-adrenergics (48 hours; Visits 1 and 2 only)
- inhaled corticosteroids (no morning dose within 1 hour)
- study medications (no morning dose until after pre-dose PFTs)

Statistical plan

This was one of two replicative studies (Protocols 205.251 and 205.252). Analysis of the data was performed both for this study alone and for combined data from both studies. Analysis of the combined data sets was prespecified.

Sample size

The sample size was based on anticipated variance and treatment effect for the primary endpoint, trough FEV_1. From previous studies, the standard deviation for trough FEV_1 was assumed to be 0.215L. With a sample of 280 evaluable patients (70 per treatment group), the powers for detecting differences of 0.13L and 0.18L at the 2.5% level of significance (one sided) are 94% and 99%, respectively. Since the comparisons were not independent, the overall power for this sample size was between 77% and 94%.

Reviewer comment:

Although a total of 280 evaluable patients were expected to provide 77-94% power, a total of 320 patients completed the study. This will not be an issue provided that the effect size demonstrated is felt to be clinically significant.

Statistical model and analysis

The primary endpoint was trough FEV_1 response determined at the end of the 12-week treatment period. The primary analysis was an ANCOVA with terms for smoking status (current or ex-smoker at study entry), center, treatment, and baseline used as covariates.

The hypothesis testing for each endpoint was performed at $\alpha = 0.025$ (one-sided). Data were analyzed in a stepwise procedure as follows:

- Tio R10 vs. placebo (superiority)
- Tio R5 vs. placebo (superiority)
- Tio R10 vs. ipratropium (non-inferiority)
- Tio R5 vs. ipratropium (non-inferiority)
- Tio R10 vs. ipratropium (superiority)
- Tio R5 vs. ipratropium (superiority)

Missing data

Missing values for spirometry were estimated using other values recorded for the patient on that test day. For patients with missing data on a given test day because rescue medication was taken, the missing data were estimated by the least favorable observation that that test day, even if it was a pre-dose value. If no data were available for that test day, missing values were estimated from previous test days. Daily diary card data for PEFR and rescue medication use were excluded during steroid and theophylline bursts for COPD exacerbations. Weekly summary data from the diary card were imputed from neighboring weeks if less than 4 observations were recorded in a week. In patients discontinuing the study early due to worsening COPD, the

missing data were imputed by the least favorable data prior to discontinuation. Missing data for patients missing a visit or discontinuing for other reasons were estimated by their last observed data.

Data sets

The full analysis set for efficacy consisted of all randomized patients with at least baseline data (pre-treatment at the end of the 2 week run-in) and at least one adequate trough following at least 5 days of randomized treatment. The safety data set consisted of all randomized patients receiving at least one dose of study medication. [Module 5, Volume 1.6, Study report 205.251, page 68-75]

10.1.2.2 Results

Population characteristics

Disposition of patients

A total of 361 male and female patients with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 88 in the tio R5 group, 93 in the tio R10 group, 89 in the ipratropium group, and 91 in the placebo group. Of these, 320 (88.6%) completed the study. The blind was not broken for any patients in the trial, neither by the site nor the sponsor. A summary of patient disposition for the trial is presented in Table 53. [Module 5, Volume 1.6, Study report 205.251, page 80-81]

Table 53: Protocol 205.251 patient disposition

	Tio R5 N (%)	Tio R10 N (%)	IB MDI36 N (%)	Placebo N (%)	Total N (%)
Enrolled					429
Not entered					68
Entered	88	93	89	91	361
Not treated	0	0	0	0	0
Treated	88(100.0)	93(100.0)	89(100.0)	91(100.0)	361(100.0)
Not prematurely discontinued from trial medication	80(90.9)	84(90.3)	72(80.9)	84(92.3)	320(88.6)
Prematurely discontinued from trial medication	8(9.1)	9(9.7)	17(19.1)	7(7.7)	41(11.4)
Adverse events	6(6.8)	5(5.4)	11(12.4)	5(5.5)	27(7.5)
Worsening of disease under study	3(3.4)	1(1.1)	9(10.1)	4(4.4)	17(4.7)
Worsening of other pre-existing disease	1(1.1)	1(1.1)	0(0.0)	0(0.0)	2(0.6)
Other adverse event	2(2.3)	3(3.2)	2(2.2)	1(1.1)	8(2.2)
Administrative	2(2.3)	4(4.3)	5(5.6)	2(2.2)	13(3.6)
Non compliant with protocol	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Lost to follow-up	2(2.3)	3(3.2)	2(2.2)	1(1.1)	8(2.2)
Consent withdrawn	0(0.0)	1(1.1)	3(3.4)	1(1.1)	5(1.4)
Other	0(0.0)	0(0.0)	1(1.1)	0(0.0)	1(0.3)

Reviewer comment:

A greater number of patients discontinued from the ipratropium group, primarily due to adverse events and worsening of COPD. The adverse event accounting for this difference was COPD exacerbation.

Demographics and baseline characteristics

The mean age of the patients was 61.9 years (range 40-87 years); 74.5% of the trial population was male and 99.2% were white. The mean duration of COPD was 9.8 years. All patients were current (42.7%) or ex-smokers (57.3%), with a mean smoking history of 42.4 pack years. The mean pre-bronchodilator FEV_1 was 1.26L with a mean percent predicted of 43.6%. The mean pre-bronchodilator FEV_1/FVC was 50.1%. The mean post-bronchodilator FEV_1 was 1.46L with a mean percent predicted of 50.4%. The overall demographic profile was balanced across the four treatment groups, and pulmonary function data were generally comparable. However, there was a substantial under representation of non-white patients, with whites representing 99.2% of patients in the study. Any differences in PFT data were dealt with in the analysis by including baseline as a covariate in the model. Demographic characteristics are provided inTable 54, and baseline PFT variables are provided in Table 55.

Table 54: Protocol 205.251 patient demographic and disease characteristics

	Tio R 5	Tio R 10	IB MDI 36	Placebo	Total
Number of patients[1]	88	93	89	91	361
Gender [N (%)]					
Male	61(69.3)	69(74.2)	69(77.5)	70(76.9)	269(74.5)
Female	27(30.7)	24(25.8)	20(22.5)	21(23.1)	92(25.5)
Race					
White	87(98.9)	91(97.8)	89(100.0)	91(100.0)	358(99.2)
Black	1(1.1)	1(1.1)	0(0.0)	0(0.0)	2(0.6)
Asian	0(0.0)	1(1.1)	0(0.0)	0(0.0)	1(0.3)
Age [years][2]					
N	88	93	89	91	361
Mean	63.3	61.2	61.5	61.5	61.9
Median	63.0	63.0	62.0	62.0	62.0
SD	8.1	8.6	8.2	8.9	8.5
Min	41.0	40.0	42.0	41.0	40.0
Max	81.0	78.0	79.0	87.0	87.0
Smoking history [N (%)]					
Never smoked	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Ex smoker	50(56.8)	58(62.4)	51(57.3)	48(52.7)	207(57.3)
Smoker	38(43.2)	35(37.6)	38(42.7)	43(47.3)	154(42.7)
Smoking history [pack years]					
N	88	93	89	91	361
Mean	43.4	41.9	42.7	41.8	42.4
Median	40.0	40.0	40.0	37.0	39.0
SD	25.8	22.1	26.1	23.8	24.3
Min	11.0	10.0	11.0	10.0	10.0
Max	135.0	100.0	195.0	121.0	195.0
Duration of COPD [years][3]					
N	88	93	89	91	361
Mean	10.4	9.4	9.9	9.7	9.8
Median	9.0	7.0	8.0	8.0	8.0
SD	7.7	7.0	6.8	7.5	7.2
Min	0.7	1.0	0.3	0.3	0.3
Max	46.0	37.3	29.0	42.0	46.0

[1]The percentages may not add up to 100% due to missing data.
[2]Calculated from date of birth and date screened
[3]Regardless of when COPD diagnosis was made
Obtained from Visit 1, Screening Visit

Table 55: Protocol 205.251 screening PFT data

	Tio R 5	Tio R 10	IB MDI 36	Placebo	Total
Number of patients	88	93	89	91	361
Pre-bronchodilator FEV1 [L]					
Mean	1.195	1.254	1.324	1.279	1.263
Min	0.52	0.50	0.46	0.53	0.46
Max	1.98	2.15	2.17	2.28	2.28
Pre-bronchodilator % predicted normal FEV1 - ECCS					
Mean	42.9	42.7	44.9	43.8	43.6
Min	19.3	16.9	12.7	20.3	12.7
Max	66.9	60.3	64.3	64.2	66.9
Pre-bronchodilator FVC [L]					
Mean	2.475	2.591	2.608	2.562	2.559
Min	1.20	1.07	1.12	1.31	1.07
Max	4.26	4.73	4.25	4.34	4.73
Pre-bronchodilator FEV1/FVC [%]					
Mean	48.9	49.6	51.3	50.5	50.1
Min	27.2	22.7	15.4	26.0	15.4
Max	70.7	88.9	72.1	81.3	88.9
Post-bronchodilator[2] FEV1 [L]					
Mean	1.377	1.472	1.501	1.491	1.461
Min	0.68	0.54	0.63	0.62	0.54
Max	2.27	2.56	2.70	2.67	2.70
Post-bronchodilator[2] % predicted normal FEV1 - ECCS					
Mean	49.8	49.9	50.9	51.1	50.4
Min	24.5	18.3	17.4	23.8	17.4
Max	77.6	74.5	76.4	103	103
Post-bronchodilator[2] FEV1 [L] change from pre-dose[1]					
Mean	0.182	0.219	0.177	0.212	0.198
Min	-0.13	-0.27	-0.12	-0.12	-0.27
Max	0.51	0.79	0.84	0.68	0.84
Post-bronchodilator[2] % change from pre-dose[1]					
Mean	16.1	18.8	14.6	16.8	16.6
Min	-9.1	-18.6	-11.7	-9.7	-18.6
Max	50.0	103.0	67.2	60.4	103.0
Post-bronchodilator[2] FVC [L]					
Mean	2.711	2.918	2.870	2.824	2.832
Min	1.18	1.08	1.20	1.23	1.08
Max	4.78	5.31	4.91	4.46	5.31

[1]Obtained from Visit 1, Screening Visit
[2]30 minutes after 400 mcg of albuterol

Protocol violations

There was no per-protocol analysis for this study; therefore, protocol violations were not used to exclude patients from any analysis. There were a total of 44 patients who were determined retrospectively to have not met entry criteria. These deviations were categorized into 5 types: 1) may not have COPD, 2) unstable at the randomization visit, 3) evidence of asthma or allergic rhinitis, 4) may have taken marketed Spiriva, and 5) significant other disease that may obscure treatment response. These patients were distributed evenly across the groups.

In addition to these entry criteria violations, there was one patient who signed informed consent one day after screening laboratories, and 6 patients either took a prohibited medication or had an improper medication washout prior to PFTs. The majority of these patients were in the tiotropium groups. [Module 5, Volume 1.6, Study report 205.251, page 81-82]

Reviewer comment:

The reported protocol violations were generally distributed evenly across the study groups or would tend to bias against the drug. Overall, these discrepancies do not affect the integrity of the data. The 14 patients who fell into the category of "may not have COPD" all exceeded spirometry requirements.

Treatment compliance

Medication compliance was determined from patient diary data. Overall reported compliance for the study was 97.8% for the Respimat inhaler and 95.8% for the MDI. [Module 5, Volume 1.6, Study report 205.251, page 87]

Concomitant respiratory medications

A total of 64.8% of patients in the study took concomitant respiratory medications (excluding rescue albuterol). During the treatment period, 41.8% of patients overall were taking inhaled steroids, and 34.3% were taking theophylline preparations. Overall, 13.9% of patients took oral corticosteroids, representing an increase from baseline levels of 9.1%. Oral corticosteroids were allowed for exacerbations. 14.4% of patients took mucolytic antioxidants, also representing an increase from baseline of 8.6%. These concomitant respiratory medications were generally balanced among groups. [Module 5, Volume 1.6, Study report 205.251, page 105]

Pharmacokinetic outcomes

No pharmacokinetic data were collected in this study.

Device performance characteristics

Approximately 690 Respimat inhalers were dispensed and used by patients in this study. One hundred-seventy contained 2.5 mcg/inhalation tiotropium (tio R5 group), 178 contained 5.0 mcg/inhalation tiotropium (tio R10 group), and 342 contained placebo inhalation solution (ipratropium and placebo groups). Three product complaints (0.4% of inhalers) were received (no spray from the device, and 2 inhalers thought to be empty). All devices reported to be malfunctioning were returned to BI for evaluation and testing. A complaint was determined to be "justified" if the inhaler performance parameters were out of specification or if the reliability of

the Respimat inhaler was imperilled. None of the 3 product complaints in this study were found to be justified.

Each of the Respimat inhalers used in the study was assembled and primed at the study site, and the number of priming actuations until the first spray was seen was recorded. Overall, 41.7% of the Respimat inhalers were actuated once until the first spray was seen, 39.7% were actuated twice and 15.8% were actuated 3 times. In addition, 77.4% of the Respimat inhalers were actuated 3 additional times after the spray was first seen before first use by the patient, as instructed in the protocol; 15.1% were only actuated twice.

Efficacy outcomes

Efficacy analyses were performed on the full analysis set (FAS), which consisted of all randomized patients with at least baseline data (pre-treatment at the end of the 2-week run-in) and at least one adequate trough FEV_1 following at least 5 days of randomized treatment. In addition the FASDRY population was defined as those patient included in the FAS who have baseline data and at least 4 days of diary data on treatment for at least one diary parameter. There was no per-protocol analysis for this study; therefore, protocol violations were not used to exclude patients from the analysis.

Of the 361 patients randomized, 16 (4.4%) patients were excluded from the primary efficacy analyses because of inadequate data following multiple administration. This included 3 (3.4%) patients in the tio R5 group, 4 (4.3%) in the tio R10 group, 5 (5.6%) in the ipratropium group, and 4 (4.4%) in the placebo group.

Primary endpoint

The overall baseline mean FEV_1 for all treatment groups combined was 1.225L (1.279L for tio R5, 1.306L for tio R10, 1.353L for ipratropium, and 1.259L for placebo).

For the primary endpoint, trough FEV_1 response at the end of 12 weeks of treatment, the tio R10 group was superior to both placebo and ipratropium. The tio R5 group was superior to placebo, but not to the ipratropium group. The mean treatment differences and 95% confidence intervals for the primary endpoint, shaded in grey, are presented in Table 56. Mean treatment differences in trough response for other time points are also presented unshaded in Table 56.

For trough FEV_1, the tio R10 group showed a mean improvement of 0.177L compared to placebo ($p<0.0001$), while the tio R5 group showed a mean improvement of 0.109L ($p=0.0034$) compared to placebo. [Module 5, Volume 1.6, Study report 205.251, pages 88-94]

Table 56: Protocol 205.251 FEV_1 trough response [L] treatment differences

Treatment comparison	Test day	Treatment difference Mean	SE	95% CI	Non-inferiority p-value*	Superiority p-value**
Tio R10 - Placebo	8	0.041	0.032	(-0.021, 0.103)		0.1984
	29	0.118	0.035	(0.050, 0.186)		0.0007
	57	0.154	0.038	(0.079, 0.229)		<.0001
	85	0.177	0.036	(0.106, 0.249)		<.0001
Tio R5 - Placebo	8	0.038	0.032	(-0.024, 0.101)		0.2274
	29	0.098	0.035	(0.030, 0.167)		0.0052
	57	0.070	0.039	(-0.006, 0.146)		0.0696
	85	0.109	0.037	(0.036, 0.181)		0.0034
Tio R10 - IB MDI 36	8	0.055	0.032	(-0.007, 0.118)	0.0005	0.0815
	29	0.089	0.035	(0.021, 0.158)	<.0001	0.0108
	57	0.146	0.038	(0.070, 0.222)	<.0001	0.0002
	85	0.117	0.037	(0.045, 0.190)	<.0001	0.0015
Tio R5 - IB MDI 36	8	0.053	0.032	(-0.010, 0.116)	0.0007	0.0981
	29	0.070	0.035	(0.000, 0.139)	0.0004	0.0491
	57	0.062	0.039	(-0.014, 0.139)	0.0021	0.1104
	85	0.049	0.037	(-0.024, 0.122)	0.0041	0.1897

tio R5: N=85; tio R10 N=89; IB MDI 36: N=84; Placebo: N=87
*one sided (p-value <0.025 indicated non-inferiority). Non-inferiority delta=0.05L
** two sided
All values are based on ANCOVA analysis with terms for treatment, smoking status at entry, center and baseline.
A separate ANCOVA is fitted at each time point.

Reviewer comment:

The mean trough FEV_1 response for the tio R5 group was 0.109L. This difference is approximately the same as the difference in trough FEV_1 response at the end of 13 weeks of treatment for Spiriva HandiHaler (18 mcg) found in pivotal trials (0.110 and 0.130L).

Ipratropium is intended for dosing four times daily, or every 6 hours. For the purposes of this study, patients were instructed to hold their morning dose of ipratropium until after pre-dose PFTs at the study visit. Given unavoidable study logistics, it is likely that PFTs were conducted beyond the 6 hour trough window for ipratropium. Therefore, comparison of tiotropium conducted at the trough level with ipratropium beyond the trough level may be biased in favor of tiotropium.

Secondary endpoints

FEV_1

By the end of the first week, the mean FEV_1 trough response was 0.09L (7% above baseline) for the tiotropium groups, numerically but not statistically above placebo. For tio R10 this difference in trough FEV_1 became statistically significant at Day 28 and remained so throughout the study. For tio R5, trough FEV_1 response was numerically greater than placebo throughout the study, but only showed a statistically significant difference on Day 85. See Table 56.

The mean FEV_1 increased by 0.306-0.349L and 0.351-0.452L over baseline after treatment administration for the tio R5 and tio R10 groups, respectively. See Table 57 for FEV_1 trough responses, AUC response, and peak response on each test day. The ipratropium group also showed a peak increase of 0.24 to 0.28L over baseline around 1-2 hours after treatment administration before gradually declining over the remainder of the 6-hour observation period. The placebo group showed changes from baseline in the range of 0.06 to 0.10L.

The differences in FEV_1 between the tiotropium groups and placebo were statistically significant ($p<0.05$) at all time points on all test days after the first dose of study medication on Test Day 8 for the tio R10 group. The differences for the tio R5 group were not statistically significant for the 5-minute time point on Test Day 1 and trough on Test Days 8 and 57.

Tio R10 was significantly better than ipratropium at trough and starting at 4-5 hours after treatment administration. In general, tio R5 was not superior to ipratropium. Ipratropium was generally superior to placebo except for trough measurements and some of the 5 and 6 hour values.

An increase in all FEV_1 parameters (trough, peak and AUC (0-6h)) was observed with each successive week of the study for both tio R10 and tio R5, suggesting that steady state was not reached. However, there appeared to be a leveling off of effect by Test Day 85 (Week 12).

Table 57: Protocol 205.251 adjusted mean FEV_1 trough, AUC (0-6h), and peak (0-6h) response [L] on each test day

Response	Test Day	Tio R 5 (N = 85) Mean (SE)		Tio R 10 (N = 89) Mean (SE)		IB MDI 36 (N = 84) Mean (SE)		Placebo (N = 87) Mean (SE)	
Trough	8	0.088	(0.023)	0.090	(0.022)	0.035	(0.023)	0.049	(0.022)
	29	0.111	(0.025)	0.131	(0.024)	0.042	(0.025)	0.013	(0.024)
	57	0.120	(0.027)	0.204	(0.027)	0.058	(0.027)	0.050	(0.027)
	85	0.112	(0.026)	0.181	(0.026)	0.063	(0.026)	0.003	(0.026)
AUC(0-6h)	1	0.206	(0.019)	0.224	(0.018)	0.232	(0.019)	0.095	(0.018)
	8	0.200	(0.025)	0.230	(0.024)	0.184	(0.025)	0.077	(0.024)
	29	0.226	(0.028)	0.251	(0.028)	0.204	(0.028)	0.077	(0.028)
	57	0.232	(0.027)	0.300	(0.027)	0.219	(0.027)	0.068	(0.027)
	85	0.235	(0.028)	0.287	(0.028)	0.230	(0.028)	0.059	(0.028)
Peak(0-6h)	1	0.324	(0.022)	0.356	(0.021)	0.358	(0.022)	0.211	(0.021)
	8	0.306	(0.026)	0.351	(0.026)	0.320	(0.026)	0.196	(0.026)
	29	0.344	(0.032)	0.385	(0.031)	0.325	(0.032)	0.183	(0.031)
	57	0.345	(0.033)	0.452	(0.033)	0.359	(0.033)	0.200	(0.033)
	85	0.349	(0.032)	0.432	(0.032)	0.353	(0.032)	0.179	(0.032)

The common baseline mean FEV_1 obtained at the -10 minute time point on Test Day 1 is 1.225L.
The means are adjusted for center, smoking status at entry, and baseline value. A separate ANCOVA was fitted at each time point.

FVC

The FVC results generally paralleled those of the FEV1. At the end of the first week of dosing, mean FVC trough responses for tio R10 and tio R5 were 0.13 and 0.11L above baseline, respectively. Following treatment administration, the mean FVC increased by another 0.19 and 0.20L, respectively. A similar pattern was generally maintained for the remainder of the trial. There was no response in the placebo group on any test day. There were significant differences between tio R10 and placebo at all time points on all test days except for trough on Day 8. Tio R5 did not show significant improvement from placebo. For AUC (0-6h) and peak, significant differences from placebo were observed for both tio R10 and tio R5. [Module 5, Volume 1.6, Study report 205.251, pages 96-102]

PEFR

Baseline mean pre-dose morning peak expiratory flow rate (PEFR) for all treatment groups was 247.5 L/min, ranging from 228.5 to 256.8 L/min. Mean differences in pre-dose morning PEFR between tio R10 and tio R5 and placebo were 14-27 L/min and 9-16 L/min respectively. This result was significant for tio R10 at all weeks and for tio R5 for 7 of 12 weeks during the trial. There were also significant differences between tio R10 and ipratropium for all weeks and

between tio R5 and ipratropium for all but 1 week. Ipratropium was not significantly different from placebo in pre-dose morning PEFR.

Results for mean evening PEFR were similar to that of morning PEFR. Tio R10 was significantly higher than both placebo and ipratropium at all time points. Tio R5 was significantly higher than placebo for all time points and significantly higher than ipratropium beginning at Week 5. Ipratropium was not significantly different from placebo. [Module 5, Volume 1.6, Study report 205.251, pages 102-105]

Rescue albuterol use

For all treatment groups combined, albuterol was used an average of 2.9 occasions/day at baseline. All active treatment groups showed a numerical decrease in the use of albuterol rescue throughout the study, ranging from 0.1-1.0 fewer rescue uses per day compared to placebo. The difference was statistically significant compared to placebo for tio R10 at all weeks, but not for tio R5 or ipratropium. [Module 5, Volume 1.6, Study report 205.251, pages 105-106]

COPD symptoms

Physician reported COPD symptoms of wheezing, shortness of breath, coughing and tightness of chest were recorded after each week of therapy using a 4-point scale (0=none to 3=severe). Overall treatment differences between the groups were generally small and not statistically significant. [Module 5, Volume 1.6, Study report 205.251, pages 106-107]

Physician's Global Evaluation

The Physician's Global Evaluation was reported on an 8 point scale, ranging from 1-2=poor to 7-8=excellent. The baseline score was 4.4. Overall, the differences between the tiotropium treatment groups and placebo were small (0.2-0.6); however, differences were statistically significant on all test days for both tio R10 and tio R5 compared to placebo. [Module 5, Volume 1.6, Study report 205.251, pages 107]

Responder analysis

Responders were defined as patients with a 15% increase in FEV_1 over baseline. Using this criteria, 66% of patients in the tio R10 group, 64% of patients in the tio R5 group, and 60% of patients in the ipratropium groups were responders at some time point on Test Day 85. At 30 minutes after dosing on Day 1, only 33% of the tio R5 group and 45% of the tio R10 group showed a 15% increase in FEV_1, with the percent of responders gradually increasing to peak at 4-5 hours.

The median onset of response was slightly longer for tio R10 than for ipratropium (27.6 versus 18.5 minutes), and approximately double for tio R5 (59.2 minutes). Duration of action was 181-276 minutes (3.0-4.6 h) for ipratropium, and could not be measured for the tiotropium groups, since both showed a significant trough response.

When response is defined more stringently according to the American Thoracic Society Criteria (ref Pelligrino, 2005) of 12% increase over baseline and an increase of at least 200 mL, the mean FEV_1 increase on Day 1 does not cross a response threshold until 2 hours for tio R5 and one hour

for tio R10. This is reduced to one hour for tio R5 and 5 minutes for tio R10 at Day 85. See Table 58.

Table 58: Protocol 205.251 adjusted mean FEV_1 [L] on Day 1

Day 1 Time point		Tio R5 (N=85) Mean	Change from Baseline	% Change	Tio R10 (N=89) Mean	Change from Baseline	% Change
Mins:	5	1.279	0.054	4.4	1.306	0.081	6.6
	15	1.346	0.121	9.9	1.367	0.142	11.6
	30	1.375	0.150	12.2	1.409	0.184	15.0
Hrs:	1	1.392	0.167	13.6	1.431	0.206	16.8
	2	1.440	0.215	17.6	1.453	0.228	18.6
	3	1.454	0.229	18.7	1.481	0.256	20.9
	4	1.455	0.230	18.8	1.476	0.251	20.5
	5	1.458	0.233	19.0	1.464	0.239	19.5
	6	1.457	0.232	18.9	1.438	0.213	17.4

Day 1 Time point		IB MDI 36 (N=84) Mean	Change from Baseline	% Change	Placebo (N=87) Mean	Change from Baseline	% Change
Mins:	5	1.353	0.128	10.4	1.259	0.034	2.8
	15	1.414	0.189	15.4	1.291	0.066	5.4
	30	1.474	0.249	20.3	1.306	0.081	6.6
Hrs:	1	1.483	0.258	21.1	1.311	0.086	7.0
	2	1.503	0.278	22.7	1.326	0.101	8.2
	3	1.482	0.257	21.0	1.329	0.104	8.4
	4	1.451	0.226	18.4	1.327	0.102	8.3
	5	1.429	0.204	16.7	1.328	0.103	8.4
	6	1.397	0.172	14.0	1.322	0.097	7.9

Common baseline mean on Test Day 1 at -10 minutes = 1.225
Means are adjusted for center, smoking status at entry, and baseline value. A separate ANCOVA was fitted to each time point.

After the end of therapy, patients were followed for an additional 3 weeks during which they continued to perform daily PEFRs and record rescue albuterol use. Based on this data, there was no rebound effect; however, PFT data were not collected. Patients instead appeared to have a gradual tapering off of effect. See Table 59 for peak flow data during the post-treatment period. [Module 5, Volume 1.6, Study report 205.251, pages 107-108]

Table 59: Protocol 205.251 unadjusted mean (of weekly mean) baseline and change from baseline pre-dose morning PEFR [L/min] for patients with post-treatment data

	Tio R5 N=76 Mean (SD)	Tio R10 N=79 Mean (SD)	IB MDI 36 N=68 Mean (SD)	Placebo N=79 Mean (SD)
Baseline	226.6 (71.3)	257.6 (92.7)	262.7 (96.3)	251.6 (76.7)
Change from baseline (treatment)				
Week 12	22.7 (52.4)	33.5 (57.3)	6.1 (63.6)	15.4 (59.4)
Change from baseline (post treatment)				
Week 1	21.9 (54.1)	33.0 (51.1)	6.0 (47.0)	21.1 (63.3)
Week 2	19.2 (56.4)	28.8 (48.8)	6.9[†] (50.0)	21.2 (64.0)
Week 3[#]	20.2 (54.8)	26.3 (51.8)	7.5 (51.2)	18.7 (63.5)

[†]N=66
[#]tio R5, N=69; tio R10, N=75; IB MDI 36, N=63; placebo, N=71

Reviewer comment:

Pharmacodynamic features of bronchodilators are customarily described in the label. The onset of action of bronchodilators is often defined as the time point after the first dose at which the mean FEV_1 reaches a clinically significant threshold. FDA has defined this threshold according to ATS standards as 12% and at least 200 mL. This threshold was used for the label for Serevent DISKUS COPD indication (NDA 20-692/S-016, approved March 2002) and Spiriva HandiHaler COPD indication (NDA 21-395, approved January 2004).

While the response reaches 12% change from baseline at 30 minutes for both tiotropium groups, it is not >200 mL. Using the common baseline value of 1.225 L for patients in this study, an improvement in FEV_1 of 16.3% is required to reach 200 mL.

While onset of action occurred within 2 hours of dosing after the first dose of tiotropium, the effects of tiotropium on FEV_1 did not appear to reach steady state within the 12 weeks of the study. Given that the maximum treatment response is not seen until after multiple dosing of tiotropium, the use of the first dose to describe the onset of action may not be optimal.

The sponsor evaluated rebound only with PEFR. PEFR is generally regarded as a secondary, supportive endpoint; therefore, data provided are not sufficiently robust to support a claim regarding rebound.

Efficacy conclusions

Both tiotropium groups met the primary endpoint for the study, increase in trough FEV_1 compared to placebo at the end of 12 weeks of treatment. Generally, the tio R10 group performed numerically better than the tio R5 group. The tio R10 group was superior to both

placebo and ipratropium, while the tio R5 group was superior to placebo, but not to the ipratropium group. Both tiotropium groups showed improvement over placebo for the majority of secondary endpoints, with tio R10 generally having a statistically significant improvement. A summary of those non-spirometric endpoints reaching and not reaching a statistically significant difference in the tiotropium groups compared to placebo is provided in Table 60. For many of these endpoints, the clinical significance of the effect size is unclear.

Table 60: Protocol 205.251 efficacy summary of non-spirometric secondary endpoints

Statistically significant difference	No statistically significant difference
Morning PEFR (tio R10 all weeks; tio R5 7 of 12 weeks)	COPD symptoms
Evening PEFR (all weeks)	Rescue albuterol use (tio R5)
Rescue albuterol use (tio R10)	
Physician's Global Evaluation	

While onset of action occurred within 2 hours of dosing after the first dose of tiotropium, the effects of tiotropium on FEV_1 did not appear to reach steady state within the 12 weeks of the study.

Safety outcomes

Safety outcomes for Study 205.251 included adverse events, laboratory findings (hematology, blood chemistry, and urinalysis at screening and at the end of treatment), ECGs (performed and interpreted by the investigator at screening and at the end of treatment), vital signs (pulse rate and blood pressure measured at the same time intervals as PFTs for the first 3 hours post-dose), and physical examinations (screening and at the end of treatment). All patients who were randomized and received at least one dose of trial medication were included in the safety analysis.

Extent of exposure

A total of 361 patients were randomized and received at least one dose of study medication. The planned exposure was 85 days. Overall, the mean treatment exposure was 81.2 days with 87.3% of the patients exposed for > 80 days. Patients randomized to the ipratropium group had a slightly shorter exposure duration than those in the other three treatment groups consistent with the larger number of drop outs in the ipratropium group. See Table 61.

Table 61: Protocol 205.252 summary of treatment exposure

	Tio R 5		Tio R 10		IB MDI 36		Placebo		Total	
Total Treated	**88**		**93**		**89**		**91**		**361**	
Maximum Exposure n(%)										
1 day	0	(0.0)	2	(2.2)	1	(1.1)	2	(2.2)	5	(1.4)
2-8 days	2	(2.3)	2	(2.2)	3	(3.4)	2	(2.2)	9	(2.5)
9-50 days	4	(4.5)	4	(4.3)	4	(4.5)	3	(3.3)	15	(4.2)
51-80 days	4	(4.5)	3	(3.2)	7	(7.9)	3	(3.3)	17	(4.7)
>80 days	78	(88.6)	82	(88.2)	74	(83.1)	81	(89.0)	315	(87.3)
Treatment Exposure (days)										
Mean	82.4		81.5		79.0		81.8		81.2	
SD	17.5		21.6		23.7		21.7		21.2	
Median	85.0		85.0		85.0		85.0		85.0	
Min	4		1		1		1		1	
Max	109		111		119		131		131	

Adverse events

Deaths

One patient (#2514052) in the tio R10 group died from respiratory failure related to a COPD exacerbation. This patient was a 66 year old male with a history of active smoking, hypertension, and Stage 3 COPD (FEV_1 20% of predicted). He had been of study therapy for approximately 3 weeks when he began to experience a COPD exacerbation. He was admitted to the hospital 4 days later with respiratory failure. The patient was provided supportive therapy but no intubation due to his poor prognosis and died of respiratory failure one day after admission. In the opinion of the investigator, there was no relationship to study medication. [Module 5, Volume 1.8, Study report 205.251, pages 745-746]

There were no other deaths in the study.

Serious adverse events

Serious AEs occurred in 5.3% of the overall study population, including 2.3% of the tio R5 group, 5.4% tio R10, 9.0% ipratropium, and 4.4% placebo. Of note, only two cardiac events (myocardial infarction and chest pain, in two different patients) occurred, both in the tio R10 group. [Module 5, Volume 1.6, Study report 205.251, pages 112-119]

Adverse events leading to discontinuation

There were a greater number of discontinuations due to adverse events in the ipratropium group (12.4% ipratropium, 6.8% tio R5, 5.5% placebo, and 5.4% tio R10). This was due to a greater number of discontinuations due to COPD exacerbations in the ipratropium group.

Overall adverse events

Adverse events (AEs) were reported in 50.4% of the patients: 47.7% in tio R5, 49.5% in tio R10, 55.1% in ipratropium, and 49.5% in placebo. Treatment emergent adverse events and were generally balanced among the groups. The most common AEs across all treatment groups were COPD exacerbation, pharyngitis, headache and cough. Common (>3%) AEs occurring more frequently in both tiotropium groups compared to placebo included diarrhea (2.3% tio R5, 4.3% tio R10 vs. 1.1% placebo), dry mouth (4.5% tio R5, 3.2% tio R10 vs. 2.2% placebo), COPD exacerbation (10.2% tio R5, 11.8% tio R10 vs. 8.8% placebo), cough (3.4% tio R5, 5.4% tio R10 vs. 2.2% placebo), and pharyngolaryngeal pain (2.3% tio R5, 3.2% tio R10 vs. 1.1% placebo).

Reviewer comment:

Generally the adverse events noted in this clinical trial are consistent with AEs typically noted in a COPD clinical trial, e.g. COPD exacerbation, cough, and pharyngolaryngeal pain. Dry mouth is a well known adverse event associated with tiotropium. Diarrhea is somewhat surprising as constipation would be expected with an anticholinergic.

Laboratory findings

Overall, the changes in laboratory values throughout the study were small. There were no clinically important differences between the treatment groups, although there was an increase in glucose noted in the tiotropium groups compared to placebo. Ten percent of patients in the tio R5 group, 7.1% in tio R10, 8.5% in ipratropium, and 3.4% of placebo patients had possible clinically significant increase from baseline glucose. The mean change from baseline was 0.15 mmol/L (2.7 mg/dL) for tio R5, 0.40 mmol/L (7.2 mg/dL) for tio R10, 0.20 mmol/L for ipratropium (3.6 mg/dL), and -0.25 mmol/L (-4.5 mg/dL) for placebo.

ECG findings

Only one patient was noted to have a clinically significant change from baseline ECG. One patient in the tio R5 group had new onset of bigeminy noted on ECG at the end of treatment, which persisted after drug was discontinued.

Physical examination

Overall changes in blood pressure and pulse rate were small without a clinically important difference between treatment groups. Fourteen patients had new or worsened findings on physical examination at the end of treatment, all of which were recorded as AEs. [Module 5, Volume 1.6, Study report 205.251, pages 119-123]

Safety conclusions

No specific safety concerns are raised from the data set for this study, considered in isolation. There was one death in the tio R10 group due to respiratory failure in the setting of a COPD exacerbation. A greater number of patients in the ipratropium group discontinued due to AEs, primarily due to COPD exacerbation. There was not a dose-related effect observed in anticholinergic side-effects for tiotropium, although the sample size may have been too small to definitively determine this change.

10.1.2.3 Summary and conclusions

Both tiotropium groups met the primary endpoint for the study, increase in trough FEV_1 compared to placebo at the end of 12 weeks of treatment. The tio R10 group was superior to both placebo and ipratropium, while the tio R5 group was superior to placebo, but not to the ipratropium group. Both tiotropium groups showed improvement over placebo for the majority of secondary endpoints, with tio R10 generally having a statistically significant improvement. A summary of those non-spirometric endpoints reaching and not reaching a statistically significant difference in the tiotropium groups compared to placebo is provided in Table 60. For many of these endpoints, the clinical significance of the effect size is unclear.

While onset of action occurred within 2 hours of dosing after the first dose of tiotropium, the effects of tiotropium on FEV_1 did not appear to reach steady state within the 12 weeks of the study.

No specific safety concerns are raised from the data set for this study, considered in isolation. There was one death in the tio R10 group due to respiratory failure in the setting of a COPD exacerbation. A greater number of patients in the ipratropium group discontinued due to AEs, primarily due to COPD exacerbation. There was not a dose-related effect observed in anticholinergic side-effects for tiotropium, although the sample size may have been too small to definitively determine this change.

10.1.3 Study 205.252

10.1.3.1 Protocol

Study title

A randomized, double-blind, double-dummy, placebo-and active-controlled, parallel group efficacy and safety comparison of 12-week treatment of two doses [5 mcg (2 actuations of 2.5 mcg) and 10 mcg (2 actuations of 5 mcg)] of tiotropium inhalation solution delivered by the Respimat inhaler, placebo and ipratropium bromide inhalation aerosol (MDI) in patients with chronic obstructive pulmonary disease (COPD) [Module 5, Volume 1.9, Study report 205.252, page 1]

Design

The design of this study was identical to Protocol 205.251, with the exception of a patient satisfaction and preference questionnaire. Protocol Amendment 3, which added additional questions to the patient satisfaction and preference questionnaire regarding patient handling and use of the inhalers (Respimat and MDI) was not enacted until after study start. Thus, not all patients who completed the patient satisfaction and preference questionnaire answered the additional questions. This questionnaire was completed by patients at US sites only. [Module 5, Volume 1.9, Study report 205.252, pages 56-65]

Reviewer comment:

The patient satisfaction and preference questionnaire is the only difference between this study (205.252) and Study 205.251. This questionnaire provides information about inhaler preference and does not affect safety or efficacy data from the trials.

Duration

The duration of active treatment was 12 weeks. Prior to active treatment, patients participated in a 2-week run-in period. The study was performed during the period of November 22, 2002 to December 11, 2003. The final study report is dated August 25, 2004. [Module 5, Volume 1.9, Study report 205.252, page 1]

Investigators and centers

The study was conducted in 25 different centers in the United States and Canada: 14 from the US and 11 from Canada. no sites participated in both Study 205.251 and 205.252. [Module 5, Volume 1.9, Study report 205.252, page 28]

Materials

The study treatments were:

- tio R5: tiotropium Respimat 5 mcg (2 inhalations of 2.5 mcg) once daily in the morning and MDI placebo four times daily
- tio R10: tiotropium Respimat 10 mcg (2 inhalations of 5 mcg) once daily in the morning and MDI placebo four times daily
- ipratropium: ipratropium bromide HFA inhalation aerosol (MDI) 36 mcg (2 inhalations of 18 mcg) four times daily and Respimat placebo once daily in the morning
- placebo: Respimat placebo once daily in the morning and MDI placebo four times daily

The tiotropium bromide inhalation solution, placebo inhalation solution and Respimat inhalers were manufactured at Boehringer Ingelheim Pharma KG (Ingelheim, Germany). The ipratropium bromide inhalation aerosol and placebo inhalation aerosol supplies were manufactured (b) (4) . Batch numbers and expiration dates of investigational product are provided in Table 62. This study utilized the A4 Respimat device. The proposed device for marketing is the A5 Respimat device, which differs from the A4 by the inclusion of a locking mechanism to lock the Respimat A5 after 30 doses (60 actuations).

Table 62: Protocol 205.252 identity of investigational product

Investigational Product	Expiration Date	Ingelheim Batch No.
Tiotropium Bromide Inhalation Solution, 2.5 µg Tiotropium PA	04/2004	202948
Respimat Inhaler (A4)		WE01070187
Tiotropium Bromide Inhalation Solution, 5 µg Tiotropium PA	08/2004	202821
Respimat Inhaler (A4)		WE01080199
Placebo Inhalation Solution (for Tiotropium Bromide)	08/2004	202942
Respimat Inhaler (A4)		WE02050101
Ipratropium Bromide Inhalation Aerosol 0.021 mg TTV, 10 mL	06/2004	PD-2210
Placebo Inhalation Aerosol, 10 mL (0.1% Soya, for Ipratropium Bromide)	09/2004	PD-2098

Reviewer comment:

Typically we recommend that the Applicant conduct pivotal studies with the to be marketed product. The addition of a locking mechanism to the A5 model is unlikely to have a significant impact on device performance. The CMC reviewer, Alan Schroeder, indicates that the in vitro data shows that the two models perform similarly. Thus, the data from clinical trials utilizing the A4 Respimat model can be relied upon to support the safety and efficacy of tiotropium Respimat.

10.1.3.2 Results

Population characteristics

Disposition of patients

A total of 358 male and female patients with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 92 in the tio R5 group, 87 in the tio R10 group, 89 in the ipratropium group, and 90 in the placebo group. Of these, 312 (87.2%) completed the study. The blind was broken for one patient in the trial by the sponsor safety officer due to a serious, drug-related, unexpected adverse event. This patient was a 79 year old female who developed atrial fibrillation with rapid ventricular response. Unblinding revealed that the patient was randomized to the ipratropium group. The investigator and site staff were not informed of the treatment assignment and remained blinded to the randomization code for all patients during the course of the trial. A

summary of patient disposition for the trial is presented in Table 63. [Module 5, Volume 1.9, Study report 205.252, page 83-84]

Table 63: Protocol 205.252 patient disposition

	Tio R 5 N (%)	Tio R 10 N (%)	IB MDI 36 N (%)	Placebo N (%)	Total N (%)
Enrolled					491
Not entered					133
Entered	92	87	89	90	358
Not treated	0	0	0	0	0
Treated	92(100.0)	87(100.0)	89(100.0)	90(100.0)	358(100.0)
Not prematurely discontinued from trial medication	84(91.3)	78(89.7)	75(84.3)	75(83.3)	312(87.2)
Prematurely discontinued from trial medication	8(8.7)	9(10.3)	14(15.7)	15(16.7)	46(12.8)
Adverse events	7(7.6)	7(8.0)	10(11.2)	11(12.2)	35(9.8)
Worsening of disease under study	3(3.3)	2(2.3)	2(2.2)	7(7.8)	14(3.9)
Worsening of other pre-existing disease	1(1.1)	2(2.3)	1(1.1)	0(0.0)	4(1.1)
Other adverse event	3(3.3)	3(3.4)	7(7.9)	4(4.4)	17(4.7)
Administrative	0(0.0)	2(2.3)	3(3.4)	2(2.2)	7(2.0)
Non compliant with protocol	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Lost to follow-up	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Consent withdrawn	0(0.0)	2(2.3)	3(3.4)	2(2.2)	7(2.0)
Other	1(1.1)	0(0.0)	1(1.1)	2(2.2)	4(1.1)

Reviewer comment:

A greater number of patients discontinued in the ipratropium and placebo groups. In the placebo group this was due primarily to COPD exacerbations.

Demographics and baseline characteristics

The mean age of the patients was 66.2 years (range 40-87 years); 64.2% of the trial population was male and 95.5% were white. The mean duration of COPD was 9.6 years. All patients were current (35.5%) or ex-smokers (64.5%), with a mean smoking history of 59.7 pack years. The mean pre-bronchodilator FEV_1 was 1.03L with a mean percent predicted of 37.7%. The mean pre-bronchodilator FEV_1/FVC was 44.8%. The mean post-bronchodilator FEV_1 was 1.24L with a mean percent predicted of 45.2%. The overall demographic profile was generally balanced across the four treatment groups, although a smaller percentage of females were randomized to the tiotropium groups. Pulmonary function data at baseline were generally comparable. Any differences in PFT data were dealt with in the analysis by including baseline as a covariate in the model. Demographic characteristics are provided in Table 64, and baseline PFT variables are provided in Table 65. [Module 5, Volume 1.9, Study report 205.252, page 86-90]

Table 64: Protocol 205.252 patient demographic and disease characteristics

	Tio R 5	Tio R 10	IB MDI 36	Placebo	Total
Number of patients[1]	92	87	89	90	358
Gender [N (%)]					
Male	64(69.6)	60(69.0)	51(57.3)	55(61.1)	230(64.2)
Female	28(30.4)	27(31.0)	38(42.7)	35(38.9)	128(35.8)
Race					
White	89(96.7)	80(92.0)	88(98.9)	85(94.4)	342(95.5)
Black	2(2.2)	7(8.0)	0(0.0)	5(5.6)	14(3.9)
Asian	1(1.1)	0(0.0)	1(1.1)	0(0.0)	2(0.6)
Age [years][2]					
Mean	65.5	66.1	67.8	65.4	66.2
Median	66.5	67.0	67.0	66.5	67.0
SD	9.5	8.8	7.3	8.4	8.6
Min	41.0	44.0	49.0	40.0	40.0
Max	84.0	87.0	84.0	82.0	87.0
Smoking history [N (%)]					
Never smoked	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Ex smoker	64(69.6)	55(63.2)	56(62.9)	56(62.2)	231(64.5)
Smoker	28(30.4)	32(36.8)	33(37.1)	34(37.8)	127(35.5)
Smoking history [pack years]					
Mean	60.0	65.0	54.0	60.0	59.7
Median	50.5	60.0	50.0	50.0	51.5
SD	32.1	35.1	21.9	33.0	31.1
Min	10.0	11.0	15.0	20.0	10.0
Max	171.0	168.0	135.0	200.0	200.0
Duration of COPD [years][3]					
Mean	10.3	9.8	9.7	8.6	9.6
Median	9.0	7.0	8.0	6.5	7.7
SD	7.3	9.9	6.4	6.8	7.7
Min	0.4	0.8	1.0	0.3	0.3
Max	32.5	50.0	30.0	36.0	50.0

1 The percentages may not add up to 100% due to missing data.
2 Calculated from date of birth and date screened.
3 Regardless of when COPD diagnosis was made.
Obtained from Visit 1, screening visit

Table 65: Protocol 205.252 screening PFT data

	Tio R 5	Tio R 10	IB MDI 36	Placebo	Total
Number of patients	92	87	89	90	358
Pre-bronchodilator FEV1 [L]					
Mean	1.015	1.009	0.990	1.116	1.033
Min	0.35	0.40	0.31	0.41	0.31
Max	2.42	2.09	1.98	1.89	2.42
Pre-bronchodilator % predicted normal FEV1 - ECCS					
Mean	36.7	35.9	37.9	40.5	37.7
Min	10.0	14.9	15.1	12.6	10.0
Max	60.7	60.2	60.2	60.1	60.7
Pre-bronchodilator FVC [L]					
Mean	2.330	2.323	2.257	2.500	2.353
Min	0.71	1.11	0.55	0.89	0.55
Max	4.32	4.12	4.94	5.61	5.61
Pre-bronchodilator FEV1/FVC [%]					
Mean	44.6	44.1	45.2	45.5	44.8
Min	19.8	15.3	19.2	20.5	15.3
Max	64.3	67.1	68.5	67.8	68.5
Post-bronchodilator FEV1 [L]					
Mean	1.228	1.207	1.189	1.315	1.235
Min	0.48	0.44	0.49	0.49	0.44
Max	2.71	2.39	2.55	2.76	2.76
Post-bronchodilator[2] % predicted normal FEV1 - ECCS					
Mean	44.4	43.1	45.5	47.7	45.2
Min	14.1	19.4	16.0	14.8	14.1
Max	81.4	71.3	72.1	77.7	81.4
Post-bronchodilator[2] FEV1 [L] change from pre-dose[1]					
Mean	0.214	0.194	0.199	0.203	0.203
Min	-0.01	-0.13	-0.07	-0.06	-0.13
Max	0.66	0.55	0.57	0.87	0.87
Post-bronchodilator[2] % change from pre-dose[1]					
Mean	23.5	20.5	22.3	19.3	21.5
Min	-1.2	-12.0	-8.0	-3.4	-12.0
Max	85.7	55.3	59.4	50.5	85.7
Post-bronchodilator[2] FVC [L]					
Mean	2.732	2.671	2.629	2.853	2.722
Min	1.10	1.01	1.08	1.04	1.01
Max	6.05	4.78	5.48	6.41	6.41

[1] Obtained from Visit 1, Screening Visit
[2] 30 minutes after 400 µg of albuterol

Protocol violations

There was no per-protocol analysis for this study; therefore, protocol violations were not used to exclude patients from any analysis. There were a total of 12 patients who were determined retrospectively to have not met entry criteria. These deviations were categorized into 3 types: 1) may not have COPD, 2) unstable at the randomization visit, 3) evidence of asthma or allergic rhinitis. These patients were distributed evenly across the groups.

In addition to these entry criteria violations, there were 6 patients who signed informed consent after initiating a washout procedure for prohibited medications. There were also 3 patients who either took a prohibited medication or took an incorrect trial medication. [Module 5, Volume 1.9, Study report 205.252, pages 84-85]

Reviewer comment:

The reported protocol violations were distributed evenly across the study groups. Overall, these discrepancies do not affect the integrity of the data. One patient in the ipratropium group fell into the category of "may not have COPD" due to a baseline FEV_1/FVC ratio of 72.9% (1.29/1.77L).

Treatment compliance

Medication compliance was determined from patient diary data. Overall reported compliance for the study was 97.8% for the Respimat inhaler and 95.8% for the MDI. [Module 5, Volume 1.9, Study report 205.252, page 90]

Concomitant respiratory medications

A total of 58.7% of patients in the study took concomitant respiratory medications (excluding rescue albuterol). Overall, during the treatment period 50.8% of patients were taking inhaled steroids, and 8.1% were taking theophylline preparations. Overall, 9.2% of patients took oral corticosteroids, representing an increase from baseline levels of 3.6%. Oral corticosteroids were allowed for exacerbations. These concomitant respiratory medications were generally balanced among groups. [Module 5, Volume 1.9, Study report 205.252, page 105]

Pharmacokinetic outcomes

No pharmacokinetic data were collected in this study.

Device performance characteristics

A total of 675 Respimat inhalers were dispensed and used by patients in this study. One hundred-seventy-seven contained 2.5 mcg/inhalation tiotropium (tio R5 group), 167 contained 5.0 mcg/inhalation tiotropium (tio R10 group), and 331 contained placebo inhalation solution. Eight product complaints (1.2% of inhalers) were received. Complaints included mist seen during priming and after dosing, indicator shows near empty, no mist after actuation, "rusty" looking valve, and dispenser button locked. All devices reported to be malfunctioning were returned to BI for evaluation and testing. A complaint was determined to be "justified" if the inhaler performance parameters were out of specification or if the reliability of the Respimat inhaler was

imperilled. None of the 8 product complaints in this study were found to be justified. [Module 5, Volume 1.9, Study report 205.252, page 79-82]

Each of the Respimat inhalers used in the study was assembled and primed at the study site, and the number of priming actuations until the first spray was seen was recorded. Overall, 71.3% of the Respimat inhalers were actuated once until the first spray was seen and 27.0% were actuated twice. In addition, 96.7% of the Respimat inhalers were actuated 3 additional times after the spray was first seen before first use by the patient, as instructed in the protocol. [Module 5, Volume 1.9, Study report 205.252, page 90]

Efficacy outcomes

Efficacy analyses were performed on the full analysis set (FAS), which consisted of all randomized patients with at least baseline data (pre-treatment at the end of the 2-week run-in) and at least one adequate trough FEV_1 following at least 5 days of randomized treatment. In addition the FASDRY population was defined as those patient included in the FAS who have baseline data and at least 4 days of diary data on treatment for at least one diary parameter. There was no per-protocol analysis for this study; therefore, protocol violations were not used to exclude patients from the analysis.

Of the 358 patients randomized, 344 (3.9%) patients were excluded from the primary efficacy analyses because of inadequate data following multiple administration. This included 2 (2.2%) patients in the tio R5 group, 3 (3.4%) in the tio R10 group, 3 (3.4%) in the ipratropium group, and 6 (6.7%) in the placebo group.

Primary endpoint

The overall baseline mean FEV_1 for all treatment groups combined was 1.015L (0.995L for tio R5, 0.981L for tio R10, 0.957L for ipratropium, and 1.130L for placebo).

For the primary endpoint, trough FEV_1 at the end of 12 weeks of treatment, both tiotropium groups were superior to both placebo and ipratropium. At the end of 12 weeks of treatment, the tiotropium groups showed a mean improvement of 0.115 (tio R10) and 0.124L (tio R5) compared to placebo ($p \leq 0.0001$). The mean treatment differences and 95% confidence intervals for the primary endpoint, shaded in grey, are presented in Table 66. Mean treatment differences in trough response for other time points are also presented unshaded in Table 66. [Module 5, Volume 1.9, Study report 205.252, pages 91-97]

Table 66: Protocol 205.252 FEV_1 trough response [L] treatment differences

Treatment comparison	Test day	Treatment difference Mean	SE	95% CI	Non-inferiority p-value*	Superiority p-value**
Tio R10 - Placebo	8	0.146	0.025	(0.097, 0.194)		<.0001
	29	0.139	0.028	(0.085, 0.193)		<.0001
	57	0.139	0.029	(0.082, 0.196)		<.0001
	85	0.115	0.029	(0.057, 0.173)		0.0001
Tio R5 - Placebo	8	0.139	0.024	(0.092, 0.187)		<.0001
	29	0.130	0.027	(0.077, 0.183)		<.0001
	57	0.111	0.029	(0.055, 0.168)		0.0001
	85	0.124	0.029	(0.067, 0.181)		<.0001
Tio R10 - IB MDI 36	8	0.090	0.024	(0.042, 0.138)	<.0001	0.0002
	29	0.103	0.027	(0.049, 0.156)	<.0001	0.0002
	57	0.094	0.029	(0.037, 0.150)	<.0001	0.0012
	85	0.071	0.029	(0.014, 0.129)	<.0001	0.0145
Tio R5 - IB MDI 36	8	0.084	0.024	(0.037, 0.130)	<.0001	0.0005
	29	0.094	0.027	(0.041, 0.146)	<.0001	0.0005
	57	0.066	0.028	(0.011, 0.122)	<.0001	0.0195
	85	0.080	0.029	(0.024, 0.136)	<.0001	0.0055

tio R5: N=90; tio R10 N=84; IB MDI 36: N=86; Placebo: N=84
*one sided (p-value <0.025 indicated non-inferiority). Non-inferiority delta=0.05L
** two sided
All values are based on ANCOVA analysis with terms for treatment, smoking status at entry, center and baseline.
A separate ANCOVA is fitted at each time point.

Reviewer comment:

The mean trough FEV_1 response for the tio R5 group was 0.124L. This difference is approximately the same as the difference in trough FEV_1 response at the end of 13 weeks of treatment for Spiriva HandiHaler (18 mcg) found in pivotal trials (0.110 and 0.130L).

Ipratropium is intended for dosing four times daily, or every 6 hours. For the purposes of this study, patients were instructed to hold their morning dose of ipratropium until after pre-dose PFTs at the study visit. Given unavoidable study logistics, it is likely that PFTs were conducted beyond the 6 hour trough window for ipratropium. Therefore, comparison of tiotropium conducted at the trough level with ipratropium beyond the trough level may be biased in favor of tiotropium.

Secondary endpoints

FEV_1

By the end of the first week, the mean FEV_1 trough response compared to placebo was 0.146L (11.5% above baseline) and 0.139L (10.8% above baseline) for the tio R10 and tio R5 groups, respectively. This difference was statistically significant for both tiotropium groups at all weeks tested. See Table 66.

The mean peak FEV_1 increased by 0.270-0.308L and 0.286-0.314L over baseline after treatment administration for the tio R5 and tio R10 groups, respectively. See Table 67 for FEV_1 trough responses, AUC response, and peak response on each test day. The ipratropium group also showed a peak increase of 0.250 to 0.267L over baseline around 1-2 hours after treatment administration before gradually declining over the remainder of the 6-hour observation period. The placebo group showed changes from baseline in the range of 0.053 to 0.116L.

The differences in FEV_1 between the tiotropium groups and placebo were statistically significant ($p<0.01$) at all time points on all tests days. In addition, FEV_1 was significantly increased in both tiotropium groups compared to ipratropium at trough and starting at 3-4 hours after treatment administration.

The mean FEV_1 AUC (0-6h) response for the tiotropium groups was 0.19-0.21L over baseline (0.19-0.24L greater than placebo) throughout the study. These values were all statistically significantly higher than placebo. Tio R10 and tio R5 were also significantly higher than placebo in peak AUC. Tiotropium groups were generally higher than ipratropium in AUC (0-6h), although not significantly so. Based on FEV_1 parameters, both tiotropium groups achieved a steady state in terms of effectiveness by the end of the first week of dosing. [Module 5, Volume 1.9, Study report 205.252, pages 97-99]

Table 67: Protocol 205.252 adjusted mean FEV_1 trough, AUC (0-6h), and peak (0-6h) response [L] on each test day

Response	Test Day	Tio R 5 (N = 90) Mean (SE)		Tio R 10 (N = 84) Mean (SE)		IB MDI 36 (N = 86) Mean (SE)		Placebo (N = 84) Mean (SE)	
Trough	8	0.110	0.017	0.117	0.017	0.027	0.017	-0.029	0.017
	29	0.114	0.019	0.123	0.019	0.020	0.019	-0.016	0.020
	57	0.094	0.020	0.121	0.020	0.028	0.020	-0.018	0.021
	85	0.094	0.020	0.085	0.021	0.014	0.020	-0.030	0.021
AUC(0-6h)	1	0.185	0.014	0.194	0.014	0.164	0.014	0.019	0.014
	8	0.207	0.019	0.212	0.019	0.150	0.019	-0.024	0.019
	29	0.201	0.019	0.203	0.020	0.137	0.020	0.003	0.020
	57	0.186	0.021	0.211	0.022	0.142	0.021	-0.007	0.022
	85	0.203	0.021	0.192	0.022	0.154	0.022	-0.002	0.023
Peak(0-6h)	1	0.277	0.015	0.291	0.015	0.263	0.015	0.116	0.015
	8	0.304	0.021	0.314	0.021	0.262	0.021	0.053	0.022
	29	0.288	0.021	0.303	0.021	0.250	0.021	0.085	0.022
	57	0.270	0.023	0.313	0.024	0.253	0.024	0.077	0.024
	85	0.303	0.023	0.286	0.024	0.267	0.024	0.088	0.024

The common baseline mean FEV_1 obtained at the -10 minute time point on Test Day 1 is 1.225L
The means are adjusted for center, smoking status at entry, and baseline value. A separate ANCOVA was fitted at each time point.

FVC

The FVC results paralleled those of the FEV_1. At the end of the first week of dosing, mean FVC trough responses for tio R10 and tio R5 were 0.25 and 0.22L above baseline, respectively. Following treatment administration, the mean FVC increased by another 0.28 and 0.26L, respectively. A similar pattern was maintained for the remainder of the trial. There was no response in the placebo group on any test day. There were significant differences between the tiotropium groups and placebo at all time points on all test days. For AUC (0-6h) and peak, significant differences from placebo were observed for both tio R10 and tio R5. [Module 5, Volume 1.9, Study report 205.252, pages 99-105]

PEFR

Baseline mean pre-dose morning peak expiratory flow rate (PEFR) for all treatment groups was 219.9 L/min, ranging from 209.8 to 230.1 L/min. Mean differences from placebo in pre-dose morning PEFR for tio R10 and tio R5 were 18-27 L/min and 22-36 L/min, respectively. These differences were significant for all 12 weeks during the trial ($p<0.01$). There were also significant differences between tio R5 and ipratropium for all weeks, but tio R10 and ipratropium were not significantly different. Ipratropium was significantly different from placebo in pre-dose morning PEFR for 9 of 12 weeks during the study. [Module 5, Volume 1.9, Study report 205.252, pages 105-110]

Results for mean evening PEFR were similar to that of morning PEFR. Both tiotropium groups were significantly higher than placebo at all time points. Tio R5, but not tio R10, was significantly higher than ipratropium for all time points. Ipratropium was significantly different from placebo at all weeks. [Module 5, Volume 1.9, Study report 205.252, pages 105-110]

Rescue albuterol use

For all treatment groups combined, albuterol was used an average of 2.6 occasions/day at baseline. All active treatment groups showed a numerical decrease in the use of albuterol rescue throughout the study, ranging from 0.3-0.7 fewer rescue uses per day. The difference was statistically significant compared to placebo for tio R10 for 8 of 12 weeks and for tio R5 for 5 of 12 weeks. The ipratropium group was not significantly different from placebo. [Module 5, Volume 1.9, Study report 205.252, pages 108-109]

COPD symptoms

Physician-reported COPD symptoms of wheezing, shortness of breath, coughing and tightness of chest were recorded after each week of therapy using a 4 point scale (0=none to 3=severe). Overall treatment differences between the groups were generally small and not statistically significant. [Module 5, Volume 1.9, Study report 205.252, pages 110-111]

Physician's Global Evaluation

The Physician's Global Evaluation was reported on an 8 point scale, ranging from 1-2=poor to 7-8=excellent. Overall, the differences between treatment groups were small and not statistically significant. [Module 5, Volume 1.9, Study report 205.252, page 111]

Responder analysis

Responders were defined as patients with a 15% increase in FEV_1 over baseline. Using this criteria, 64-73% of patients in the tio R10 group, 62-68% of patients in the tio R5 group, and 57-65% of patients in the ipratropium groups were responders. At 30 minutes after dosing on Day 1, only 42% of the tio R5 group and 52% of the tio R10 group showed a 15% increase in FEV_1, with the percent of responders gradually increasing to peak at 3-4 hours.

The median onset of response was slightly longer for tio R10 than for ipratropium (16.5 versus 13.1 minutes), and approximately double for tio R5 (30.1 minutes). Duration of action was 190.6-208.9 minutes (3.2-3.5 h) for ipratropium, and could not be measured for the tiotropium groups, since both showed a significant trough response.

When response is defined more stringently according to the American Thoracic Society Criteria (ref Pelligrino, 2005) of 12% increase over baseline and an increase of at least 200 mL, the mean FEV_1 increase on Day 1 does not cross a response threshold until 2 hours for the tiotropium groups. This is reduced to one hour at Day 85. See Table 68.

Table 68: Protocol 205.252 adjusted mean FEV_1 [L] on Day 1

Day 1 Time point		Tio R5 (N=90) Mean	Change from Baseline	% Change	Tio R10 (N=84) Mean	Change from Baseline	% Change
Mins:	5	1.079	0.064	6.3	1.093	0.078	7.7
	15	1.119	0.104	10.2	1.145	0.130	12.8
	30	1.156	0.141	13.9	1.175	0.160	15.8
Hrs:	1	1.180	0.165	16.2	1.204	0.189	18.6
	2	1.208	0.193	19.0	1.220	0.205	20.1
	3	1.214	0.199	19.6	1.239	0.224	22.1
	4	1.220	0.205	20.2	1.224	0.209	20.6
	5	1.221	0.206	20.3	1.204	0.189	18.6
	6	1.218	0.203	20.0	1.208	0.193	19.0

Day 1 Time point		IB MDI 36 (N=86) Mean	Change from Baseline	% Change	Placebo (N=84) Mean	Change from Baseline	% Change
Mins:	5	1.133	0.118	11.6	1.015	0	0
	15	1.172	0.157	15.5	1.034	0.019	1.9
	30	1.203	0.188	18.5	1.040	0.025	2.5
Hrs:	1	1.219	0.204	20.1	1.058	0.043	4.2
	2	1.202	0.187	18.4	1.048	0.033	3.3
	3	1.192	0.177	17.4	1.028	0.013	1.3
	4	1.179	0.164	16.2	1.034	0.019	1.9
	5	1.144	0.129	12.7	1.020	0.005	0.5
	6	1.127	0.112	11.0	1.016	0.001	0.1

Common baseline mean on Test Day 1 at -10 minutes = 1.015
Means are adjusted for center, smoking status at entry, and baseline value. A separate ANCOVA was fitted to each time point.

After the end of therapy, patients were followed for an additional 3 weeks during which they continued to perform daily PEFRs and record rescue albuterol use. Based on this data, there was no rebound effect; however, PFT data were not collected. Patients instead appeared to have a gradual tapering off of effect. See Table 69 for peak flow data during the post-treatment period. [Module 5, Volume 1.9, Study report 205.252, pages 111-112]

Table 69: Protocol 205.252 unadjusted mean (of weekly mean) baseline and change from baseline pre-dose morning PEFR [L/min] for patients with post-treatment data

	Tio R5 N=81 Mean (SD)	Tio R10 N=76 Mean (SD)	IB MDI 36 N=73 Mean (SD)	Placebo N=72 Mean (SD)
Baseline	212.0	223.3	217.0	235.4
Change from baseline (treatment)				
Week 12	31.5	19.7	8.9	-8.6
Change from baseline (post treatment)				
Week 1	29.7	18.5	11.1	4.1
Week 2[†]	24.7	14.0	11.9	4.7
Week 3[#]	24.7	13.3	14.9	6.3

[†] tio R5, N=81; tio R10, N=75; IB MDI 36, N=72; placebo, N=72
[#]tio R5, N=79; tio R10, N=75; IB MDI 36, N=71; placebo, N=68

Reviewer comment:

Pharmacodynamic features of bronchodilators are customarily described in the label. The onset of action of bronchodilators is often defined as the time point after the first dose at which the mean FEV_1 reaches a clinically significant threshold. FDA has defined this threshold according to ATS standards as 12% and at least 200 mL. This threshold was used for the label for Serevent DISKUS COPD indication (NDA 20-692/S-016, approved March 2002) and Spiriva HandiHaler COPD indication (NDA 21-395, approved January 2004).

While the response reaches 12% change from baseline at 30 minutes for both tiotropium groups, it is not >200 mL. Using the common baseline value of 1.015 L for patients in this study, an improvement in FEV_1 of 19.7% is required to reach 200 mL.

Onset of action occurred within 2-3 hours of dosing after the first dose of tiotropium. The effects of tiotropium on FEV_1 appeared to reach steady state by Day 8 of the study. Given that the maximum treatment response is not seen until after multiple dosing of tiotropium, the use of the first dose to describe the onset of action may not be optimal.

The sponsor evaluated rebound only with PEFR. PEFR is generally regarded as a secondary, supportive endpoint; therefore, data provided are not sufficiently robust to support a claim regarding rebound.

Device satisfaction and preference questionnaire

Patients at the 14 US sites completed a patient satisfaction and preference questionnaire at the end of treatment. The questionnaire consisted of 15 questions about Respimat and MDI satisfaction in two categories, performance/reliability and convenience. Each response was given on a 7 point scale ranging from 1=very dissatisfied to 7=very satisfied. For all treatment groups combined, the mean satisfaction scores for the 15 attributes ranged from 4.5-6.3, indicating that patients were generally satisfied with the inhalers. A significant difference showing greater satisfaction with the Respimat was shown on 3 attributes: 1) ability to tell the amount of medication left in the container, 2) inhaler durability, and 3) inhaler is environmentally friendly. Patients scored the MDI significantly higher than the Respimat in terms of overall convenience with carrying the inhaler. [Module 5, Volume 1.9, Study report 205.252, page 112]

Efficacy conclusions

Both tiotropium groups met the primary endpoint for the study, increase in trough FEV_1 compared to placebo at the end of 12 weeks of treatment. In addition, both tiotropium groups were superior to ipratropium for the primary endpoint, and both tiotropium groups showed significant improvement over placebo for the majority of secondary endpoints.

A summary of those non-spirometric endpoints reaching and not reaching a statistically significant difference in the tiotropium groups compared to placebo is provided in Table 70. For many of these endpoints, the clinical significance of the effect size is unclear.

Table 70: Protocol 205.252 efficacy summary of non-spirometric secondary endpoints

Statistically significant difference	No statistically significant difference
Morning PEFR (all weeks)	COPD symptoms
Evening PEFR (all weeks)	Physician's Global Evaluation
Rescue albuterol use (tio R10 8 of 12 weeks; tio R5 5 of 12 weeks)	

Onset of action occurred within 2-3 hours of dosing after the first dose of tiotropium. The effects of tiotropium on FEV_1 appeared to reach steady state by Day 8 of the study.

Safety outcomes

Safety outcomes for Study 205.251 included adverse events, laboratory findings (hematology, blood chemistry, and urinalysis at screening and at the end of treatment), ECGs (performed and interpreted by the investigator at screening and at the end of treatment), vital signs (pulse rate and blood pressure measured at the same time intervals as PFTs for the first 3 hours post-dose), and physical examinations (screening and at the end of treatment). All patients who were randomized and received at least one dose of trial medication were included in the safety analysis.

Extent of exposure

A total of 358 patients were randomized and received at least one dose of study medication. The planned exposure was 85 days. Overall, the mean treatment exposure was 80.9 days with 87.7% of the patients exposed for > 80 days. Patients randomized to the ipratropium and placebo groups had a slightly shorter exposure duration than those in the other three treatment groups consistent with the larger number of drop outs in these groups. See Table 71.

Table 71: Protocol 205.252 summary of treatment exposure

	Tio R 5		Tio R 10		IB MDI 36		Placebo		Total	
Total Treated	92		87		89		90		358	
Maximum Exposure n (%)										
1 day	0	(0.0)	0	(0.0)	1	(1.1)	1	(1.1)	2	(0.6)
2-8 days	0	(0.0)	0	(0.0)	1	(1.1)	4	(4.4)	5	(1.4)
9-50 days	6	(6.5)	5	(5.7)	7	(7.9)	5	(5.6)	23	(6.4)
51-80 days	2	(2.2)	2	(2.3)	4	(4.5)	6	(6.7)	14	(3.9)
>80 days	84	(91.3)	80	(92.0)	76	(85.4)	74	(82.2)	314	(87.7)
Treatment Exposure (days)										
Mean	83.0		82.9		79.1		78.4		80.9	
SD	16.2		15.9		20.5		23.3		19.3	
Median	85.0		85.0		85.0		85.0		85.0	
Min	10		15		1		1		1	
Max	120		104		100		128		128	

Adverse events

Deaths

There were 3 deaths in the study, one in the tio R10 group, one in the tio R5 group, and one in the ipratropium group. The causes of death were COPD exacerbation, COPD exacerbation associated with lung cancer, and metastatic pancreatic carcinoma, respectively.

Patient number 2619 in the tio R10 group was a 76 year old female who received approximately 6 weeks of study medication prior to experiencing a COPD exacerbation. She was admitted to the hospital two days after onset of symptoms and died one day later in her sleep.

Patient number 2694 in the tio R5 group was a 61 year old male who completed approximately 6 weeks of study therapy prior to admission to the hospital with a COPD exacerbation requiring intubation and eventual tracheostomy. Study medication was discontinued on admission. His hospital course was complicated by a lower GI bleed. A right upper lobe mass, probably malignant, was discovered approximately (b) (6) after admission. The patient was transferred to a palliative care unit and died (b) (6), thought secondary to his pulmonary malignancy.

Patient number 1563 in the ipratropium group was a 56 year old male with a past medical history of alcoholic liver disease (b) (6) after beginning trial medication, the patient was admitted to the hospital with severe abdominal pain, poor appetite, and jaundice. A CT guided biopsy revealed poorly differentiated pancreatic ductal carcinoma. The patient was transferred to hospice and trial drug was discontinued. The patient died (b) (6) later.

Serious adverse events

Serious AEs occurred in 4.7% of the overall study population, including 2.2% of the tio R5 group, 5.7% tio R10, 10.1% ipratropium, and 1.1% placebo. The most common SAEs were atrial fibrillation (2 patients) and COPD exacerbation (3 patients). There were 9 serious cardiac system events, all in either the tio R10 or the ipratropium groups. These included 4 patients in the tio R10 group with the following AEs: one angina, one atrial fibrillation, one cardiac arrest, one coronary artery disease, and one myocardial infarction.

Adverse events leading to discontinuation

The most common AE leading to discontinuation was COPD exacerbation. There were a greater number of discontinuations due to adverse events in the placebo group (12.2% placebo, 11.2% ipratropium, 8.0% tio R10, and 7.6% tio R5). This was due to a greater number of discontinuations due to COPD exacerbations in the placebo group.

Overall adverse events

Adverse events (AEs) were reported in 65.4% of the patients: 57.6% in tio R5, 71.3% in tio R10, 64.0% in ipratropium, and 68.9% in placebo. The most common AEs across all treatment groups were COPD exacerbation, dry mouth, and pharyngitis. Common (>3%) AEs occurring more frequently in both tiotropium groups compared to placebo included dry mouth (17.2% tio R10, 12.0% tio R5 vs. 2.2% placebo), urinary tract infection (7.6% tio R5, 2.3% tio R10, vs. 1.1% placebo), dizziness (3.3% tio R5, 5.7% tio R10 vs. 1.1% placebo), COPD exacerbation (8.7% tio R5, 17.2% tio R10 vs. 14.4% placebo), cough (4.3% tio R5, 5.7% tio R10 vs. 4.4% placebo), and hoarseness (tio R5 4.3%, tio R10 2.3% vs. 0% placebo).

[Module 5, Volume 1.9, Study report 205.252, pages 116-127]

Laboratory findings

The changes in laboratory values throughout the study were small. There were no clinically important differences between the treatment groups. [Module 5, Volume 1.9, Study report 205.252, pages 127-30]

ECG findings

ECG findings included one patient in the tio R5 group and one in the tio R10 group with new onset QT prolongation. In addition, one patient in the ipratropium group had premature atrial contractions and one had atrial fibrillation noted after 12 weeks of treatment but not at baseline.

Physical examination

Likewise, overall changes in blood pressure and pulse rate were small without a clinically important difference between treatment groups. There were a total of 20 patients with clinically

significant new or worsened findings on physical examination at the completion of therapy. Patients with new or worsened physical examination findings were balanced across the 4 treatment groups.

Safety conclusions

No specific safety concerns are raised from the data set for this study, considered in isolation. There were a greater number of discontinuations due to adverse events in the placebo group (12.2% placebo, 11.2% ipratropium, 8.0% tio R10, and 7.6% tio R5). This was due to a greater number of discontinuations due to COPD exacerbations in the placebo group. Patients randomized to the ipratropium and placebo groups had a slightly shorter exposure duration than those in the other three treatment groups consistent with the larger number of drop outs in these groups.

There were 3 deaths in the study, one in the tio R10 group, one in the tio R5 group, and one in the ipratropium group. The causes of death were COPD exacerbation, COPD exacerbation associated with lung cancer, and metastatic pancreatic carcinoma, respectively. Adverse events demonstrated a dose-related effect for tiotropium in the anticholinergic side-effect of dry mouth.

10.1.3.3 Summary and conclusions

Both tiotropium groups met the primary endpoint for the study, increase in trough FEV_1 compared to placebo at the end of 12 weeks of treatment. In addition, both tiotropium groups were superior to ipratropium for the primary endpoint, and both tiotropium groups showed significant improvement over placebo for the majority of secondary endpoints.

A summary of those non-spirometric endpoints reaching and not reaching a statistically significant difference in the tiotropium groups compared to placebo is provided in Table 70. For many of these endpoints, the clinical significance of the effect size is unclear.

Onset of action occurred within 2-3 hours of dosing after the first dose of tiotropium. The effects of tiotropium on FEV_1 appeared to reach steady state by Day 8 of the study.

No specific safety concerns are raised from the data set for this study, considered in isolation. There were a greater number of discontinuations due to adverse events in the placebo group (12.2% placebo, 11.2% ipratropium, 8.0% tio R10, and 7.6% tio R5). This was due to a greater number of discontinuations due to COPD exacerbations in the placebo group. Patients randomized to the ipratropium and placebo groups had a slightly shorter exposure duration than those in the other three treatment groups consistent with the larger number of drop outs in these groups.

There were 3 deaths in the study, one in the tio R10 group, one in the tio R5 group, and one in the ipratropium group. The causes of death were COPD exacerbation, COPD exacerbation associated with lung cancer, and metastatic pancreatic carcinoma, respectively. Adverse events demonstrated a dose-related effect for tiotropium in the anticholinergic side-effect of dry mouth.

10.1.4 Study 205.254

10.1.4.1 Protocol

Study title

A randomized, double-blind, placebo-controlled, parallel group efficacy and safety comparison of one-year treatment of two doses (5 mcg [2 actuations of 2.5 mcg] and 10 mcg [2 actuations of 5 mcg]) of tiotropium inhalation solution delivered by the Respimat inhaler in patients with chronic obstructive pulmonary disease (COPD) [Module 5, Volume 11, Study report 205.254, page 3]

Design

The study was a multicenter, multinational, randomized, double-blind, parallel group study to compare the long-term efficacy and safety of two doses (5 mcg [2 actuations of 2.5 mcg] and 10 mcg [2 actuations of 5 mcg]) of tiotropium inhalation solution administered by the Respimat inhaler compared with placebo in patients with COPD. The placebo group received a Respimat placebo product. All patients also received albuterol MDI inhalers for rescue use. [Module 5, Volume 11, Study report 205.252, page 48]

Duration

The duration of active treatment was 48 weeks. Prior to randomized treatment, patients participated in a 2 week run-in period. There was also a 3-week follow up period after completion of randomized treatment. The study was performed during the period of February 3, 2003 to June 1, 2005. The final study report is dated December 6, 2005, and was revised January 5, 2006. [Module 5, Volume 11, Study report 205.254, page 1]

Investigators and centers

The study was conducted at 77 centers from 14 different countries. Countries were included from Europe, North America, and Australia. [Module 5, Volume 11, Study report 205.254, page 27]

Reviewer comment:

No center participated in both Study 205.254 and 205.255.

Materials

The study treatments were:

- tio R5: tiotropium Respimat 5 mcg (2 inhalations of 2.5 mcg) once daily in the morning
- tio R10: tiotropium Respimat 10 mcg (2 inhalations of 5 mcg) once daily in the morning
- placebo: identical to Respimat inhalation solution (2 inhalations) once daily in the morning

The tiotropium bromide inhalation solution, placebo inhalation solution, and Respimat inhalers were manufactured at Boehringer Ingelheim Pharma KG (Ingelheim, Germany). Open label commercial albuterol inhalation aerosol (HFA MDI, 100 mcg per actuation) was also provided to each site for reversibility testing and dispensing to the patients for rescue use throughout the study. Batch numbers and expiration dates of investigational product are provided in Table 72. This study utilized the A4 Respimat device. The proposed device for marketing is the A5 Respimat device, which differs from the A4 by the inclusion of a locking mechanism to lock the Respimat A5 after 30 doses (60 actuations).

Table 72: Protocol 205.254 identity of investigational product

Investigational Product	Expiration Date	Ingelheim Batch No.
Tiotropium Bromide Inhalation Solution, 2.5 µg Tiotropium PA	08/2005	202820
Respimat Inhaler (A4)		WE01070189
Tiotropium Bromide Inhalation Solution, 5 µg Tiotropium PA	08/2005	202821
Respimat Inhaler (A4)		WE01070188
Placebo Inhalation Solution (for Tiotropium Bromide)	08/2005	202942
Respimat Inhaler (A4)		WE02050101

Reviewer comment:

Typically we recommend that the Applicant conduct pivotal studies with the to be marketed product. The addition of a locking mechanism to the A5 model is unlikely to have a significant impact on the device performance. The CMC reviewer, Alan Schroeder, indicates that the in vitro data shows that the two models perform similarly. Thus, the data from clinical trials utilizing the A4 Respimat model can be relied upon to support the safety and efficacy of tiotropium Respimat.

Objectives

The primary objective of this study was to compare two doses (5 mcg and 10 mcg) of tiotropium inhalation solution delivered by the Respimat inhaler once daily to placebo in patients with COPD, with respect to bronchodilator efficacy, effect on health status, effect on dyspnea and effect on frequency of exacerbations. Secondary endpoints included comparison of health resource utilization and safety outcomes. [Module 5, Volume 11, Study report 205.254, page 3]

Population

A total of 983 male and female patients with stable moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 332 in the tio R5 group, 332 in the tio R10 group, and 319 in the

placebo group. Of these, 782 (79.6%) completed the study. [Module 5, Volume 1.11, Study report 205.254, page 101]

Inclusion criteria

Notable inclusion criteria included: [Module 5, Volume 1.11, Study report 205.254, pages 50-51]

- Diagnosis of COPD and with the following spirometric criteria:
  - $FEV_1 \leq 60\%$ of predicted normal and $FEV_1 \leq 70\%$ of FVC
- Male or female patients 40 years of age or older
- Current or ex-smokers with a smoking history of more than 10 pack-years

Exclusion criteria

Notable exclusion criteria included: [Module 5, Volume 1.11, Study report 205.252, pages 51-54]

- History (6 months or less) of myocardial infarction
- Unstable/life-threatening arrhythmia or hospitalized for heart failure within the past year
- Malignancy within the last 5 years
- Narrow-angle glaucoma
- History of asthma, allergic rhinitis or total blood eosinophil count $\geq 600/mm^3$
- History of life-threatening pulmonary obstruction, cystic fibrosis or bronchiectasis
- Active tuberculosis
- Thoracotomy with pulmonary resection
- Pulmonary rehabilitation program within 6 weeks
- Daytime oxygen use
- Oral beta-adrenergics
- Cromolyn sodium or nedocromil sodium
- Antihistamines, antileukotrienes or leukotriene receptor antagonists
- Oral corticosteroids > 10 mg prednisone/day

Reviewer comment:
Enrollment criteria were the same for all 4 pivotal trials in the tiotropium Respimat program (205.251, 205.252, 205.254, and 205.255). Of note, bronchodilatory reversibility was not an inclusion criterion.

Procedures

Following an initial screening, patients entered a two-week run-in period. Patients who successfully complete this phase were randomized into the one-year (48 week), double-blind treatment period in which they received tiotropium 5 mcg (tio R5), tiotropium 10 mcg (tio R10),

or placebo. The drugs were administered using the Respimat inhaler as two inhalations taken once daily in the morning. Open label albuterol MDI was also provided as rescue medications.

Study visits were conducted two weeks after randomization and every 2 months thereafter. Patients were evaluated for an additional three weeks following completion of the randomized treatment period. Patients completed a daily Diary Card indicating each dose of study medication taken and the number of occasions of rescue albuterol use. Compliance with study medication, based on the patient's daily Diary Card, was assessed at each study visit.

The protocol and protocol amendments, patient informed consent, and patient information sheet were approved by the appropriate IRBs or IECs prior to shipment of study drug or enrollment of patients. The Applicant states that the study was conducted according to FDA regulations and guidelines and that written informed consent was obtained from each patient prior to participation in the study. [Module 5, Volume 1.11, Study report 205.254, page 25]

The study flow chart as revised by protocol Amendment 3 is presented in Table 73. [Module 5, Volume 1.11, Study report 205.254, pages 65-76]

Table 73: Protocol 205.254 study flow chart

	Screen		Treatment Period								Follow-up
Visit Number **Week** **Day**	**1** **-2** **-14**	**2*** **-** **-1**	**2** **0** **1**	**3** **2** **15**	**4** **8** **57**	**5** **16** **113**	**6** **24** **169**	**7** **32** **225**	**8** **40** **281**	**9 4** **8** **337**	**10** **+3** **+21**[5]
Informed consent	X[1]										
Demographics	X										
Medical history	X										
Inclusion/exclusion criteria	X		X								
Physical examination	X									X[8]	
Vital signs (seated)	X		X	X	X	X	X	X	X	X[8]	
Laboratory tests (fasted)	X									X[8]	
12-lead ECG	X		(X)[7]			(X)[7]			(X)[7]	X[8]	
Holter monitoring		(X)[6]				(X)[6]			(X)[6]		
Training in use of Respimat	X		X								
Issue of diary cards	X		X	X	X	X	X	X	X	X	
Collect and review diary cards			X	X	X	X	X	X	X	X	X
Issue peak flow meter	X										
Conclusion of screening			X								
Randomization			X								
Medication washout check	X		X	X	X	X	X	X	X	X	
Dispense Respimat test medication inhaler			X		X	X	X	X	X		
Collect Respimat test medication inhaler					X	X	X	X	X	X	
Dispense rescue medication	X		X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	

Table 22: Protocol 205.254 study flow chart (continued)

	Screen		Treatment Period								Follow-up
Visit Number **Week** **Day**	**1** **-2 -** **14**	**2*** **-** **-1**	**2** **0** **1**	**3** **2** **15**	**4** **8** **57**	**5** **16** **113**	**6** **24** **169**	**7** **32** **225**	**8** **40** **281**	**9** **48** **337**	**10** **+3 +21[5]**
Administration of test medication in clinic			X	X	X	X	X	X	X	X	
Drug accountability check				X	X	X	X	X	X	X	
PFTs (FEV1 /FVC)	X[2]	(X)[6]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	
SGRQ			X		X	X		X		X	X
Mahler BDI			X								
Mahler TDI					X	X	X	X	X	X	X
Health Resource Utilization			X	X	X	X	X	X	X	X[8]	X
Review smoking status	X					X				X[8]	
COPD symptom scores			X	X	X	X	X	X	X	X	X
Physician's Global Evaluation			X	X	X	X	X	X	X	X	X
Patient's Global Rating					X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X
Concomitant medication	X		X	X	X	X	X	X	X	X	X
Termination of Trial Medication										X	

1. All patients must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial i.e. before medication washout/restriction. It may be necessary for the patient to attend the clinic between 1 and 7 days prior to Visit 1 in order to give consent.
2. To include reversibility testing using 4 puffs Albuterol (100µg per actuation)
3. Measured 10 minutes prior to drug administration and at 5 minutes, 30 minutes, 1, 2, and 3 hours post dose.
4. As required
5. Post-treatment period
6 In a subset of up to 300 patients in selected sites
7. At pre-dose and at 5 minutes and at 2 hours post-dose (in a subset of up to 300 patients at selected sites only). Pulmonary function testing at 5 minutes post dose at Visits 2, 5 and 8 will be omitted for the subset of patients having 12-lead ECG measurements at this time point.
8. To be completed by all patients who discontinue early

Efficacy endpoints

Primary

- trough FEV_1 response at the end of the 48-week treatment period (Day 337)
- total SGRQ score at the end of the 48-week treatment period (Day 337)
- Mahler TDI focal score at the end of the 48-week treatment period (Day 337). Data were combined with Study 205.255.
- number of COPD exacerbations occurring in a year. Data were combined with Study 205.255.

FEV_1

Trough FEV_1 was defined as the FEV_1 measured at the -10 minute time point at the end of the dosing interval 24 hours post drug administration. Trough FEV_1 response was defined as the change from baseline in trough FEV_1. Baseline FEV_1 was the pre-treatment FEV_1 value measured at Visit 2 in the morning 10 minutes prior to administration of the first dose of study medication.

Pulmonary function testing was to occur both prior to and following test-drug administration on weeks 2, 8, 16, 24, 32, 40, and 48. At Visit 2, patients used a newly primed Respimat inhaler and MDI. At subsequent visits the Respimat inhaler and MDI in current use by the patient were to be used to administer the test-dose. Spirometry was performed according to ATS criteria using standardized equipment (KoKo spirometer, and study-specific software). The highest FEV_1 and FVC of three maneuvers were recorded regardless of whether they came from the same or different maneuvers. For each patient, PFTs started at approximately the same time of day ±30 minutes in the morning between 7 and 10 am. Although not an enrollment criteria, reversibility was tested at baseline after administration of 400 mcg albuterol aerosol.

A number of medications were appropriately restricted prior to PFT testing:

- short-acting theophylline (at least 24 hour washout)
- long-acting theophylline (at least 48 hour washout)
- short-acting anticholinergic bronchodilators (at least 8 hour washout)
- short-acting beta-adrenergic bronchodilators (at least 8 hour washout)
- long-acting beta-adrenergics (at least 48 hour washout)
- inhaled corticosteroids (not to be taken 1 hour prior)
- study medications (not to be taken prior to test-day pre-dose PFTs)

In addition, patients were to refrain from strenuous exercise, smoking, caffeinated or ice-cold beverages, cold temperatures, dust, and environmental smoke the morning prior to spirometry.

St. George's Respiratory Questionnaire

The St. George's Respiratory Questionnaire (SGRQ)[6] is a self-administered health related quality of life measure divided into three components: symptoms, activity, and impacts. The symptoms component contains items concerned with the level of symptomatology, including frequency of cough, sputum production, wheeze, breathlessness, and the duration and frequency of breathlessness or wheeze. The activity component is concerned with physical activities that either cause of are limited by breathlessness. The impacts component covers such factors as employment, being in control of health, panic, stigmatization, the need for medication and its side effects, expectations for health and disturbance of daily life. Scores ranging from 0 to 100 are calculated for each component, as well as a total score which summarizes the responses to all items. A zero score indicates no impairment of quality of life. The questionnaire takes approximately 10 minutes to complete.

The SGRQ was administered to the patient to complete at the end of the run-in period (Visit 2, randomization visit) and repeated at the end of 8, 16, 32, and 48 weeks of treatment as well as at the end of the 3-week follow up period. The SGRQ was administered prior to PFTs.

Mahler Transitional Dyspnea Index

The Mahler Baseline Dyspnea Index (BDI) was performed at the end of the run-in period (Visit 2, randomization visit). The TDI was performed at the end of 8, 16, 32, and 48 weeks of treatment as well as at the end of the 3-week follow up period. The Mahler TDI measures change from baseline and is a structured interview administered by trained medical personnel. Investigators were provided with worksheets which had to be used at the baseline visit to document the activities which caused the patient to feel breathless. The worksheet was also used to document the level and extent at which activities could be performed before that patient felt breathless. The worksheet completed at baseline had to be reviewed at each subsequent assessment of the patient's breathlessness prior to selecting an appropriate score from the TDI questionnaire.

Reviewer comment:

DPAP held a type C meeting with the sponsor on December 29, 2004 to discuss the possibility of a labeled indication for relief of dyspnea in COPD patients. Limitations of the self-administered computerized Mahler Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) instrument Boehringer Ingelheim proposed to support the dyspnea indication had been previously discussed in the September 6, 2002 DPAP Advisory Committee meeting for tiotropium HandiHaler. Although the sponsor addressed many of the concerns raised by the Advisory Committee, the Division advised the applicant that the BDI/TDI could not be utilized to support a dyspnea indication due to fundamental inherent weaknesses of the instrument.

The Applicant has not included any labeling claims regarding dyspnea or the Mahler TDI instrument.

COPD exacerbations

For the purposes of this study, a COPD exacerbation was defined as "a complex of respiratory events/symptoms with a duration of three days of more requiring a change in 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
- 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)

The onset of an exacerbation was defined by the onset of the first recorded symptom. The end of the exacerbation was recorded as defined by the investigator. Patients were asked about exacerbations during each visit and the data were recorded on a specific exacerbation case report form.

Reviewer comment:

The definition of COPD includes both a change in symptoms and a treatment requirement. Inclusion of both components of the definition is likely to increase uniformity in the study, as therapy patterns are known to vary across geographic regions. Advair is the only other medication that has a labeling claim (and indication) for reduction of COPD exacerbations so we now have a regulatory path established for this particular claim. No well-accepted definition of exacerbations, although in general the definition is acceptable.

Secondary

- trough FEV_1 response after 2, 8, 16, 24, 32, and 40 weeks
- trough FVC response after 2, 8, 16,24, 32, 40, and 48 weeks
- FEV_1 and FVC $AUC_{0\text{-}3h}$ response after 0, 2, 8, 16, 24, 32, 40, and 48 weeks
- individual FEV_1 and FVC measurements at each time point
- weekly mean morning pre-dose and evening PEFRs

- weekly mean number of occasions of rescue therapy used as required (PRN albuterol)
- data from patient questionnaire collected over the treatment period, i.e. the 3 Mahler Dyspnea Indices (functional impairment, magnitude of task, and magnitude of effort) and the impacts, activity and symptoms scores from the SGRQ
- COPD symptoms scores (wheezing, shortness of breath, coughing, and tightness of chest)
- Physician's Global Evaluation
- Patient's Global Rating
- number of patients with at least on COPD exacerbation, time to first exacerbation, and number of exacerbation days
- number of patients with at least one hospitalization for COPD exacerbations, time to first hospitalization associated with COPD exacerbations, number of hospitalizations, and number of hospitalization days due to COPD exacerbations during the treatment period
- health resource utilization beyond the study protocol, relating to the patient's respiratory condition (hospitalizations, emergency department visits, physician and other health care provider visits)

[Module 5, Volume 1.11, Study report 205.254, pages 81-82]

The patient received a diary card at each visit. This card was used to record twice daily PEFR, test medication use, and rescue albuterol use. An additional card was given to record health-related comments. Patients were also to record the number of actuations until a spray was first seen from the Respimat and the number of further actuations before first use. The card was returned and reviewed with the patient at each visit. The best of three PEFR measurements at each time point was to be recorded. Baseline PEFR and rescue therapy use were defined the average during the last week of the run-in (Week -1).

COPD symptom scores were recorded by the investigator in four categories: wheezing, shortness of breath, coughing, and tightness of chest. The scores were based on the investigator's assessment of the patient's condition during the week just prior to the visit and were evaluated just prior to PFTs. The severity of symptoms was rated on a four-point scale as follows:

- not present = no symptoms
- mild = awareness of symptom which is easily tolerated
- moderate = discomfort enough to cause interference with usual activity
- severe = incapacitating with inability to do work or usual activity

The Physician's Global Evaluation was made prior to PFTs and was to reflect the investigator's opinion of the patient's overall clinical condition. The Physician's Global Evaluation was reported on an 8 point scale, ranging from 1-2=poor to 7-8=excellent. The evaluation was based on the need for concomitant therapy, number and severity of exacerbations, severity of cough,

ability to exercise, amount of wheezing and other relevant clinical observations since the patient's last visit.

Safety endpoints

- adverse events
- pulse rate and blood pressure
- laboratory tests, ECG, and physical examination at the start of the two-week fun-in and at the end of the treatment period
- 12-lead ECG pre-dose and at 5 minutes and 2-hours post-dose on test days 1, 113, and 281 (subset of patients at selected sites)
- 24-hour Holter monitoring on test days 1, 113, and 281 (in a subset of patients at selected sites)

No significant AEs were prespecified for this study. All AEs were recorded at each visit after review of the patient's diary card and discussion with the patient. COPD exacerbations were also reported as AEs. Particular attention was paid to respiratory events indicative of bronchoconstriction related to administration of the study drug, specifically drop in $FEV_1 \geq 15\%$ from study day baseline, need for rescue medication, cough, wheeze and dyspnea within 30 minutes after inhaling randomized treatment on each test day.

Pulse rate and blood pressure were measured and recorded at the same time intervals as pulmonary function testing for the first three hours post-dose. Measurements were obtained immediately before PFTs with the patient seated and rested for a minimum of five minutes. Blood pressure was to be performed by the same person using the same blood pressure instrument on the same arm.

A standard 12-lead ECG was to be performed on all patients at the screening visit and repeated at the end of the treatment period. The ECG was to be performed prior to the test-day pre-dose PFT. All ECGs were interpreted by the investigator or other qualified site personnel. ECG equipment and reading were not standardized across sites. In addition, a subset of up to 300 patients from this study and Study 205.255 received additional 12-lead ECG measurements and 24-hour Holter monitoring studies that were reviewed centrally.

A complete physical examination was to be performed on all patients at the screening visit and repeated at the end of the treatment period. New abnormal findings or worsening of baseline conditions detected at follow-up physical examination were recorded as AEs.

[Module 5, Volume 1.11, Study report 205.254, pages 82-83]

Concomitant therapy

The following medications were permitted by the protocol:

- Open-label albuterol was provided for rescue use throughout the study. Patients were to record use on their daily diary card.

- Temporary increases in dose or addition of theophylline and oral corticosteroids were permitted during randomized therapy. PFTs were to be conducted at least 7 days after the last administered dose of an increase or addition.
- The use of antibiotics was not restricted.

The protocol included the following restrictions regarding concomitant therapy during the course of the study:

- Minimal doses of oral corticosteroids (10 mg or less of prednisone daily), orally inhaled corticosteroids, theophylline preparations, and mucolytic agents were permitted if stabilized for at least 6 weeks prior to the study.
- Anticholinergic drugs including Atrovent Inhalation Aerosol, Atrovent Nasal Spray, and Spiriva HandiHaler were allowed during the baseline and follow up periods but not during the treatment period.
- Orally inhaled short and long-acting beta adrenergics were allowed during the baseline and follow-up periods but not during the treatment period, except for provided albuterol.
- Anti-leukotrienes and leukotriene receptor antagonists were permitted only if prescribed for conditions other than asthma or excluded allergic conditions.
- Patients using fixed combinations inhaled corticosteroids/long-acting beta adrenergics were to be switched to the inhaled corticosteroid monoproduct prior to randomization without a change in corticosteroid dose.
- Patients using fixed dose combination anticholinergic/short-acting beta adrenergic medications were to be switched to Atrovent prior to the baseline period without a change in the anticholinergic dose. Atrovent was to be discontinued during the active treatment period.
- All other investigational drugs and oral beta agonists were not allowed for at least one month prior to the baseline period. Cromolyn sodium and nedocromil sodium were not allowed for at least 3 months prior to the baseline period.

Statistical plan

This study is one of two twin studies with identical protocol (205.254 and 205.255). Each study was analyzed separately. In addition, two of the primary endpoints (Mahler TDI and exacerbations) were analyzed on the combined data set from the two studies. This combined analysis was prespecified in the protocol and statistical analysis plan. Each of the four co-primary efficacy endpoints were tested in order, only testing a dose for that endpoint when the dose had shown significant efficacy compared to placebo for all previous endpoints. All tests were two-tailed at the 5% level of significance.

[Module 5, Volume 1.11, Study report 205.254, pages 80-96]

Sample size

From previous studies, the standard deviation for rough FEV_1 was assumed to be 0.215L. Therefore, a sample of 810 patients (270 per treatment group) was adequate to detect a difference of 0.13L in mean trough FEV_1 response between tiotropium and placebo at the 5% level of significance with at least 99% power using a two-tailed t-test.

The combined analysis of 1620 evaluable patients (Protocols 205.254 and 205.255) had at least 95% power to detect a difference of 0.05 L in mean trough FEV_1 response between the two doses of tiotropium at the 5% level of significance (two-sided).

From previous studies in the EU and US, the standard deviation for the number of exacerbations in one year was assumed to be 2.4, and the expected difference in mean was assumed to be 0.4. The pooled sample of 1620 patients was adequate to detect a significant difference between treatments, with a 5% level of significance (two-sided) and 76% power using the Wilcoxon-Mann-Whitney test. This estimate assumes that all previous steps in the analysis (primary endpoints 1-3) were significant.

Statistical model and analysis

The endpoints of spirometry, SGRQ, TDI, Physician's Global Evaluation, COPD symptom scores, PEFR and rescue medication use were analyzed using fixed effects analysis of covariance (ANCOVA) with terms for smoking status at trial entry (current or ex-smoker), center and treatment group. The baseline value was used as a linear covariate. A separate ANCOVA was performed for each repeated measure.

COPD exacerbations were analyzed using the Kruskal-Wallis and Wilcoxon-Mann-Whitney tests for differences in location. Since the incidence rates depend on the extent of exposure, the numbers of exacerbations were calculated per day of extent of exposure for each patient in each treatment group.

Each of the four co-primary efficacy endpoints were tested in order, only testing a dose for that endpoint when the dose had shown significant efficacy compared to placebo for all previous endpoints. All tests were two-tailed at the 5% level of significance.

Two populations were defined for the study:

- all randomized patients who received at least one dose of trial medication (safety set)
- all randomized patients in the safety population who had baseline data and adequate post-treatment data (full analysis set)

Adequate post-treatment data for each endpoint was considered to be at least one measurement after 5 or more days of therapy.

[Module 5, Volume 1.11, Study report 205.254, pages 80-96]

Missing data

Missing values for spirometry were estimated using other values recorded for the patient on that test day. For patients with missing data on a given test day because rescue medication was taken, the missing data were estimated by the least favorable observation that test day, even if it was a pre-dose value. If no data were available for that test day, missing values were estimated from previous test days. Daily diary card data for PEFR and rescue medication use were excluded during steroid and theophylline bursts for COPD exacerbations. Weekly summary data from the diary card were imputed from neighboring weeks if less than 4 observations were recorded in a week. In patients discontinuing the study early due to worsening COPD, the missing data were imputed by the least favorable data prior to discontinuation. Missing data for patients missing a visit or discontinuing for other reasons were estimated by their last observed data. [Module 5, Volume 1.11, Study report 205.254, page 91]

Data sets

The full analysis set for efficacy consisted of all randomized patients with at least baseline data (pre-treatment at the end of the 2 week run-in) and at least one adequate trough following at least 5 days of randomized treatment. The safety data set consisted of all randomized patients receiving at least one dose of study medication. [Module 5, Volume 1.11, Study report 205.254, page 192]

10.1.4.2 Results

Population characteristics

Disposition of patients

A total of 983 male and female patients with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were randomized; 332 in the tio R5 group, 332 in the tio R10 group, and 319 in the placebo group. Of these, 782 (79.6%) completed the study. The blind was broken for two patients in the trial, one for the serious adverse event of prostate surgery (tio R10) and one for the serious adverse event of pneumonia (tio R5). A summary of patient disposition for the trial is presented in Table 74. [Module 5, Volume 1.11, Study report 205.254, pages 101-102]

Table 74: Protocol 205.254 patient disposition

	Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Enrolled				**1245**
Not entered				262
Entered	332	332	319	983
Not treated	0	0	0	0
Treated	332 (100.0)	332 (100.0)	319 (100.0)	983 (100.0)
Not prematurely discontinued from trial medication	277 (83.4)	277 (83.4)	228 (71.5)	782 (79.6)
Prematurely discontinued from trial medication	55 (16.6)	55 (16.6)	91 (28.5)	201 (20.4)
Adverse events	31 (9.3)	32 (9.6)	48 (15.0)	111 (11.3)
Worsening of disease under study	13 (3.9)	12 (3.6)	33 (10.3)	58 (5.9)
Worsening of other pre-existing disease	2 (0.6)	2 (0.6)	3 (0.9)	7 (0.7)
Other adverse event	16 (4.8)	18 (5.4)	12 (3.8)	46 (4.7)
Administrative	18 (5.4)	16 (4.8)	34 (10.7)	68 (6.9)
Non compliant with protocol	2 (0.6)	2 (0.6)	4 (1.3)	8 (0.8)
Lost to follow-up	4 (1.2)	5 (1.5)	11 (3.4)	20 (2.0)
Consent withdrawn	12 (3.6)	9 (2.7)	19 (6.0)	40 (4.1)
Other	6 (1.8)	7 (2.1)	9 (2.8)	22 (2.2)

Reviewer comment:

A greater percentage of patients discontinued from the placebo group, primarily due to adverse events and worsening of COPD. The adverse event accounting for this difference was COPD exacerbation.

Demographics and disease characteristics

The mean age of the patients was 64.8 years (range 40-90 years); 70% of the trial population was male and 92.3% were white. The mean duration of COPD was 9.2 years. All patients were current (35.5%) or ex-smokers (64.5%), with a mean smoking history of 47.4 pack years. The mean pre-bronchodilator FEV_1 was 1.09L with a mean percent predicted of 38.2%. The mean pre-bronchodilator FEV_1/FVC was 43.2%. The mean post-bronchodilator FEV_1 was 1.27L with a mean percent predicted of 44.6%. The overall demographic profile was generally balanced across the four treatment groups. Pulmonary function data at baseline were generally comparable. Any differences in PFT data were dealt with in the analysis by including baseline as a covariate in the model. Demographic characteristics are provided in Table 75, and baseline PFT variables are provided in Table 75. [Module 5, Volume 1.11, Study report 205.254, pages 104-109]

Table 75: Protocol 205.254 patient demographic and disease characteristics

	Tio R5	Tio R10	Placebo	Total
Number of patients[1]	332	332	319	983
Gender [N (%)]				
Male	243 (73.2)	252 (75.9)	252 (79.0)	747 (76.0)
Female	89 (26.8)	80 (24.1)	67 (21.0)	236 (24.0)
Race [N (%)]				
Missing	22 (6.6)	19 (5.7)	19 (6.0)	60 (6.1)
White	304 (91.6)	311 (93.7)	292 (91.5)	907 (92.3)
Black	5 (1.5)	1 (0.3)	8 (2.5)	14 (1.4)
Asian	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.2)
Age [years][2]				
N	332	332	319	983
Mean	65.0	64.6	64.7	64.8
Median	66.0	65.0	65.0	65.0
SD	8.2	8.4	8.9	8.5
Min	42.0	41.0	40.0	40.0
Max	90.0	88.0	87.0	90.0
Smoking history [N (%)]				
Ex smoker	208 (62.7)	209 (63.0)	217 (68.0)	634 (64.5)
Smoker	124 (37.3)	123 (37.0)	102 (32.0)	349 (35.5)
Smoking history [pack years]				
N	332	332	319	983
Mean	46.8	49.7	45.8	47.4
Median	42.0	43.0	40.0	42.0
SD	28.6	27.8	25.4	27.4
Min	10.0	11.0	11.0	10.0
Max	250.0	165.0	180.0	250.0
Duration of COPD [years][3]				
N	332	332	319	983
Mean	8.6	9.2	9.9	9.2
Median	7.0	7.0	8.0	7.0
SD	6.5	7.8	8.1	7.5
Min	0.0	0.0	0.1	0.0
Max	33.0	48.0	43.0	48.0

1 The percentages may not add up to 100% due to missing data.
2 Calculated from date of birth and date screened
3 Regardless of when COPD diagnosis was made
*Obtained from Visit 1, screening visit

Table 76: Protocol 205.254 screening PFT data

	Tio R5	Tio R10	Placebo	Total
Number of patients	332	332	319	983
Pre-bronchodilator FEV_1 [L]				
Mean	1.067	1.105	1.087	1.086
Min	0.36	0.40	0.16	0.16
Max	2.27	2.25	2.44	2.44
Pre-bronchodilator % predicted normal FEV_1 – ECCS				
Mean	38.3	38.5	37.8	38.2
Min	11.9	12.8	5.5	5.5
Max	61.3	64.1	59.8	64.1
Pre-bronchodilator FVC [L]				
Mean	2.551	2.597	2.575	2.574
Min	0.81	0.47	0.19	0.19
Max	5.51	5.49	5.31	5.51
Pre-bronchodilator FEV_1 / FVC [%]				
Mean	42.9	43.5	43.1	43.2
Min	17.7	19.4	15.8	15.8
Max	82.7	85.1	84.2	85.1
Post-bronchodilator FEV_1 [L]				
Mean	1.243	1.292	1.261	1.266
Min	0.20	0.44	0.24	0.20
Max	2.56	2.51	2.68	2.68
Post-bronchodilator[2] % predicted normal FEV_1 – ECCS				
Mean	44.6	45.1	44.1	44.6
Min	11.5	14.0	8.4	8.4
Max	80.7	80.5	79.2	80.7
Post-bronchodilator[2] FEV_1 [L] change from pre-dose[1]				
Mean	0.174	0.188	0.174	0.179
Min	-0.38	-0.39	-0.69	-0.69
Max	1.19	0.92	1.36	1.36
Post-bronchodilator[2] FEV1 % change from pre-dose[1]				
Mean	18.2	19.1	20.6	19.3
Min	-65.5	-26.2	-42.9	-65.5
Max	228.8	158.6	850.0	850.0
Post-bronchodilator[2] FVC [L]				
Mean	2.898	2.926	2.929	2.917
Min	0.98	0.84	1.06	0.84
Max	5.62	5.84	7.83	7.83

1 Obtained from Visit 1, Screening Visit
2 30 minutes after 400µg of albuterol

Protocol violations

There was no per-protocol analysis for this study; therefore, protocol violations were not used to exclude patients from any analysis. There were a total of 19 patients who were determined retrospectively to have not met entry criteria. These deviations were categorized into 2 types: 1) may not have COPD and 2) unstable at the randomization visit. These patients were distributed evenly across the groups.

In addition to these entry criteria violations, there were 38 patients who took a prohibited medication, 19 who had an incorrect medication washout, and 35 who were incorrectly dosed at the clinic, primarily due to use of the Respimat inhaler for more than 65 days. Finally, there were 6 patients who were categorized as non-compliant with study medication. [Module 5, Volume 1.11, Study report 205.254, page 103]

Reviewer comment:

The reported protocol violations were distributed evenly across the study groups. Overall, these discrepancies do not affect the integrity of the data. There were 12 patients who were listed as "may not have had COPD." Of these, 5 exceeded spirometric criteria and 7 had evidence of asthma or allergic rhinitis. Of the 7 with evidence of asthma or allergic rhinitis, 5 had an eosinophil count ≥ 600/mm^3, but no medical history of asthma or allergic rhinitis.

Treatment compliance

Medication compliance was determined from patient diary data. Overall reported compliance for the study was 96.9% for the tio R5 group, 96.1% for the tio R10 group, and 95.5% for the placebo group. [Module 5, Volume 1.11, Study report 205.254, page 109]

Concomitant respiratory medications

A total of 85.9% of patients in the study took baseline concomitant respiratory medications. At baseline, 47.6% of patients were taking inhaled short-acting anticholinergics, 28.2% were taking inhaled long-acting ß-agonists, 53.0% were taking short-acting ß-agonists, and 18.6% were taking theophylline preparations. In addition, 52.0% of patients overall were taking inhaled steroids, and 2.7% were taking oral corticosteroids. These baseline respiratory medications were generally balanced among groups. [Module 5, Volume 1.11, Study report 205.254, pages 109]

Pharmacokinetic outcomes

No pharmacokinetic data were collected in this study.

Efficacy outcomes

Efficacy analyses were performed on the full analysis set (FAS), which consisted of all randomized patients with at least baseline data (pre-treatment at the end of the 2-week run-in) and at least one adequate endpoint measurement of the variable under evaluation. For trough FEV_1, this was defined as at least one spirometric value following at least 5 days of randomized treatment. For calculation of the fourth primary endpoint of COPD exacerbation rate, the ITT population was utilized. There was no per-protocol analysis for this study; therefore, protocol violations were not used to exclude patients from the analysis.

Of the 983 patients randomized, 41 (4.2%) patients were excluded from the first primary efficacy analysis of FEV_1 trough because of inadequate data following multiple administrations. This included 6 (1.8%) patients in the tio R5 group, 12 (3.6%) in the tio R10 group, and 23 (7.2%) in the placebo group.

Primary

Trough FEV_1 at 48 weeks

For the first co-primary endpoint, trough FEV_1 at the end of 48 weeks of treatment, both tiotropium groups were superior to placebo. At the end of 48 weeks of treatment, the adjusted mean FEV_1 trough value was 1.173L for the tio R5 group and 1.193L for the tio R10 group as compared to 1.031L in the placebo group. This difference was statistically significant at $p<0.0001$. Means were adjusted for center, smoking status at entry and baseline value. The mean treatment differences and 95% confidence intervals for the primary endpoint, shaded in grey, are presented in Table 77. Mean treatment differences in trough response for other time points are also presented unshaded in Table 77. [Module 5, Volume 1.11, Study report 205.254, pages 114-118]

Table 77: Protocol 205.254 FEV_1 trough response [L] treatment difference

Treatment comparison	Test day	Treatment difference Mean	SE	95% C.I.	p-value*
Tio R5 – Placebo	15	0.105	0.017	(0.073, 0.137)	<.0001
	57	0.127	0.018	(0.092, 0.162)	<.0001
	113	0.143	0.020	(0.104, 0.181)	<.0001
	169	0.135	0.019	(0.099, 0.171)	<.0001
	225	0.148	0.019	(0.110, 0.186)	<.0001
	281	0.138	0.019	(0.101, 0.176)	<.0001
	337	**0.142**	**0.019**	**(0.104, 0.181)**	**<.0001**
Tio R10 – Placebo	15	0.121	0.017	(0.088, 0.153)	<.0001
	57	0.154	0.018	(0.119, 0.189)	<.0001
	113	0.147	0.020	(0.108, 0.186)	<.0001
	169	0.131	0.019	(0.094, 0.167)	<.0001
	225	0.157	0.019	(0.119, 0.195)	<.0001
	281	0.164	0.019	(0.127, 0.202)	<.0001
	337	**0.161**	**0.020**	**(0.123, 0.200)**	**<.0001**

Tio R 5: N = 326, Tio R 10: N = 320, Placebo: N = 296

* Based on a two sided test

All values in this table are based on an ANCOVA analysis with terms for treatment, smoking status at entry, center, and baseline value. A separate ANCOVA is fitted at each time point.

Reviewer comment:

The mean trough FEV_1 response for the tio R5 group was 0.142L after 48 weeks of treatment. This difference is greater than the FEV_1 response at the end of 13 weeks of treatment for Spiriva HandiHaler (18 mcg) found in pivotal trials (0.110 and 0.130L) and also greater than the difference observed in the 12 week Respimat studies (Protocol 205.251 and 205.252). However, comparing with the results at Day 57 (8 weeks of therapy) shows comparable results.

SGRQ

The second co-primary endpoint was SGRQ total score at 48 weeks. The overall baseline score was 44.9, ranging from 44.1 to 45.4. All three treatment groups achieved a reduction in mean SGRQ total score at Test Day 57, which was maintained throughout the treatment period. Both

tiotropium groups showed a statistical difference from placebo, with a reduction compared to placebo of -3.3 points (p=0.0011) and -4.2 points (p<0.0001) for the tio R5 and tio R10 groups, respectively. See Table 78 for the SGRQ total score treatment differences. [Module 5, Volume 1.11, Study report 205.254, pages 118-120]

Table 78: Protocol 205.254 SGRQ total score treatment differences

Treatment Comparison	Test Day	Treatment difference Mean	(SE)	95% C.I.	p-value*
Tio R5 - Placebo	57	-2.6	0.8	(-4.3, -1.0)	0.0016
	113	-3.5	0.9	(-5.3, -1.7)	0.0001
	225	-3.5	1.0	(-5.4, -1.6)	0.0003
	337	**-3.3**	**1.0**	**(-5.2, -1.3)**	**0.0011**
Tio R10 - Placebo	57	-3.0	0.8	(-4.7, -1.4)	0.0003
	113	-2.7	0.9	(-4.5, -0.9)	0.0033
	225	-3.5	1.0	(-5.4, -1.6)	0.0003
	337	**-4.2**	**1.0**	**(-6.2, -2.3)**	**<.0001**

Tio R5: N = 318, Tio R10: N = 315, Placebo: N = 275

* Based on a two sided test

All values in this table are based on an ANCOVA analysis with terms for treatment, smoking status at entry, centre and baseline value.

A separate ANCOVA is fitted at each time point.

Reviewer comment:

A clinically meaningful difference in SGRQ total score is reported to be 4 points. This is the difference used in the responders analysis (see secondary endpoints). While the differences between the tiotropium groups and placebo reach a high level of statistical significance, differences of less than 4 may not be clinically meaningful. However, the result is supportive of the improvement observed in FEV_1.

The Applicant is not making labeling claims regarding SGRQ.

Mahler Transition Dyspnea Index (TDI) Focal Score

It was prespecified that the third co-primary endpoint, Mahler TDI, would be analyzed based on combined data from this study (205.254) and study 205.255. However, the sponsor also analyzed the studies separately for this endpoint.

All three treatment groups showed an improvement from baseline in the adjusted mean TDI focal score at Test Day 57, with the increase for the tiotropium groups being approximately double

that of the placebo group. In general, this improvement was maintained for the remainder of the treatment period. The differences between the tio R5 group and placebo (1.1) and the tio R10 group and placebo (1.3) were both statistically significant (p<0.0001). [Module 5, Volume 1.11, Study 205.254, pages 120-123]

Reviewer comment:

Due to fundamental weaknesses of the TDI instrument, this result cannot be utilized to support a dyspnea indication. The company has defined a responder for this endpoint to be a difference of 1 from baseline. The mean difference from placebo ranges from 0.8 to 1.3, suggesting that the clinical meaning of the difference in TDI scores is unknown.

The Applicant is not making labeling claims regarding dyspnea.

COPD Exacerbations

The fourth co-primary efficacy endpoint was the number of COPD exacerbations during the 48 week treatment period. It was prespecified that this co-primary endpoint would be analyzed based on combined data from this study (205.254) and study 205.255. [Module 5, Volume 1.1, Study 205.254, page 124]

Reviewer comment:

At the request of FDA, the Applicant also provided an analysis of COPD exacerbations found in the individual studies, previously provided only as part of the statistical documentation. These results show a mean exacerbation rate per patient year of 0.72 for tio R5 compared to 0.91 for placebo, with a 95% CI of 0.63-0.99 (p=0.45). The time to first exacerbation for patients in the tio R5 group was 173 days compared to 112 days for placebo (p=0.09). See Table 79. Evaluation of parameters per number of days on therapy was used to correct for the greater number of discontinuations and shorter treatment duration observed in the placebo group. According to the statistical reviewer, Ruthanna Davi, this is a reasonable correction.

Table 79: Protocol 205.254 COPD exacerbation rates and time to first exacerbation (Poisson regression)

	Tio R5	Placebo
Number of patients		
exposed to randomized treatment	332	319
at least one COPD exacerbation	127	131
% of patients with exacerbations	38%	41%
Mean treatment exposure (days)	307	272
Exacerbation rate per patient year		
Mean	0.72	0.91
Rate ratio (RR) versus placebo	0.79	
95% CI for RR	0.63-0.99	
p-value for RR	0.045	
Time to first exacerbation (days)		
Lower quartile	173	112
p-value versus placebo	0.09	

The analysis provided by the Applicant in response to the FDA request was performed using a Poisson regression model with correction for overdispersion (increased variance in data compared to the mean). While this is a valid method according to the statistical reviewer, it was not prespecified in the protocol. Evaluating the data using the protocol specified Wilcoxin-Mann-Whitney test, which is what was used for the combined analysis, gives a mean COPD exacerbation rate of 0.77 in the tio R5 group, 0.83 in the tio R10 group, and 1.88 in the placebo group. Based on this result, neither tiotropium group had a statistically significant difference from placebo (0.18 and 0.07 for tioR 5 and tio R10, respectively).

Although a statistically significant result was obtained for the primary endpoint using the Poisson regression analysis, evaluating the data with a different statistical test suggests that the results are not robust.

Secondary endpoints

FEV_1 trough, $AUC_{(0-3h)}$, and peak $_{(0-3h)}$ response

The pairwise differences for FEV_1 between both the active groups and placebo were statistically significant ($p<0.0001$) at all time points post-dose on all test days. While the tio R10 group generally showed some increase over the tio R5 group at most time points, the differences were small and not statistically significant. The trough response compared to placebo was maintained at similar levels at all time points measured. However, trough FEV_1 in all groups declined slightly over the 48 week study, although the decline was greatest in the placebo group. See Table 77 for FEV_1 trough response at all time points and Table 80 for FEV_1 trough, AUC, and peak FEV_1. [Module 5, Volume 1.11, Study report 205.254, pages 114-118]

Table 80: Protocol 205.254 adjusted mean FEV_1 trough, AUC (0-3h), and peak (0-3h) response [L] on each test day

Response	Test day	Tio R5 (N = 326) Mean (SE)		Tio R10 (N = 320) Mean (SE)		Placebo (N = 296) Mean (SE)	
Trough	15	0.118	(0.011)	0.133	(0.011)	0.013	(0.012)
	57	0.124	(0.012)	0.150	(0.012)	-0.004	(0.013)
	113	0.121	(0.013)	0.125	(0.014)	-0.022	(0.014)
	169	0.125	(0.013)	0.121	(0.013)	-0.009	(0.013)
	225	0.124	(0.013)	0.132	(0.013)	-0.025	(0.014)
	281	0.107	(0.013)	0.133	(0.013)	-0.031	(0.014)
	337	0.097	(0.013)	0.116	(0.014)	-0.046	(0.014)
AUC (0-3h)	1	0.194	(0.008)	0.220	(0.008)	0.045	(0.008)
	15	0.256	(0.012)	0.258	(0.012)	0.045	(0.013)
	57	0.246	(0.013)	0.274	(0.013)	0.041	(0.014)
	113	0.241	(0.014)	0.248	(0.014)	0.024	(0.015)
	169	0.242	(0.014)	0.241	(0.014)	0.026	(0.014)
	225	0.239	(0.014)	0.240	(0.014)	0.019	(0.015)
	281	0.225	(0.014)	0.233	(0.014)	0.003	(0.015)
	337	0.212	(0.014)	0.226	(0.014)	-0.008	(0.015)
Peak (0-3h)	1	0.289	(0.011)	0.317	(0.011)	0.126	(0.011)
	15	0.342	(0.013)	0.347	(0.013)	0.129	(0.014)
	57	0.331	(0.014)	0.360	(0.014)	0.118	(0.015)
	113	0.322	(0.015)	0.327	(0.015)	0.094	(0.016)
	169	0.326	(0.015)	0.318	(0.015)	0.098	(0.015)
	225	0.318	(0.015)	0.315	(0.015)	0.090	(0.016)
	281	0.301	(0.015)	0.309	(0.015)	0.079	(0.016)
	337	0.288	(0.015)	0.305	(0.015)	0.064	(0.016)

The common baseline mean obtained at the -10 minute time point of Test Day 1 was 1.077L.
The means are adjusted for center, smoking status at entry and baseline value.
A separate ANCOVA was fitted at each time point.

The mean FEV_1 AUC $_{(0\text{-}3h)}$ response for the tiotropium groups ranged from 0.194 to 0.272L above the baseline value and was generally consistent throughout the treatment period. The response for the placebo group was approximately 0.200L less than that seen for the active treatment groups. The differences between the tiotropium groups and placebo were highly statistically significant ($p<0.0001$).

The mean FEV_1 peak $_{(0\text{-}3h)}$ response for the tiotropium groups ranged from 0.288 to 0.360L above the baseline value and was generally consistent throughout the treatment period. The response for the placebo group was approximately 0.200L less than that seen for the active treatment groups. The differences between the tiotropium groups and placebo were highly statistically significant ($p<0.0001$).

The effects of tiotropium on FEV_1 appeared to reach steady state after 15 days of dosing.

Reviewer comment:

The AUC and peak are not completely comparable to those obtained in the 12 week studies. For Protocols 205.251 and 205.252, AUC and peak FEV_1 were measured over 6 hours rather than 3 hours as in the 48 week studies (Protocols 205.254 and 205.255). Regardless, the FEV_1 AUC and peak FEV_1 are supportive of the efficacy of tiotropium.

FVC

The FVC results generally paralleled the FEV_1 results. By the end of the treatment period, the adjusted mean FVC trough value was 2.667L for the tio R5 group and 2.822L for the tio R10 group. This compared to an adjusted mean FVC trough of 2.499L in the placebo group. The mean FVC value increased to 2.903 and 3.018L three hours after treatment for the tio R5 and tio R10 groups, respectively.

The difference in FVC between the tiotropium groups and placebo were statistically significant ($p<0.01$) at all time points post-dose on all test days. In general, the tio R10 group showed some improvement over the tio R5 group, but the differences were small and not significant.

The mean FVC $AUC_{(0\text{-}3h)}$ response for the tio R5 group ranged from 0.312 to 0.421L above the baseline value compared to 0.422 to 0.538L for the tio R10 group. The response for the placebo group was 0.2-0.4L less than that seen for the active treatment groups. The differences between the tiotropium groups and placebo were highly statistically significant ($p<0.0001$).

The mean FVC $peak_{(0\text{-}3h)}$ response for the tio R5 group ranged from 0.480-0.608L above the baseline value compared to 0.610 to 0.729L for the tio R10 group. The response for the placebo group was 0.2-0.4L less than that seen for the active treatment groups. The differences between the tiotropium groups and placebo were highly statistically significant ($p<0.0001$).

[Module 5, Volume 1.11, Study report 205.254, pages 127-130]

SGRQ component scores

The SGRQ was analyzed for the following component scores: symptoms, activities, and impacts. The difference between the tiotropium groups and placebo were statistically significant compared to placebo for the symptoms and impacts components. The difference from placebo for the activities component was statistically significant for the tio R10 group ($p=0.0047$), but not for the tio R5 group ($p=0.0569$).

Using a difference in total SGRQ score from baseline of 4 points or greater to define responders, 52.2% of patients in the tio R5 group, 53.3% in the tio R10 group, and 40.4% in the placebo group responded to therapy at Test Day 336. Differences in response rate between the tiotropium groups and placebo were statistically significant on all test days ($p<0.05$).

Mahler TDI component scores

The Mahler TDI was analyzed for the following component scores: functional impairment, magnitude of task, and magnitude of effort. The difference between the tiotropium groups and placebo were statistically significant ($p<0.0001$) for all three components.

Using a difference in total score from baseline of 1 point or greater to define responders, 54.4% of patients in the tio R5 group, 54.0% of patients in the tio R10 group, and 40.3% in the placebo group responded. Differences in response rate between the tiotropium groups and placebo were statistically significant on all test days ($p<0.0005$).

PEFR

Baseline mean pre-dose morning peak expiratory flow rate (PEFR) for all treatment groups was 240.9 L/min. Mean differences compared to placebo in pre-dose morning PEFR for tio R5 and tio R10 compared to placebo were 16.0-24.5 L/min and 22.5-34.5 L/min respectively. These differences were significant for all 48 weeks during the trial ($p<0.001$). Mean differences compared to placebo in mean evening PEFR were also highly significant for all weeks ($p<0.0001$). [Module 5, Volume 1.11, Study report 205.254, pages 133-135]

Rescue albuterol use

For all treatment groups combined, albuterol was used an average of 2.5 occasions/day at baseline. Compared to placebo, the tiotropium groups showed a significant decrease in the use of albuterol rescue throughout the study, ranging from 0.6-1.0 fewer rescue uses per day. [Module 5, Volume 1.11, Study report 205.254, pages 135-136]

Reviewer comment:

The Applicant seeks a labeling statement regarding reduction of rescue medication use. Since a significant difference in rescue medication use was observed both in this trial and Protocol 205.255, the statement is supported.

COPD symptoms

Physician-reported COPD symptoms of wheezing, shortness of breath, coughing and tightness of chest were recorded after each week of therapy using a 4 point scale (0=none to 3=severe). Overall, the differences between treatment groups were small and not statistically significant for the coughing and chest tightness scores, but were significant at $p<0.05$ for the wheezing and shortness of breath scores. [Module 5, Volume 1.11, Study report 205.254, pages 136-137]

Physician's Global Evaluation

The Physician's Global Evaluation was reported on an 8 point scale, ranging from 1-2=poor to 7-8=excellent. In general, the PGE scores increased gradually throughout the study (indicated an improvement in the patient's condition) for the tiotropium groups and stayed the same for the placebo group. The difference between the tiotropium groups and placebo were statistically significant on all test days. [Module 5, Volume 1.9, Study report 205.254, page 137-138]

Patient's Global Rating

Patients were asked to rate their health at each visit compared to the day before they commenced study treatment. Ratings were reported on a 7 point scale: much better, somewhat better, a little better, about the same, a little worse, somewhat worse, and much worse. Much better was given a score of 1, while much worse was given a score of 7. The tiotropium groups showed significant

improvement over placebo for all test days ($p<0.001$ for tio R5 and $p<0.0001$ for tio R10). [Module 5, Volume 1.9, Study report 205.254, pages 70 and 138]

Efficacy conclusions

Both tiotropium groups met 3 primary endpoints for the study, increase in trough FEV_1 response, improvement in SGRQ score, improvement in Mahler TDI at the end of 48 weeks of treatment. Reduction in COPD exacerbations compared to placebo showed improvement that did not meet statistical significance. The tio R10 group was not significantly better than the tio R5 group in terms of efficacy. The effects of tiotropium on FEV_1 appeared to reach steady state after 15 days of dosing. In addition, both tiotropium groups showed significant improvement over placebo for the majority of secondary endpoints, particularly PFT variables. A summary of non-spirometric endpoints reaching and not reaching a statistically significant difference in the tiotropium groups compared to placebo is provided in Table 81. For many of these endpoints, the clinical significance of the effect size is unclear, but they are generally supportive of efficacy.

Table 81: Protocol 205.254 efficacy summary of non-spirometric secondary endpoints

Statistically significant difference	No statistically significant difference
SGRQ component scores (tio R10)	SGRQ component scores (tio R5)
SGRQ response rate	COPD symptoms (cough and chest tightness)
TDI component scores	
TDI response rate	
COPD symptom scores (wheeze and shortness of breath)	
Morning PEFR (all weeks)	
Evening PEFR (all weeks)	
Rescue albuterol use	
Physician's Global Evaluation	
Patient's Global Evaluation	

Safety outcomes

Safety outcomes for Study 205.254 included adverse events, laboratory findings (hematology, blood chemistry, and urinalysis at screening and at the end of treatment), ECGs (performed and interpreted by the investigator at screening and at the end of treatment), vital signs (pulse rate and blood pressure measured at the same time intervals as PFTs for the first 3 hours post-dose), and physical examinations (screening and at the end of treatment). In addition ECGs and Holter monitors read centrally were obtained on a subset of patients. All patients who were randomized and received at least one dose of trial medication were included in the safety analysis.

Extent of exposure

A total of 983 COPD patients were randomized and received at least one dose of study medication. The planned exposure for each patient was 48 weeks (337 days). Overall, the mean exposure was 295.1 days. Patients randomized to the tio R5 group had the longest mean duration of exposure of 307.3 days. The tio R10 group was exposed for 304.9 days, and the placebo group for 272.3 days, consistent with a larger number of discontinuations in the placebo group. See Table 82. [Module 5, Volume 1.11, Study report 205.254, pages142-143]

Table 82: Protocol 205.254 summary of treatment exposure

	Tio R5	Tio R10	Placebo	Total
Total Treated N	**332**	**332**	**319**	**983**
Maximum Exposure n (%)				
1 day	2 (0.6%)	0 (0.0%)	3 (0.9%)	5 (0.5%)
2 – 7 days	0 (0.0%)	1 (0.3%)	5 (1.6%)	6 (0.6%)
8 – 60 days	13 (3.9%)	18 (5.4%)	41 (12.9%)	72 (7.3%)
61 – 100 days	8 (2.4%)	7 (2.1%)	4 (1.3%)	19 (1.9%)
101 – 200 days	13 (3.9%)	17 (5.1%)	19 (6.0%)	49 (5.0%)
201 – 330 days	37 (11.1%)	36 (10.8%)	35 (11.0%)	108 (11.0%)
>330 days	259 (78.0%)	253 (76.2%)	212 (66.5%)	724 (73.7%)
Treatment Exposure (days)				
N	332	332	319	983
Mean	307.3	304.9	272.3	295.1
SD	84.3	88.5	120.5	99.9
Median	337.0	337.0	337.0	337.0
Min	1	6	1	1
Max	390	450	409	450

Adverse events

Deaths

There were 20 deaths in the study, 7 in the tio R5 group, 8 in the tio R10 group, and 5 in the placebo group. The primary cause of death is reported in Table 83. Of these deaths, 2 were reported as due to events in the cardiac system, 4 were due to events in the respiratory system, 2 were cerebrovascular accidents, 5 were neoplasms, and 1 was due to gastrointestinal

hemorrhage. Seven patients, 5 in the tio R10 group and 2 in the placebo group, died of unreported causes. All of these patients died at home. Five of the 7 were at sites in Moscow, Russia. [Module 5, Volume 1.1, Study report 205.254, pages 151-158]

Reviewer comment:
There is a small imbalance in deaths in this study in favor of the placebo group. Of concern are the deaths with unreported causes. The sponsor states this imbalance is due to the higher percentage of discontinuations in the placebo group (mean total exposure approximately 34 days lower in the placebo group compared to tiotropium groups). Additional follow up on these discontinued patients is reviewed in Study 205.392. Review of the narratives and cause of death does not suggest a particular safety signal as many deaths were of unknown cause.

Table 83: Protocol 205.254 fatal events by treatment group and primary cause of death

Primary events leading to death†	Tio R5 [n=332]	Tio R10 [n=332]	Placebo [n=319]
Total deaths	7	8	5
Cardiac failure	1	0	0
Coronary artery insufficiency	0	1	0
Gastrointestinal hemorrhage	0	0	1
Death	0	5	2
Neoplasms	2	1	1
Cerebrovascular accident	0	1	1
Acute pulmonary edema	1	0	0
COPD exacerbated	1	0	0
Pneumonia	1	0	0
Respiratory failure	1	0	0

†event grouping by reviewer

Serious adverse events

Serious AEs occurred in 15.5% of the overall study population, including 13.6% of the tio R5 group, 16.0% tio R10, and 16.9% placebo with a total of 152 patients with a SAE. The most common serious adverse event was COPD exacerbation, occurring in 3.9% of the tio R5 group, 3.3% of the tio R10 group, and 5.3% of the placebo group. Serious cardiac events occurred in 1.8% of patients overall, including 2.1% of the tio R5 group, 1.5% of the tio R10 group, and

1.9% of the placebo group. There were 11 ischemic cardiac events, including AE terms of angina, coronary artery disease, coronary artery insufficiency, and myocardial infarction. Of these ischemic cardiac events, 4 occurred in the tio R5 group, 3 in the tio R10 group, and 5 in the placebo group. There were 6 stroke events, 5 of which were SAEs, including AE terms of cerebral infarction, cerebrovascular accident, ischemic stroke, and transient ischemic attack. Of the serious stroke events, none occurred in the tio R5 group, 3 in the tio R10 group, and 2 in the placebo group.

Adverse events leading to discontinuation

There were a greater number of discontinuations due to adverse events in the placebo group (14.7% placebo, 9.3% tio R5, and 9.6% tio R10). This was due to a greater number of discontinuations due to COPD exacerbations in the placebo group (2.1% tio R5, 2.7% tio R10, and 7.5% placebo). Two patients in each tiotropium group discontinued due to dry mouth.

Overall adverse events

Adverse events (AEs) were reported in 74.2% of the patients: 72.3% in tio R5, 76.2% in tio R10, and 74.0% in placebo. Dry mouth and urinary tract infection occurred with increased frequency in the tiotropium groups in a dose related fashion, consistent with the known anticholinergic mechanism of action of the drug. There were also three patients with urinary retention and one with urinary tract obstruction in the tio R10 group, but none in the tio R5 or placebo groups.The incidence of pneumonia was also increased in the tiotropium groups, although the dose-relationship is less clear. Adverse events occurring in ≥3% of patients in any treatment group are presented in Table 84.

Table 84: Protocol 205.254 adverse events occurring in ≥3% of patients by treatment group

MedDRA System Organ Class MedDRA Preferred Term	Treatment			
	Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Total treated N (%)	332 (100.0)	332 (100.0)	319 (100.0)	983 (100.0)
Total with adverse events	240 (72.3)	253 (76.2)	236 (74.0)	729 (74.2)
Gastrointestinal disorders	60 (18.1)	88 (26.5)	40 (12.5)	188 (19.1)
Abdominal pain#	11 (3.3)	5 (1.5)	6 (1.9)	22 (2.2)
Dyspepsia	3 (0.9)	10 (3.0)	2 (0.6)	15 (1.5)
Mouth dry#	18 (5.4)	49 (14.8)	4 (1.3)	71 (7.2)
Infections and infestations	31 (9.3)	46 (13.9)	39 (12.2)	116 (11.8)
Urinary tract infections#	4 (1.2)	13 (3.9)	2 (0.6)	19 (1.9)
Musculoskeletal and connective tissues disorders	46 (13.9)	42 (12.7)	41 (12.9)	129 (13.1)
Arthralgia	10 (3.0)	7 (2.1)	7 (2.2)	24 (2.4)
Back pain	18 (5.4)	14 (4.2)	15 (4.7)	47 (4.8)
Nervous system disorders	34 (10.2)	29 (8.7)	30 (9.4)	93 (9.5)
Headache	12 (3.6)	14 (4.2)	9 (2.8)	35 (3.6)
Respiratory system disorders* (Lower)	150 (45.2)	141 (42.5)	164 (51.4)	455 (46.3)
Bronchitis#	13 (3.9)	11 (3.3)	11 (3.4)	35 (3.6)
COPD exacerbation#	105 (31.6)	101 (30.4)	126 (39.5)	332 (33.8)
Cough	14 (4.2)	16 (4.8)	16 (5.0)	46 (4.7)
Dyspnea#	23 (6.9)	14 (4.2)	23 (7.2)	60 (6.1)
Lower respiratory tract infection	15 (4.5)	16 (4.8)	13 (4.1)	44 (4.5)
Pneumonia#	10 (3.0)	11 (3.3)	4 (1.3)	25 (2.5)
Respiratory system disorders* (Upper)	97 (29.2)	92 (27.7)	80 (25.1)	269 (27.4)
Influenza	13 (3.9)	8 (2.4)	13 (4.1)	34 (3.5)
Nasopharyngitis	41 (12.3)	31 (9.3)	30 (9.4)	102 (10.4)
Pharyngolaryngeal pain	11 (3.3)	10 (3.0)	4 (1.3)	25 (2.5)
Upper respiratory tract infection#	26 (7.8)	22 (6.6)	24 (7.5)	72 (7.3)
Vascular disorders	15 (4.5)	16 (4.8)	12 (3.8)	43 (4.4)
Hypertension	13 (3.9)	12 (3.6)	6 (1.9)	31 (3.2)

Percentages are calculated using total number of patients per treatment as the denominator

BI collapsed preferred terms include multiple MedDRA preferred terms

* All system organ classes are defined by MedDRA with the exception of respiratory, thoracic and mediastinal disorders which have been divided into three separate classes of respiratory system disorders lower, upper, and other.

MedDRA version 8.0 was used for reporting.

A specific analysis looking for paradoxical bronchospasm in response to tiotropium was conducted. The term 'aggravated bronchospasm' was used to describe a spontaneously reported AE of "aggravated' or 'paradoxical bronchospasm' which occurred within 30 minutes of study medication inhalation. The term 'administration related bronchoconstriction' was used to describe occurrence of at least 2 of the following 3 events: 1) use of rescue medication, 2) any potentially bronchospastic AE (cough, wheeze, dyspnea, etc.) and 3) ≥15% fall in FEV_1 below test-day pre-dose FEV_1. To fulfill the definition, each event must have occurred within 30 minutes of study medication inhalation. No patients fulfilled the definition of 'aggravated bronchospasm.' One patient in the tio R10 group had 'administration related bronchoconstriction.' The incidence of asymptomatic falls in FEV_1 of 15% or more ranged from 8.1% in the tio R5 group to 15.4% in the placebo group. [Module 5, Volume 1.11, Study report 205.254, pages 149-151]

Laboratory findings

The Applicant presented the laboratory data as mean change from baseline, clinically significant changes and shift tables. These data were reviewed. Overall, the changes in laboratory values throughout the study were small. There were no clinically important differences between the treatment groups.

ECG findings

There were a total of 12 patients with new or worsened ECG findings at the completion of therapy. These included 5 patients in the tio R5 group, 2 in the tio R10 group, and 5 in the placebo group. Additional ECGs were performed at Visit 2 and at Visit 5 and 8 in a subset of 300 patients from this trial and trial 205.255. 24-hour Holter monitoring was also performed on this subset of patients. Results of these additional ECGs and Holter studies are reviewed under the combined data from studies 205.254 and 205.255. [Module 5, Volume 1.11, Study report 205.254, pages 158-161]

Physical examination

Overall changes in blood pressure and pulse rate were small without a clinically important difference between treatment groups. Eighteen patients in the tio R5 group, 22 in tio R10, and 20 in placebo had new or worsened findings on physical examination during the study. These changes were all recorded as adverse events.

Safety conclusions

There is a small imbalance in deaths in this study in favor of the placebo group. Of concern are the deaths with unreported causes; however, attributing all deaths of unknown etiology to ischemic cardiac events does not result in an overall cardiac signal for tiotropium. There were a greater number of discontinuations in the placebo group, which may have contributed to this imbalance (83% of patients completed in the tiotropium groups compared to 72% in the placebo group). Additional follow up on these discontinued patients is reviewed in Study 205.392. There was also a dose-related effect observed for tiotropium in the anticholinergic side-effects of dry mouth and urinary tract infection. Other common adverse events noted are consistent with what is expected in a study in COPD patients. No evidence of paradoxical bronchospasm was observed. The laboratory and physical examination data did not suggest a safety signal.

10.1.4.3 Summary and conclusions

Both tiotropium groups met all 4 primary endpoints for the study, increase in trough FEV_1, improvement in SGRQ score, improvement in Mahler TDI, and reduction in COPD exacerbations compared to placebo at the end of 48 weeks of treatment. The tio R10 group was not significantly better than the tio R5 group in terms of efficacy. The effects of tiotropium on FEV_1 appeared to reach steady state after 15 days of dosing. In addition, both tiotropium groups showed significant improvement over placebo for the majority of secondary endpoints, particularly PFT variables. A summary of non-spirometric endpoints reaching and not reaching a statistically significant difference in the tiotropium groups compared to placebo is provided in Table 81. For many of these endpoints, the clinical significance of the effect size is unclear.

There is a small imbalance in deaths in this study in favor of the placebo group. Of concern are the deaths with unreported causes; however, attributing all deaths of unknown etiology to ischemic cardiac events does not result in an overall cardiac signal for tiotropium. There were a greater number of discontinuations in the placebo group, which may have contributed to this imbalance (83% of patients completed in the tiotropium groups compared to 72% in the placebo group). Additional follow up on these discontinued patients is reviewed in Study 205.392. There was also a dose-related effect observed for tiotropium in the anticholinergic side-effects of dry mouth and urinary tract infection. Other common adverse events noted are consistent with what is expected in a study in COPD patients. No evidence of paradoxical bronchospasm was observed. The laboratory and physical examination data did not suggest a safety signal.

10.1.5 Study 205.255

10.1.5.1 Protocol

Study title

A randomized, double-blind, placebo-controlled, parallel group efficacy and safety comparison of one-year treatment of two doses (5 mcg [2 actuations of 2.5 mcg] and 10 mcg [2 actuations of 5 mcg]) of tiotropium inhalation solution delivered by the Respimat inhaler in patients with chronic obstructive pulmonary disease (COPD) [Module 5, Volume 14, Study report 205.255, page 3]

Design

The design of this study was identical to Protocol 205.254. See Section 10.1.4.1.

Duration

The duration of active treatment was 48 weeks. Prior to randomized treatment, patients participated in a 2 week run-in period. There was also a 3-week follow up period after completion of randomized treatment. The study was performed during the period of March 11, 2003 to June 7, 2005. The final study report is dated December 12, 2005. [Module 5, Volume 14, Study report 205.254, page 1]

Investigators and centers

The study was conducted at 79 centers from 15 different countries. Countries were included from Europe, North America, Africa, and Australia. [Module 5, Volume 14, Study report 205.255, page 27]

Materials

The study treatments were:

- tio R5: tiotropium Respimat 5 mcg (2 inhalations of 2.5 mcg) once daily in the morning
- tio R10: tiotropium Respimat 10 mcg (2 inhalations of 5 mcg) once daily in the morning
- placebo: identical to Respimat inhalation solution (2 inhalations) once daily in the morning

The tiotropium bromide inhalation solution, placebo inhalation solution, and Respimat inhalers were manufactured at Boehringer Ingelheim Pharma KG (Ingelheim, Germany). Open label commercial albuterol inhalation aerosol (HFA MDI, 100 mcg per actuation) was also provided to each site for reversibility testing and dispensing to the patients for rescue use throughout the study. Batch numbers and expiration dates of investigational product are provided in Table 85. This study utilized the A4 Respimat device. The proposed device for marketing is the A5 Respimat device, which differs from the A4 by the inclusion of a locking mechanism to lock the Respimat A5 after 30 doses (60 actuations). [Module 5, Volume 14, Study Report 205.255, pages 53-55]

Table 85: Protocol 205.255 identity of investigational product

Investigational Product	Expiration Date	Ingelheim Batch No.
Tiotropium Bromide Inhalation Solution, 2.5 µg Tiotropium PA	08/2005	202820
Respimat Inhaler (A4)		WE01070199
Tiotropium Bromide Inhalation Solution, 5 µg Tiotropium PA	08/2005	202821
Respimat Inhaler (A4)		WE01070181
Placebo Inhalation Solution (for Tiotropium Bromide)	08/2005	202942
Respimat Inhaler (A4)		WE02050101

Reviewer comment:

Typically we recommend that the Applicant conduct pivotal studies with the to be marketed product. The addition of a locking mechanism to the A5 model is unlikely to have a significant

impact on the device performance. The CMC reviewer, Alan Schroeder, indicates that the in vitro data shows that the two models perform similarly. Thus, the data from clinical trials utilizing the A4 Respimat model can be relied upon to support the safety and efficacy of tiotropium Respimat.

10.1.5.2 Results

Population characteristics

Disposition of patients

A total of 1007 male and female patients with stable moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were randomized; 338 in the tio R5 group, 335 in the tio R10 group, and 334 in the placebo group. Of these, 752 (74.7%) completed the study. More patients in the placebo group discontinued than in the tiotropium groups, primarily due to worsening COPD. The blind was broken for 2 patients. Both patients were unblinded in response to SAEs, one in the placebo group due to atrial fibrillation and one in the tio R5 group due to fatal GI hemorrhage. A summary of patient disposition for the trial is presented in Table 86. [Module 5, Volume 1.14, Study report 205.255, pages 96-97]

Table 86: Protocol 205.255 patient disposition

	Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Enrolled Not entered				**1299** 292
Entered Not treated Treated	338 0 338 (100.0)	335 0 335 (100.0)	334 0 334 (100.0)	1007 0 1007 (100.0)
Not prematurely discontinued from trial medication	278 (82.2)	254 (75.8)	220 (65.9)	752 (74.7)
Prematurely discontinued from trial medication Adverse events Worsening of disease under study Worsening of other pre-existing disease Other adverse event Administrative Non compliant with protocol Lost to follow-up Consent withdrawn Other	60 (17.8) 36 (10.7) 18 (5.3) 1 (0.3) 17 (5.0) 6 (1.8) 5 (1.5) 7 (2.1) 6 (1.8)	81 (24.2) 47 (14.0) 22 (6.6) 2 (0.6) 23 (6.9) 11 (3.3) 6 (1.8) 14 (4.2) 3 (0.9)	114 (34.1) 74 (22.2) 59 (17.7) 3 (0.9) 12 (3.6) 11 (3.3) 4 (1.2) 19 (5.7) 6 (1.8)	255 (25.3) 157 (15.6) 99 (9.8) 6 (0.6) 52 (5.2) 28 (2.8) 15 (1.5) 40 (4.0) 15 (1.5)

Reviewer comment:

A greater percentage of patients discontinued from the placebo group, primarily due to adverse events and worsening of COPD. The adverse event accounting for this difference was COPD exacerbation.

Demographics and disease characteristics

The mean age of the patients was 65.2 years (range 38-87 years); 72.4% of the trial population were male and 90.5% were white. The mean duration of COPD was 8.7 years. All patients were current (37.0%) or ex-smokers (63.0%), with a mean smoking history of 48.1 pack years. The mean pre-bronchodilator FEV_1 was 1.09L with a mean percent predicted of 38.8%. The mean pre-bronchodilator FEV_1/FVC was 42.4%. The mean post-bronchodilator FEV_1 was 1.29L with a mean percent predicted of 46.0%. The overall demographic profile was generally balanced across the treatment groups. Pulmonary function data at baseline were generally comparable. Any differences in PFT data were dealt with in the analysis by including baseline as a covariate in the model. Demographic characteristics are provided in Table 87, and baseline PFT variables are provided in Table 88. [Module 5, Volume 1.14, Study report 205.255, pages 101-105]

Table 87: Protocol 205.255 patient demographic and disease characteristics

	Tio R5	Tio R10	Placebo	Total
Number of patients[1]	338	335	334	1007
Gender [N (%)]				
Male	248 (73.4)	246 (73.4)	235 (70.4)	729 (72.4)
Female	90 (26.6)	89 (26.6)	99 (29.6)	278 (27.6)
Race [N (%)]				
Missing	24 (7.1)	25 (7.5)	26 (7.8)	75 (7.4)
White	307 (90.8)	302 (90.1)	302 (90.4)	911 (90.5)
Black	2 (0.6)	7 (2.1)	6 (1.8)	15 (1.5)
Asian	5 (1.5)	1 (0.3)	0 (0.0)	6 (0.6)
Age [years][2]				
N	338	335	334	1007
Mean	64.4	65.6	65.7	65.2
Median	65.0	66.0	66.0	66.0
SD	8.9	8.6	8.4	8.7
Min	38.0	43.0	41.0	38.0
Max	85.0	86.0	87.0	87.0
Smoking history [N (%)]				
Ex smoker	208 (61.5)	226 (67.5)	200 (59.9)	634 (63.0)
Smoker	130 (38.5)	109 (32.5)	134 (40.1)	373 (37.0)
Smoking history [pack years]				
Mean	47.4	47.6	49.3	48.1
Median	42.0	40.0	43.5	42.0
SD	25.1	26.0	26.7	25.9
Min	10.0	10.0	10.0	10.0
Max	250.0	165.0	180.0	250.0
Duration of COPD [years][3]				
Mean	8.1	8.8	9.0	8.7
Median	6.0	7.0	7.5	7.0
SD	6.4	7.1	6.8	6.8
Min	0.0	0.1	0.0	0.0
Max	35.8	44.0	44.0	44.0

1 The percentages may not add up to 100% due to missing data.
2 Calculated from date of birth and date screened
3 Regardless of when COPD diagnosis was made
Obtained from Visit 1, screening visit

Table 88: Protocol 205.255 screening PFT data

	Tio R5	Tio R10	Placebo	Total
Number of patients	338	335	334	1007
Pre-bronchodilator FEV_1 [L]				
Mean	1.109	1.072	1.079	1.087
Min	0.25	0.28	0.36	0.25
Max	2.78	3.88	2.37	3.88
Pre-bronchodilator % predicted normal FEV_1 – ECCS				
Mean	39.2	38.4	38.8	38.8
Min	9.6	11.6	13.3	9.6
Max	83.5	91.4	84.5	91.4
Pre-bronchodilator FVC [L]				
Mean	2.627	2.630	2.583	2.613
Min	0.56	0.84	0.99	0.56
Max	5.57	6.28	5.67	6.28
Pre-bronchodilator FEV_1 / FVC [%]				
Mean	43.0	41.7	42.4	42.4
Min	18.4	15.4	18.8	15.4
Max	76.3	70.2	82.3	82.3
Post-bronchodilator FEV_1 [L]				
Mean	1.316	1.264	1.284	1.288
Min	0.44	0.32	0.33	0.32
Max	3.14	4.08	2.80	4.08
Post-bronchodilator[2] % predicted normal FEV_1 – ECCS				
Mean	46.6	45.3	46.2	46.0
Min	18.0	11.9	14.0	11.9
Max	85.1	96.1	101.5	101.5
Post-bronchodilator[2] FEV_1 [L] change from pre-dose[1]				
Mean	0.209	0.191	0.205	0.201
Min	-0.34	0.71	0.20	0.71
Max	1.04	1.34	0.77	1.34
Post-bronchodilator[2] FEV1 % change from pre-dose[1]				
Mean	21.5	19.7	21.0	20.7
Min	-23.9	48.3	19.4	48.3
Max	293.3	100.0	89.5	293.3
Post-bronchodilator[2] FVC [L]				
Mean	3.020	2.995	2.996	3.003
Min	1.25	0.82	1.34	0.82
Max	5.88	6.71	6.34	6.71

1 Obtained from Visit 1, Screening Visit
2 30 minutes after 400µg of albuterol

Protocol violations

There was no per-protocol analysis for this study; therefore, protocol violations were not used to exclude patients from any analysis. There were a total of 38 patients who were determined retrospectively to have not met entry criteria. These deviations were categorized into 5 types: 1) target indication not met, 2) unstable at the randomization visit, 3) previous participation in the study or its replicate, 4) have taken marketed Spiriva, and 5) significant other disease which may obscure treatment response. These patients were distributed evenly across the groups.

In addition to these entry criteria violations, there were 118 patients who took a prohibited medication, had an incorrect medication washout, had incorrect dosing at the clinic, took an incorrect trial medication, or were noncompliant. [Module 5, Volume 1.14, Study report 205.255, pages 97-99]

Reviewer comment:

The reported protocol violations were distributed evenly across the study groups. Overall, these discrepancies do not affect the integrity of the data. There were 16 patients who were listed as "target indication not met." Of these, 11 exceeded spirometric criteria and 5 had evidence of asthma or allergic rhinitis. Of the 5 with evidence of asthma or allergic rhinitis, 2 had an eosinophil count ≥ 600/mm^3, but no medical history of asthma or allergic rhinitis.

Treatment compliance

Medication compliance was determined from patient diary data. Overall reported compliance for the study was 95.3% for tio R5, 94.6% for tio R10, and 96.0% for the placebo groups. [Module 5, Volume 1.14, Study report 205.255, page 106]

Concomitant respiratory medications

A total of 81.5% of patients in the study took baseline concomitant respiratory medications. At baseline, 41.6% of patients were taking inhaled short-acting anticholinergics, 30.8% were taking inhaled long-acting ß-agonists, 54.4% were taking short-acting ß-agonists, and 11.3% were taking theophylline preparations. In addition, 55.3% of patients overall were taking inhaled steroids, and 3.4% were taking oral corticosteroids. These baseline respiratory medications were generally balanced among groups. [Module 5, Volume 1.14, Study report 205.255, pages 106]

Pharmacokinetic outcomes

No pharmacokinetic data were collected in this study.

Efficacy outcomes

Efficacy analyses were performed on the full analysis set (FAS), which consisted of all randomized patients with at least baseline data (pre-treatment at the end of the 2-week run-in) and at least one adequate endpoint measurement of the variable under evaluation. For trough FEV_1, this was defined as at least one spirometric value following at least 5 days of randomized treatment. For calculation of the fourth primary endpoint of COPD exacerbation rate, the ITT population was utilized. There was no per-protocol analysis for this study; therefore, protocol violations were not used to exclude patients from the analysis.

Of the 983 patients randomized, 52 (5.2%) patients were excluded from the first primary efficacy analysis of FEV_1 trough because of inadequate data following multiple administrations. This included 14 (4.1%) patients in the tio R5 group, 11 (3.3%) in the tio R10 group, and 27 (8.1%) in the placebo group.

Primary

Trough FEV_1 response at 48 weeks

For the first co-primary endpoint, trough FEV_1 response at the end of 48 weeks of treatment, both tiotropium groups were superior to placebo. At the end of 48 weeks of treatment, the adjusted mean FEV_1 trough value was 1.137L for the tio R5 group and 1.164L for the tio R10 group as compared to 1.024L in the placebo group. This difference was statistically significant at $p<0.0001$. Means were adjusted for center, smoking status at entry and baseline value. The mean treatment differences and 95% confidence intervals for the primary endpoint, shaded in grey, are presented in Table 89. Mean treatment differences in trough response for other time points are also presented unshaded in Table 89. [Module 5, Volume 1.11, Study report 205.254, pages 110-115]

Table 89: Protocol 205.255 FEV_1 trough response [L] treatment difference

Treatment comparison	Test day	Treatment difference Mean	SE	95% C.I.	p-value*
Tio R5 – Placebo	15	0.115	0.015	(0.085, 0.144)	<.0001
	57	0.112	0.016	(0.081, 0.142)	<.0001
	113	0.126	0.017	(0.093, 0.159)	<.0001
	169	0.115	0.017	(0.082, 0.148)	<.0001
	225	0.108	0.018	(0.073, 0.143)	<.0001
	281	0.118	0.017	(0.085, 0.151)	<.0001
	337	**0.113**	**0.017**	**(0.078, 0.147)**	**<.0001**
Tio R10 – Placebo	15	0.118	0.015	(0.088, 0.147)	<.0001
	57	0.146	0.016	(0.115, 0.176)	<.0001
	113	0.141	0.017	(0.108, 0.174)	<.0001
	169	0.142	0.017	(0.109, 0.175)	<.0001
	225	0.158	0.018	(0.123, 0.192)	<.0001
	281	0.133	0.017	(0.100, 0.167)	<.0001
	337	**0.140**	**0.017**	**(0.106, 0.175)**	**<.0001**

Tio R 5: N = 324, Tio R 10: N = 324, Placebo: N = 307

* Based on a two sided test

All values in this table are based on an ANCOVA analysis with terms for treatment, smoking status at entry, center, and baseline value. A separate ANCOVA is fitted at each time point.

Reviewer comment:

The mean trough FEV_1 response for the tio R5 group was 0.113L after 48 weeks of treatment. This difference is approximately the same as the FEV_1 response at the end of 13 weeks of treatment for Spiriva HandiHaler (18 mcg) found in pivotal trials (0.110 and 0.130L).

SGRQ

The second co-primary endpoint was SGRQ total score at 48 weeks. The overall baseline score was 44.7, ranging from 44.1 to 46.0. All three treatment groups achieved a reduction in mean SGRQ total score at Test Day 57, which was maintained throughout the treatment period. Both tiotropium groups showed a statistical difference from placebo, with a reduction compared to placebo of -3.7 points (p=0.0004) and -3.4 points (p<0.0012) for the tio R5 and tio R10 groups,

respectively. See Table 90 for the SGRQ total score treatment differences. [Module 5, Volume 1.14, Study report 205.255, pages 115-117]

Table 90: Protocol 205.255 SGRQ total score treatment differences

Treatment Comparison	Test Day	Treatment difference Mean	SE	(95% C.I.)	p-value*
Tio R5 - Placebo	57	-2.6	0.8	(-4.3, -1.0)	0.0019
	113	-4.0	1.0	(-5.8, -2.1)	<.0001
	225	-2.7	1.0	(-4.8, -0.7)	0.0083
	337	**-3.7**	**1.1**	**(-5.8, -1.6)**	**0.0004**
Tio R10 - Placebo	57	-2.3	0.9	(-4.0, -0.6)	0.0075
	113	-3.4	1.0	(-5.3, -1.5)	0.0004
	225	-2.7	1.0	(-4.7, -0.6)	0.0110
	337	**-3.4**	**1.1**	**(-5.5, -1.4)**	**0.0012**

Tio R5: N = 310, Tio R10: N = 304, Placebo: N = 276

* Based on a two sided test

All values in this table are based on an ANCOVA analysis with terms for treatment, smoking status at entry, center, and baseline value.

A separate ANCOVA is fitted at each time point.

Reviewer comment:

A clinically meaningful difference in SGRQ total score is reported to be 4 points. This is the difference used in the responders analysis (see secondary endpoints). While the differences between the tiotropium groups and placebo reach a high level of statistical significance, differences of less than 4 may not be clinically meaningful. However, the result is supportive of the improvement observed in FEV_1.

The Applicant is not making labeling claims regarding SGRQ.

Mahler Transition Dyspnea Index (TDI) Focal Score

It was prespecified that this co-primary endpoint would be analyzed based on combined data from this study (205.255) and study 205.254. However, the sponsor also analyzed the studies separately for this endpoint.

All three treatment groups showed an improvement from baseline in the adjusted mean TDI focal score at Test Day 57, with the increase for the tio R10 group being approximately double that of the placebo group. In general, this improvement was maintained for the remainder of the

treatment period. The differences between the tio R5 group and placebo (1.0) and the tio R10 group and placebo (0.9) were both statistically significant (p<0.0001 and p=0.0002, respectively). [Module 5, Volume 1.14, Study 205.255, pages 117-120]

Reviewer comment:

Due to fundamental weaknesses of the TDI instrument, this result cannot be utilized to support a dyspnea indication. The company has defined a responder for this endpoint to be a difference of 1 from baseline. The mean difference from placebo ranges from 0.5 to 1.1, suggesting that the clinical meaning of the difference in TDI scores is unknown.

The Applicant is not making labeling claims regarding dyspnea.

COPD Exacerbations

The fourth co-primary efficacy endpoint was COPD exacerbations during the 48 week treatment period. It was prespecified that this co-primary endpoint would be analyzed based on combined data from this study (205.255) and study 205.254. [Module 5, Volume 1.14, Study 205.255, page 121]

Reviewer comment:

At the request of FDA, the Applicant also provided an analysis of COPD exacerbations found in the individual studies, previously provided only as part of the statistical documentation. These results show a mean exacerbation rate per patient year of 0.85 for tio R5 compared to 1.10 for placebo, with a 95% CI of 0.62-0.96 (p=0.02). The time to first exacerbation for patients in the tio R5 group was 149 days compared to 74 days for placebo (p <0.0001). See Table 91. Evaluation of parameters per number of days on therapy was used to correct for the greater number of discontinuations and shorter treatment duration observed in the placebo group. According to the statistical reviewer, Ruthanna Davi, this is a reasonable correction. The FDA also requested data from the tio R10 group, which is still pending at the time of review finalization.

Table 91: Protocol 205.255 COPD exacerbations rates and time to first exacerbation (Poisson regression)

	Tio R5	Placebo
Number of patients		
exposed to randomized treatment	338	334
at least one COPD exacerbation	122	157
% of patients with exacerbations	36	47
Mean treatment exposure (days)	302	259
Exacerbation rate per patient year		
Mean	0.85	1.10
Rate ratio (RR) versus placebo	0.77	
95% CI for RR	0.62-0.96	
p-value for RR	0.02	
Time to first exacerbation (days)		
Lower quartile	149	74
p-value versus placebo	<0.0001	

The analysis provided by the Applicant in response to the FDA request was performed using a Poisson regression model with correction for overdispersion (increased variance in data compared to the mean). While this is a valid method according to the statistical reviewer, it was not prespecified in the protocol. Evaluating the data using the protocol specified Wilcoxin-Mann-Whitney test, which is what was used for the combined analysis, gives a mean COPD exacerbation rate of 1.1 in the tio R5 group, 1.21 in the tio R10 group, and 1.95 in the placebo group. Based on this result, both tiotropium groups had a statistically significant difference from placebo (0.0034 and 0.0036 for tioR 5 and tio R10, respectively).

In this study, both statistical methodologies give significant results for the tiotropium groups compared to placebo.

FEV_1 trough, $AUC_{(0-3h)}$, and peak $_{(0-3h)}$ response

The pairwise differences for FEV_1 between both the active groups and placebo were statistically significant ($p<0.0001$) at all time points post-dose on all test days. While the tio R10 group generally showed some increase over the tio R5 group, the differences were small and not statistically significant. The trough response compared to placebo was maintained at similar levels at all time points measured. However, trough FEV_1 in all groups declined slightly over the 48 week study. See Table 89 for FEV_1 trough response at all time points and Table 92 for FEV_1 trough, AUC, and peak FEV_1. [Module 5, Volume 1.14, Study report 205.255, pages 121-123]

Table 92: Protocol 205.255 adjusted mean FEV_1 trough, AUC (0-3h), and peak (0-3h) response [L] on each test day

Response	Test Day	Tio R5 (N = 324) Mean (SE)		Tio R10 (N = 324) Mean (SE)		Placebo (N = 307) Mean (SE)	
Trough	15	0.111	(0.010)	0.114	(0.010)	-0.003	(0.011)
	57	0.099	(0.011)	0.133	(0.011)	-0.012	(0.011)
	113	0.118	(0.012)	0.132	(0.012)	-0.008	(0.012)
	169	0.104	(0.012)	0.132	(0.012)	-0.010	(0.012)
	225	0.095	(0.012)	0.145	(0.012)	-0.012	(0.013)
	281	0.091	(0.012)	0.106	(0.012)	-0.027	(0.012)
	337	0.077	(0.012)	0.105	(0.012)	-0.036	(0.012)
AUC (0-3h)	1	0.191	(0.007)	0.214	(0.007)	0.045	(0.008)
	15	0.246	(0.011)	0.257	(0.011)	0.044	(0.012)
	57	0.234	(0.012)	0.258	(0.012)	0.037	(0.013)
	113	0.235	(0.012)	0.242	(0.012)	0.026	(0.013)
	169	0.222	(0.012)	0.245	(0.012)	0.024	(0.013)
	225	0.198	(0.013)	0.241	(0.013)	0.018	(0.013)
	281	0.197	(0.012)	0.206	(0.012)	0.000	(0.012)
	337	0.181	(0.013)	0.210	(0.013)	-0.002	(0.013)
Peak (0-3h)	1	0.274	(0.009)	0.298	(0.009)	0.120	(0.009)
	15	0.328	(0.012)	0.342	(0.012)	0.115	(0.013)
	57	0.317	(0.014)	0.330	(0.014)	0.110	(0.014)
	113	0.313	(0.013)	0.318	(0.013)	0.096	(0.014)
	169	0.300	(0.014)	0.317	(0.014)	0.090	(0.014)
	225	0.279	(0.014)	0.315	(0.014)	0.079	(0.014)
	281	0.267	(0.013)	0.278	(0.013)	0.061	(0.013)
	337	0.258	(0.014)	0.281	(0.014)	0.061	(0.014)

The common baseline mean obtained at the -10 minute time point of Test Day 1 was 1.060L.
The means are adjusted for center, smoking status at entry and baseline value.
A separate ANCOVA was fitted at each time point.

The mean FEV_1 AUC $_{(0\text{-}3h)}$ response for the tiotropium groups ranged from 0.181 to 0.258L above the baseline value and was generally consistent throughout the treatment period. The response for the placebo group was approximately 0.200L less than that seen for the active treatment groups. The differences between the tiotropium groups and placebo were highly statistically significant ($p<0.0001$).

The mean FEV_1 peak $_{(0\text{-}3h)}$ response for the tiotropium groups ranged from 0.258 to 0.342L above the baseline value and was generally consistent throughout the treatment period. The response for the placebo group was approximately 0.200L less than that seen for the active treatment groups. The differences between the tiotropium groups and placebo were highly statistically

significant (p<0.0001). The effects of tiotropium on FEV_1 appeared to reach steady state after 15 days of dosing based on plateau of effect on peak FEV_1.

Reviewer comment:

The AUC and peak are not completely comparable to those obtained in the 12 week studies. For Protocols 205.251 and 205.252, AUC and peak FEV_1 were measured over 6 hours rather than 3 hours as in the 48 week studies (Protocols 205.254 and 205.255).

FVC

The FVC results generally paralleled the FEV_1 results. By the end of the treatment period, the adjusted mean FVC trough value was 2.796L for the tio R5 group and 2.808L for the tio R10 group. This compared to an adjusted mean FVC trough of 2.556L in the placebo group. The mean FVC value increased to 3.020 and 3.041L three hours after treatment for the tio R5 and tio R10 groups, respectively.

The difference in FVC between the tiotropium groups and placebo were statistically significant (p<0.0001) at all time points post-dose on all test days. In general, the tio R10 group showed some improvement over the tio R5 group, but the differences were small and not significant.

The mean FVC $AUC_{(0\text{-}3h)}$ response for the tio R5 group ranged from 0.387 to 0.513L above the baseline value compared to 0.406 to 0.522L for the tio R10 group. The response for the placebo group was 0.3-0.4L less than that seen for the active treatment groups. The differences between the tiotropium groups and placebo were highly statistically significant (p<0.0001).

The mean FVC $peak_{(0\text{-}3h)}$ response for the tio R5 group ranged from 0.564-0.707L above the baseline value compared to 0.583 to 0.711L for the tio R10 group. The response for the placebo group was 0.3-0.4L less than that seen for the active treatment groups. The differences between the tiotropium groups and placebo were highly statistically significant (p<0.0001).

[Module 5, Volume 1.14, Study report 205.255, pages 124-127]

SGRQ component scores

The SGRQ was analyzed for the following component scores: symptoms, activities, and impacts. The difference between the tiotropium groups and placebo were statistically significant compared to placebo for the symptoms and impacts components. The difference from placebo for the activities component was statistically significant for the tio R10 group (p=0.0034), but not for the tio R5 group (p=0.069).

Using a difference in total score from baseline of 4 points or greater to define responders, 48.7% of patients in the tio R5 group, 49.3% in the tio R10 group, and 40.0% in the placebo group responded to therapy at Test Day 336. Differences in response rate between the tiotropium groups and placebo were statistically significant on test days 113 and 337 (p<0.05). [Module 5, Volume 1.14, Study report 205.255, pages 127-128]

Mahler TDI component scores

The Mahler TDI was analyzed for the following component scores: functional impairment, magnitude of task, and magnitude of effort. The difference between the tiotropium groups and placebo were statistically significant ($p<0.001$) for all three components.

Using a difference in total score from baseline of 1 point or greater to define responders, 57.4% of patients in the tio R5 group, 62.0% of patients in the tio R10 group, and 47.7% in the placebo group. Differences in response rate between the tiotropium groups and placebo were statistically significant on the majority of test days ($p<0.05$). [Module 5, Volume 1.14, Study report 205.255, pages 128-130]

PEFR

Baseline mean pre-dose morning peak expiratory flow rate (PEFR) for all treatment groups was 229.7 L/min. Mean differences compared to placebo in pre-dose morning PEFR for tio R5 and tio R10 and placebo were 18.6-31.5 L/min and 18.3-35.4 L/min respectively. These differences were significant for all 48 weeks during the trial ($p<0.0001$). Mean differences compared to placebo in mean evening PEFR were also highly significant for all weeks ($p<0.0001$).

Rescue albuterol use

For all treatment groups combined, albuterol was used an average of 2.7 occasions/day at baseline. The tiotropium groups showed a significant decrease in the use of albuterol rescue throughout the study, ranging from 0.3-1.0 fewer rescue uses per day. [Module 5, Volume 1.14, Study report 205.255, pages 132-133]

Reviewer comment:

The Applicant seeks a labeling statement regarding reduction of rescue medication use. Since a significant difference in rescue medication use was observed both in this trial and Protocol 205.254, the statement is supported.

COPD symptoms

Physician-reported COPD symptoms of wheezing, shortness of breath, coughing and tightness of chest were recorded after each week of therapy using a 4 point scale (0=none to 3=severe). Overall, the differences between treatment groups were small and not statistically significant for the coughing and chest tightness scores, but were significant at $p<0.05$ for the shortness of breath scores. [Module 5, Volume 1.14, Study report 205.255, pages 133-34]

Physician's Global Evaluation

The Physician's Global Evaluation was reported on an 8 point scale, ranging from 1-2=poor to 7-8=excellent. In general the PGE scores increased gradually throughout the study (indicated an improvement in the patient's condition) for the tiotropium groups and stayed the same for the placebo group. The difference between the tiotropium groups and placebo were statistically significant on all test days. [Module 5, Volume 1.14, Study report 205.255, pages 134-135]

Patient's Global Rating

Patients were asked to rate their health at each visit compared to the day before they commenced study treatment. Ratings were reported on a 7 point scale: much better, somewhat better, a little better, about the same, a little worse, somewhat worse, and much worse. Much better was given a score of 1, while much worse was given a score of 7. The tiotropium groups showed significant improvement over placebo for all test days ($p<0.01$). [Module 5, Volume 1.14, Study report 205.255, page 135]

Efficacy conclusions

Both tiotropium groups met all 4 primary endpoints for the study, increase in trough FEV_1, improvement in SGRQ score, improvement in Mahler TDI, and reduction in COPD exacerbations compared to placebo at the end of 48 weeks of treatment. The tio R10 group was not significantly better than the tio R5 group in terms of efficacy. The effects of tiotropium on FEV_1 appeared to reach steady state after 15 days of dosing. In addition, both tiotropium groups showed significant improvement over placebo for the majority of secondary endpoints, particularly PFT variables. A summary of non-spirometric endpoints reaching and not reaching a statistically significant difference in the tiotropium groups compared to placebo is provided in Table 93. For many of these endpoints, the clinical significance of the effect size is unclear.

Table 93: Protocol 205.255 efficacy summary of non-spirometric secondary endpoints

Statistically significant difference	No statistically significant difference
SGRQ component scores (symptoms, impacts)	SGRQ component scores (activities, tio R5)
SGRQ component scores (activities, tio R5)	SGRQ response rate (Day 225 and 337)
SGRQ response rate (Day 57 and 113)	TDI response rate (2 of 6 time points)
TDI component scores	COPD symptoms (cough, chest tightness, and shortness of breath—most days)
TDI response rate (4 of 6 time points)	
COPD symptom scores (wheeze)	
Morning PEFR (all weeks)	
Evening PEFR (all weeks)	
Rescue albuterol use	
Physician's Global Evaluation	
Patient's Global Evaluation	

Safety outcomes

Safety outcomes for Study 205.254 included adverse events, laboratory findings (hematology, blood chemistry, and urinalysis at screening and at the end of treatment), ECGs (performed and interpreted by the investigator at screening and at the end of treatment), vital signs (pulse rate and blood pressure measured at the same time intervals as PFTs for the first 3 hours post-dose), and physical examinations (screening and at the end of treatment). In addition ECGs and Holter monitors read centrally were obtained on a subset of patients. All patients who were randomized and received at least one dose of trial medication were included in the safety analysis.

Extent of exposure

A total of 1007 COPD patients were randomized and received at least one dose of study medication. The planned exposure for each patient was 48 weeks (337 days). Overall, the mean exposure was 283.8 days. Patients randomized to the tio R5 group had the longest mean duration of 302.2 days. The tio R10 group was exposed for 289.7 days, and the placebo group for 259.2 days, consistent with a larger number of discontinuations in the placebo group. See Table 94. [Module 5, Volume 1.14, Study report 205.255, page 139]

Table 94: Protocol 205.255 summary of treatment exposure

	Tio R5	Tio R10	Placebo	Total
Total Treated N	**332**	**332**	**319**	**983**
Maximum Exposure n (%)				
1 day	0 (0.0%)	1 (0.3%)	3 (0.9%)	4 (0.4%)
2 – 7 days	3 (0.9%)	2 (0.6%)	9 (2.7%)	14 (1.4%)
8 – 60 days	20 (5.9%)	23 (6.9%)	44 (13.2%)	87 (8.6%)
61 – 100 days	6 (1.8%)	12 (3.6%)	9 (2.7%)	27 (2.7%)
101 – 200 days	14 (4.1%)	19 (5.7%)	25 (7.5%)	58 (5.8%)
201 – 330 days	35 (10.4%)	38 (11.3%)	32 (9.6%)	105 (10.4%)
>330 days	260 (76.9%)	240 (71.6%)	212 (63.5%)	712 (70.7%)
Treatment Exposure (days)				
Mean	302.2	289.7	259.2	283.8
SD	91.3	103.2	126.2	109.2
Median	337.0	337.0	336.5	337.0
Min	2	1	1	1
Max	412	444	414	444

Adverse events

Deaths

There was a dose-related mortality increase in the tiotropium groups. Overall, there were 14 deaths in the study, 5 in the tio R5 group, 9 in the tio R10 group, and 0 in the placebo group. The primary cause of death is reported in Table 95. Of these deaths, 6 were reported as due to events in the respiratory system, 2 were due to events in the gastrointestinal system, 2 were neoplasms, 1 was due to renal failure, 1 due to right heart failure, and 1 was a suicide. One patient died of unreported causes, from a site in Russia. All of the patients with death of unreported cause died at home. [Module 5, Volume 1.14, Study report 205.255, pages 149-155]

Reviewer comment:

The sponsor states that the mortality signal observed in this study is due to the absence of deaths in the placebo group and the higher percentage of discontinuations. The mean total exposure is approximately 37 days lower in the placebo group compared to the tiotropium groups. Additional follow up on these discontinued patients is reviewed in Study 205.239. Clinically, the observed mortality in the tiotropium groups is not unexpected, while the absence of mortality observed in the placebo group is. However, the observed signal raises concern.

Table 95: Protocol 205.255 fatal events by treatment group and primary cause of death

Events leading to death†	Tio R-5 [n=338]	Tio R-10 [n=335]	Placebo [n=334]
Total deaths	**5**	**9**	**0**
Right ventricular failure	1	0	0
Gastrointestinal hemorrhage	0	1	0
Hernial eventration	0	1*	0
Peritonitis	0	1	0
Death	0	1	0
Neoplasms	0	2	0
Suicide	1	0	0
Renal failure acute	1	0	0
COPD exacerbated	1	3*	0
Pneumonia	0	2*	0
Respiratory failure	1	0	0

*one patient had all 3 causes listed as fatal

Serious adverse events

Serious AEs occurred in 19.0% of the overall study population, including 18.6% of the tio R5 group, 21.5% tio R10, and 16.8% placebo. There was a small dose-related increase in serious adverse events in the tiotropium groups. The most common serious adverse event was COPD exacerbation, occurring in 5.9% of the tio R5 group, 8.7% of the tio R10 group, and 6.0% of the

placebo group. Serious cardiac events occurred in 1.8% of patients overall, including 2.1% of the tio R5 group, 1.5% of the tio R10 group, and 1.9% of the placebo group. The rate of serious adverse events of pneumonia was double in the tiotropium groups compared to placebo (2.1% versus 1.2%). There were 14 ischemic cardiac events, including AE terms of acute coronary syndrome, angina, coronary artery disease, myocardial infarction, and myocardial ischemia. Of these ischemic cardiac events, 3 occurred in the tio R5 group, 7 in the tio R10 group, and 4 in the placebo group. There were 4 stroke events, including AE terms of cerebrovascular accident, ischemic cerebral infarction, ischemic stroke, and transient ischemic attack. Of these stroke events, none occurred in the tio R5 group, 3 in the tio R10 group, and 1 in the placebo group.

Adverse events leading to discontinuation

There were a greater number of discontinuations due to adverse events in the placebo group (10.7% tio R5, 13.1% tio R10, and 22.2% placebo,). This was due to a greater number of discontinuations due to COPD exacerbations in the placebo group (4.4% tio R5, 5.1% tio R10, and 11.7% placebo).

Overall adverse events

Adverse events (AEs) were reported in 79.7% of the patients: 78.4% in tio R5, 81.2% in tio R10, and 79.6% in placebo. Dry mouth and urinary tract infection occurred with increased frequency in the tiotropium groups in a dose related fashion, consistent with the known anticholinergic mechanism of action of the drug. Bronchitis, cough, and pneumonia were also increased in the tiotropium groups, while COPD exacerbations were decreased. Adverse events occurring in ≥3% of patients in any treatment group are presented in Table 96.

Table 96: Protocol 205.255 adverse events occurring in ≥3% of patients by treatment group

MedDRA System Organ Class MedDRA Preferred Term	Treatment Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Total Treated N (%)	338 (100.0)	335 (100.0)	334(100.0	1007 (100.0)
Total with adverse events	265 (78.4)	272 (81.2)	266 (79.6)	803 (79.7)
Cardiac disorders	27 (8.0)	31 (9.3)	20 (6.0)	78 (7.7)
Angina#	6 (1.8)	10 (3.0)	3 (0.9)	19 (1.9)
Gastrointestinal disorders	82 (24.3)	105 (31.3)	57 (17.1)	244 (24.2)
Abdominal pain#	13 (3.8)	11 (3.3)	7 (2.1)	31 (3.1)
Constipation	11 (3.3)	9 (2.7)	6 (1.8)	26 (2.6)
Diarrhea	6 (1.8)	12 (3.6)	11 (3.3)	29 (2.9)
Mouth dry#	30 (8.9)	48 (14.3)	10 (3.0)	88 (8.7)
General disorders and administration site conditions	54 (16.0)	33 (9.9)	39 (11.7)	126 (12.5)
Chest pain	13 (3.8)	4 (1.2)	7 (2.1)	24 (2.4)
Edema#	15 (4.4)	9 (2.7)	9 (2.7)	33 (3.3)
Infections and infestations	59 (17.5)	49 (14.6)	40 (12.0)	148 (14.7)
Urinary tract infections#	13 (3.8)	15 (4.5)	5 (1.5)	33 (3.3)
Musculoskeletal and connective tissues disorders	48 (14.2)	58 (17.3)	37 (11.1)	143 (14.2)
Back pain	12 (3.6)	13 (3.9)	7 (2.1)	32 (3.2)
Nervous system disorders	41 (12.1)	36 (10.7)	36 (10.8)	113 (11.2)
Headache	19 (5.6)	16 (4.8)	15 (4.5)	50 (5.0)
Respiratory system disorders* (Lower)	154 (45.6)	158 (47.2)	196 (58.7)	508 (50.4)
Bronchitis#	16 (4.7)	24 (7.2)	16 (4.8)	56 (5.6)
COPD exacerbation#	115 (34.0)	115 (34.3)	149 (44.6)	379 (37.6)
Cough	19 (5.6)	25 (7.5)	11 (3.3)	55 (5.5)
Dyspnea#	18 (5.3)	13 (3.9)	28 (8.4)	59 (5.9)
Pneumonia#	12 (3.6)	11 (3.3)	7 (2.1)	30 (3.0)
Respiratory system disorders* (Upper)	111 (32.8)	111 (33.1)	91 (27.2)	313 (31.1)
Epistaxis	4 (1.2)	11 (3.3)	7 (2.1)	22 (2.2)
Influenza	14 (4.1)	15 (4.5)	17 (5.1)	46 (4.6)
Nasopharyngitis	53 (15.7)	33 (9.9)	24 (7.2)	110 (10.9)
Pharyngolaryngeal pain	19 (5.6)	17 (5.1)	9 (2.7)	45 (4.5)
Rhinitis	4 (1.2)	11 (3.3)	8 (2.4)	23 (2.3)
Sinusitis	10 (3.0)	9 (2.7)	8 (2.4)	27 (2.7)
Upper respiratory tract infection	27 (8.0)	27 (8.1)	28 (8.4)	82 (8.1)
Vascular disorders	15 (4.4)	25 (7.5)	23 (6.9)	63 (6.3)
Hypertension	10 (3.0)	14 (4.2)	12 (3.6)	36 (3.6)

Percentages are calculated using total number of patients per treatment as the denominator.

BI Collapsed Preferred Terms include multiple MedDRA Preferred Terms.

All system organ classes are defined by MedDRA with the exception of respiratory, thoracic and mediastinal disorders which have been divided into 3 separate classes of respiratory system disorders lower, upper, and other.

MedDRA version 8.0 was used for reporting.

A specific analysis looking for paradoxical bronchospasm in response to tiotropium was conducted. The term 'aggravated bronchospasm' was used to describe a spontaneously reported AE of "aggravated' or 'paradoxical bronchospasm' which occurred within 30 minutes of study medication inhalation. The term 'administration related bronchoconstriction' was used to describe occurrence of at least 2 of the following 3 events: 1) use of rescue medication, 2) any potentially bronchospastic AE (cough, wheeze, dyspnea, etc.) and 3) ≥15% fall in FEV_1 below test-day pre-dose FEV_1. To fulfill the definition, each event must have occurred within 30 minutes of study medication inhalation. No patients fulfilled the definition of 'aggravated bronchospasm.' Five patients had 'administration related bronchoconstriction,' 2 in tio R5, 2 in tio R10, and 1 in placebo groups. The incidence of asymptomatic falls in FEV_1 of 15% or more ranged from 5.3% in the tio R5 group to 13.8% in the placebo group. [Module 5, Volume 1.14, Study report 205.255, pages 147-148]

Laboratory findings

The Applicant analyzed the laboratory data as mean change from baseline, clinically significant abnormalities, and shift tables. The laboratory data were reviewed, and the changes in laboratory values throughout the study were small. There were no clinically important differences between the treatment groups.

ECG findings

There were a total of 16 patients with new or worsened ECG findings at the completion of therapy. These included 5 patients in the tio R5 group, 4 in the tio R10 group, and 7 in the placebo group. Additional ECGs were performed at Visit 2 and at Visit 5 and 8 in a subset of 300 patients from this trial and trial 205.255. Twenty-four-hour Holter monitoring was also performed on this subset of patients. Results of these additional ECGs and Holter studies are reviewed under the combined data from studies 205.254 and 205.255. [Module 5, Volume 1.11, Study report 205.254, pages 158-161]

Physical examination

Overall changes in blood pressure and pulse rate were small without a clinically important difference between treatment groups. Thirty-two patients in the tio R5 group, 26 in tio R10, and 48 in placebo had new or worsened findings on physical examination during the study. These changes were all recorded as adverse events.

Safety conclusions

There was a dose-related increase in deaths in this study in favor of the placebo group. Death occurred in 1.5% of tio R5, 2.7% of tio R10 and 0 placebo patients. There were a greater number of discontinuations in the placebo group, which may have contributed to this imbalance (74% of patients completed in the tiotropium groups compared to 64% in the placebo group). Many of these discontinuations were due to COPD exacerbations. Additional follow up on these discontinued patients is reviewed in Study 205.392. There was also a dose-related effect

observed for tiotropium in the anticholinergic side-effect of dry mouth, as well as an increase in urinary tract infections and an increase in pneumonia in the tiotropium groups.

10.1.5.3 Summary and conclusions

Both tiotropium groups met all 4 primary endpoints for the study, increase in trough FEV_1, improvement in SGRQ score, improvement in Mahler TDI, and reduction in COPD exacerbations compared to placebo at the end of 48 weeks of treatment. The tio R10 group was not significantly better than the tio R5 group in terms of efficacy. The effects of tiotropium on FEV_1 appeared to reach steady state after 15 days of dosing. In addition, both tiotropium groups showed significant improvement over placebo for the majority of secondary endpoints, particularly PFT variables. A summary of non-spirometric endpoints reaching and not reaching a statistically significant difference in the tiotropium groups compared to placebo is provided in Table 93. For many of these endpoints, the clinical significance of the effect size is unclear.

There was a dose-related increase in deaths in this study in favor of the placebo group. Death occurred in 1.5% of tio R5, 2.7% of tio R10 and 0 placebo patients. There were a greater number of discontinuations in the placebo group, which may have contributed to this imbalance (74% of patients completed in the tiotropium groups compared to 64% in the placebo group). Many of these discontinuations were due to COPD exacerbations. Additional follow up on these discontinued patients is reviewed in Study 205.392. There was also a dose-related effect observed for tiotropium in the anticholinergic side-effect of dry mouth, as well as an increase in urinary tract infections and an increase in pneumonia in the tiotropium groups.

10.1.6 Combined data sets from Studies 205.254 and 205.255 reported as Protocol 205.9992

10.1.6.1 Protocol

Study title

A combined analysis of efficacy and safety data obtained in studies 205.254 and 205.255—two randomized, double-blind, efficacy and safety comparisons of one year treatment of two doses (5 mcg [2 actuations of 2.5 mcg] and 10 mcg [2 actuations of 5 mcg]) of tiotropium inhalation solution delivered by the Respimat® inhaler in patients with chronic obstructive pulmonary disease (COPD) [Module 5, Volume 1.22, Study report 205.9992, page 1]

Objectives, design, endpoints, procedures, and statistical plan

Objectives, design, endpoints, procedures, and statistical plan are described in Sections 10.1.4 and 10.1.5. There were no design differences between the studies. Although this prespecified combined analysis was given a separate protocol number, no additional patients were enrolled nor were additional data collected.

Investigators and centers

Subjects from all investigative centers were combined in this statistical report. No center participated in both studies, resulting in patients from a total of 157 centers in 20 countries in the combined data set. [Module 5, Volume 1.22, Study report 205.9992, pages 67-72]

10.1.6.2 Results

Population characteristics

Disposition of patients

A total of 1990 male and female patients with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were randomized; 670 in the tio R5 group, 667 in the tio R10 group, and 653 in the placebo group. Of these, 1534 (77.1%) completed the study. A summary of patient disposition for the trial is presented in Table 97. [Module 5, Volume 1.22, Study report 205.9992, page 73]

Table 97: Protocol 205.9992 (combined studies 205.254 and 205.255) patient disposition

	Tio R5 N (%)	Tio R10 N (%)	Placebo N (%)	Total N (%)
Enrolled				2544
Not entered				554
Entered	670	667	653	1990
Not treated	0	0	0	0
Treated	670 (100.0)	667 (100.0)	653 (100.0)	1990 (100.0)
Not prematurely discontinued from trial medication	555 (82.8)	531 (79.6)	448 (68.6)	1534 (77.1)
Prematurely discontinued from trial medication	115 (17.2)	136 (20.4)	205 (31.4)	456 (22.9)
Adverse events	67 (10.0)	79 (11.8)	122 (18.7)	268 (13.5)
Worsening of disease under study	31 (4.6)	34 (5.1)	92 (14.1)	157 (7.9)
Worsening of other pre-existing disease	3 (0.4)	4 (0.6)	6 (0.9)	13 (0.7)
Other adverse event	33 (4.9)	41 (6.1)	24 (3.7)	98 (4.9)
Administrative				
Non compliant with protocol	8 (1.2)	13 (1.9)	15 (2.3)	36 (1.8)
Lost to follow-up	9 (1.3)	11 (1.6)	15 (2.3)	35 (1.8)
Consent withdrawn	19 (2.8)	23 (3.4)	38 (5.8)	80 (4.0)
Other	12 (1.8)	10 (1.5)	15 (2.3)	37 (1.9)

Reviewer comment:

A greater percentage of patients discontinued from the placebo group, primarily due to adverse events and worsening of COPD. The adverse event accounting for this difference was COPD exacerbation. Comparing the two studies, disposition of patients was generally similar.

Demographics and baseline characteristics

The mean age of the patients was 65.0 years (range 38-90 years); 74.2% of the trial population were male and 91.4% were white. The mean duration of COPD was 8.9 years. All patients were current (36.3%) or ex-smokers (63.7%), with a mean smoking history of 47.8 pack years. The mean pre-bronchodilator FEV1 was 1.09L with a mean percent predicted of 38.5%. The mean pre-bronchodilator FEV1/FVC was 42.8%. The mean post-bronchodilator FEV1 was 1.28L with a mean percent predicted of 45.3%. The overall demographic profile was generally balanced across the treatment groups. Pulmonary function data at baseline were generally comparable. Any differences in PFT data were dealt with in the analysis by including baseline as a covariate in the model. Demographic characteristics are provided in Table 98, and baseline PFT variables are provided in Table 98. [Module 5, Volume 1.22, Study report 205.9992, pages 80-88]

Table 98: Protocol 205.9992 (combined studies 205.254 and 205.255) patient demographic and disease characteristics

	Tio R5	Tio R10	Placebo	Total
Number of patients[1]	670	667	653	1990
Gender [N (%)]				
Male	491 (73.3)	498 (74.7)	487 (74.6)	1476 (74.2)
Female	179 (26.7)	169 (25.3)	166 (25.4)	514 (25.8)
Race [N (%)]				
Missing	46 (6.9)	44 (6.6)	45 (6.9)	135 (6.8)
White	611 (91.2)	613 (91.9)	594 (91.0)	1818 (91.4)
Black	7 (1.0)	8 (1.2)	14 (2.1)	29 (1.5)
Asian	6 (0.9)	2 (0.3)	0 (0.0)	8 (0.4)
Age [years][2]				
Mean	64.7	65.1	65.2	65.0
Median	65.0	65.0	66.0	65.0
SD	8.6	8.5	8.7	8.6
Min	38.0	41.0	40.0	38.0
Max	90.0	88.0	87.0	90.0
Smoking history [N (%)]				
Ex smoker	416 (62.1)	435 (65.2)	417 (63.9)	1268 (63.7)
Smoker	254 (37.9)	232 (34.8)	236 (36.1)	722 (36.3)
Smoking history [pack years]				
Mean	47.1	48.6	47.6	47.8
Median	42.0	41.5	42.0	42.0
SD	26.9	26.9	26.1	26.6
Min	10.0	10.0	10.0	10.0
Max	250.0	208.0	180.0	250.0
Duration of COPD [years][3]				
Mean	8.3	9.0	9.5	8.9
Median	6.5	7.0	8.0	7.0
SD	6.4	7.4	7.5	7.1
Min	0.0	0.0	0.0	0.0
Max	35.8	48.0	44.0	48.0

1 The percentages may not add up to 100% due to missing data.
2 Calculated from date of birth and date screened
3 Regardless of when COPD diagnosis was made
Obtained from Visit 1, screening visit

Table 99: Protocol 205.9992 (combined studies 205.254 and 205.255) screening PFT data

	Tio R5	Tio R10	Placebo	Total
Number of patients	670	667	653	1990
Pre-bronchodilator FEV_1 [L]				
Mean	1.088	1.088	1.083	1.086
Min	0.25	0.28	0.16	0.16
Max	2.78	3.88	2.44	3.88
Pre-bronchodilator % predicted normal FEV_1 – ECCS				
Mean	38.7	38.5	38.3	38.5
Min	9.6	11.5	11.6	11.5
Max	83.5	91.4	84.5	91.4
Pre-bronchodilator FVC [L]				
Mean	2.589	2.613	2.579	2.594
Min	0.56	0.47	0.19	0.19
Max	5.57	6.28	5.67	6.28
Pre-bronchodilator FEV_1 / FVC [%]				
Mean	43.0	42.6	42.7	42.8
Min	41.7	41.9	42.1	41.9
Max	82.7	85.1	84.2	85.1
Post-bronchodilator FEV_1 [L]				
Mean	1.280	1.278	1.273	1.277
Min	0.20	0.32	0.24	0.20
Max	3.14	4.08	2.80	4.08
Post-bronchodilator[2] % predicted normal FEV_1 – ECCS				
Mean	45.6	45.2	45.2	45.3
Min	11.5	11.9	8.4	8.4
Max	85.1	96.1	101.5	101.5
Post-bronchodilator[2] FEV_1 [L] change from pre-dose[1]				
Mean	0.192	0.189	0.190	0.190
Min	-0.38	-0.71	-0.69	-0.71
Max	1.19	1.34	1.36	1.36
Post-bronchodilator[2] FEV1 % change from pre-dose[1]				
Mean	19.9	19.4	20.8	20.0
Min	-65.5	-48.3	-42.9	-65.5
Max	293.3	158.6	850.0	850.0
Post-bronchodilator[2] FVC [L]				
Mean	2.959	2.960	2.963	2.961
Min	0.98	0.82	1.06	0.82
Max	5.88	6.71	7.83	7.83

1 Obtained from Visit 1, Screening Visit
2 30 minutes after 400µg of albuterol

Reviewer comment:

Baseline characteristics were generally comparable between the two studies, suggesting that combining the data is a scientifically valid approach from the standpoint of the patient population.

Protocol violations

There was no per-protocol analysis for this study; therefore, protocol violations were not used to exclude patients from any analysis. 16.4% of patients overall were determined to have important protocol violations. Of these, there were 57 patients (2.9% of randomized patients) who were determined retrospectively to have not met entry criteria. These deviations were categorized into 5 types: 1) may not have COPD, 2) unstable at the randomization visit, 3) evidence of asthma or allergic rhinitis, 4) have taken marketed Spiriva, and 5) significant other disease which may obscure treatment response. These patients were distributed evenly across the groups.

In addition to these entry criteria violations, there were patients who took a prohibited medication, had an incorrect medication washout, had incorrect dosing at the clinic, took an incorrect trial medication, or were noncompliant. Protocol violations were also recorded for missing data. [Module 5, Volume 1.22, Study report 205.9992, page 75]

Reviewer comment:
The reported protocol violations were distributed evenly across the study groups. Overall, these discrepancies do not affect the integrity of the data.

Treatment compliance

Medication compliance was determined from patient diary data. Overall reported compliance for the study was 96.1% for tio R5, 95.4% for tio R10, and 95.7% for the placebo groups. [Module 5, Volume 1.22, Study report 205.255, page 130, Table 15.1.5: 1]

Concomitant respiratory medications

A total of 83.7% of patients in the study took baseline concomitant respiratory medications. At baseline, 44.6% of patients were taking inhaled short-acting anticholinergics, 29.5% were taking inhaled long-acting ß-agonists, 53.7% were taking short-acting ß-agonists, and 14.9% were taking theophylline preparations. In addition, 53.7% of patients overall were taking inhaled steroids, and 3.1% were taking oral corticosteroids. These baseline respiratory medications were generally balanced among groups. [Module 5, Volume 1.22, Study report 205.9994, pages 89-91]

Pharmacokinetic outcomes

No pharmacokinetic data were collected in this study.

Efficacy outcomes

Primary

The primary endpoints of trough FEV_1 response and the SGRQ were analyzed only for the individual studies.

Reviewer comment:

At the request of the Division, the Applicant provided a subgroup analysis of the primary endpoint, trough FEV_1 for the combined data sets for studies 205.254 and 205.255 for patients both inside and outside of the United States. See Table 100. A significant difference in trough FEV_1 in the tiotropium groups compared to placebo was shown for both US and non-US sites, although the mean treatment difference was slightly lower in US patients compared to non-US patients.

Table 100: Protocol 205.9992 (combined studies 205.254 and 205.255) mean trough FEV_1 response [L] treatment differences on test day 337 for US and non-US sites

	US sites only†	
	tio R5 vs. placebo	**tio R10 versus placebo**
Mean treatment difference [L]	0.117	0.126
Standard error [L]	0.027	0.027
95% confidence interval	0.064, 0.171	0.072, 0.180
p-value	<0.0001	<0.0001
	non-US sites only‡	
Mean treatment difference [L]	0.129	0.154
Standard error [L]	0.015	0.015
95% confidence interval	0.100, 0.157	0.126, 0.183
p-value	<0.0001	<0.0001

†tio R5 (N=107), tio R10 (N=107), placebo (N=89)
‡tio R5 (N=543), tio R10 (N=537), placebo (N=514)

Mahler TDI

The Mahler TDI at the end of 48 weeks of treatment was the third co-primary endpoint. The statistical analysis plan for the studies prespecified that the combined data set would be utilized for the analysis. The Mahler TDI was analyzed for the following component scores: functional impairment, magnitude of task, and magnitude of effort. All 3 treatment groups showed improvement in the adjusted mean TDI focal score at test day 57, with the improvement in the tiotropium groups being approximately double that observed in the placebo group. This improvement was generally maintained for the remainder of the treatment period. The difference between each tiotropium group and placebo was statistically significant (p<0.0001). [Module 5, Volume 1.22, Study report 205.9992, pages 28-31]

Reviewer comment:

Due to fundamental weaknesses of the TDI instrument, this result cannot be utilized to support a dyspnea indication. The company has defined a responder for this endpoint to be a difference of 1 from baseline. The mean difference from placebo ranges from 0.8 to 1.3, suggesting that the clinical meaning of the difference in TDI scores is unknown.

The Applicant is not making labeling claims regarding dyspnea.

COPD exacerbations

The number of COPD exacerbations during the 48 week treatment period was the fourth co-primary endpoint. The statistical analysis plan for the studies prespecifed that the combined data set would be utilized for the analysis. A COPD exacerbation was defined as a complex of respiratory events reported as adverse events with a duration of 3 days or more requiring treatment with antibiotics and/or oral corticosteroids. The change in or requirement of treatment were not defined or initiated by patients in the study. A complex of respiratory events means an increase of symptom or new onset of at least 2 of the following:

- shortness of breath/dyspnea/shallow, rapid breathing
- sputum production (volume)
- occurrence of purulent sputum
- cough
- wheezing
- chest tightness

Since the incidence rates depend on the extent of exposure, the number of COPD exacerbations was calculated per day of extent of exposure for each patient in each treatment group. This analysis was also performed without any adjustment for the number of days the patient was on randomized treatment.

The mean COPD exacerbation rate per patient year for all patients in the study was 0.93 for the tio R5 group, 1.02 for the tio R10 group, and 1.91 for the placebo group. This result is statistically significant for both tiotropium groups compared to placebo (p=0.002 and p=0.0008, respectively). The effect is smaller when not adjusted for treatment days, but is still present.

The number of exacerbations per patient during the treatment period ranged from 0 to 7 for the tiotropium groups and from 0 to 6 for the placebo group. However, there were fewer patients in the tiotropium groups with any exacerbations compared to the placebo group, with 37.2% of the tio R5 group, 36.9% of the tio R10 group, and 44.1% of the placebo group having at least 1 exacerbation. This difference is statistically significant at p=0.0031 and p=0.0028 for tio R5 and tio R10, respectively. Because the majority of patients had no exacerbations, the median number of exacerbations is zero for all treatment groups.

The distribution of intensity of exacerbations was similar within each of the treatment groups with approximately 60% being classed as moderate, 25% as mild, and 15% as severe. The average number of days of corticosteroids per exacerbation was similar for all three treatment groups, 4.5 days. The two tiotropium groups had on average a numerically greater number of days of antibiotic use per exacerbation compared to placebo (tio R5 = 6.7 days, tio R10 = 6.4 days, and placebo 5.4 days). This difference was not statistically significant. There were no differences between the groups in hospitalizations for COPD exacerbations or all cause hospitalizations.

Table 101: Protocol 205.9992 (combined studies 205.254 and 205.255) COPD exacerbations

	Tio R5 N=670	Tio R10 N=667	Placebo N=653
COPD exacerbation rate			
Mean	0.93	1.02	1.91
p-value vs. placebo	0.0020	0.0008	
Number of COPD exacerbations			
Mean	0.66	0.59	0.73
p-value vs. placebo	0.0002	<.0001	
Time to first COPD exacerbation			
Lower Quartile	160	178	86
p-value vs. placebo	<.0001	<.0001	
Number of patients with at least one COPD exacerbation			
N (%)	249 (37.2%)	246 (36.9%)	288 (44.1%)
p-value vs. placebo	0.0031	0.0028	
% of time in COPD exacerbation			
Mean	4.0	3.9	5.6
p-value vs. placebo	0.0089	0.0027	

Reviewer comment:

In general, the definition of COPD exacerbation is appropriate, taking into consideration both symptoms and treatment. The number of days between exacerbations is not specified, which could be a confounding factor. If a patient "recovers" from an exacerbation then has a second exacerbation within a day or two, this likely represents a continuation of the first event rather than a second, distinct exacerbation.

According to the FDA statistical reviewer, Dr. Ruthanna Davi, there were 17 instances of exacerbations with a start date occurring less than 7 days after the ending date of a previous exacerbation. These instances occurred once in each of 9 placebo patients, 3 tio R5 patients, and 5 tio R10 patients. Given the low incidence of such events if a 7-day between exacerbation definition were applied, there would likely be little impact on the results, with a slightly greater benefit seen in the tiotropium groups. Therefore, the limitation in definition as a potential confounder does not bias the outcome of this study.

At the request of the Division, the Applicant provided a subgroup analysis of the primary endpoint, COPD exacerbation rate for the combined data sets for studies 205.254 and 205.255 for patients both inside and outside of the United States. See Table 102. A numerically lower exacerbation rate in the tiotropium groups compared to placebo was shown for both US and

non-US sites. This difference did not reach statistical significance in the US sites, as the sample size was not powered to show this effect in subgroups. Of note, the overall exacerbation rate was lower for all treatment groups in the US compared to non-US sites, although the magnitude of change with tiotropium compared to placebo was similar (21% fewer exacerbations in the US versus 22% outside the US).

Table 102: Protocol 205.9992 (combined studies 205.254 and 205.255) COPD exacerbation rate (per year) and rate ratios for US and non-US sites

Treatment	N	Mean rate [rate ratio]	95% CI	p-value
		US sites		
Tio R5	110	0.62	0.46, 0.84	
Tio R10	107	0.66	0.50, 0.89	
Placebo	99	0.78	0.58, 1.06	
Tio R5 vs. placebo		[0.79]	0.52, 1.21	0.28
Tio R10 vs. placebo		[0.85]	0.56, 1.29	0.44
		Non-US sites		
Tio R5	560	0.81	0.72, 0.92	
Tio R10	560	0.74	0.65, 0.84	
Placebo	554	1.04	0.92, 1.17	
Tio R5 vs. placebo		[0.78]	0.66, 0.93	0.005
Tio R10 vs. placebo		[0.71]	0.60, 0.85	0.0002

Secondary

Secondary efficacy endpoints were not analyzed for the combined data set.

Efficacy summary

The primary endpoints of trough FEV_1 response and the SGRQ were analyzed only for the individual studies. However, a combined subgroup analysis of trough FEV_1 comparing US to non-US patients demonstrated significant improvement in trough FEV_1 in both regions.

The number of COPD exacerbations during the 48 week treatment period was the fourth co-primary endpoint. The mean COPD exacerbation rate per patient year for all patients in the study was 0.93 for the tio R5 group, 1.02 for the tio R10 group, and 1.91 for the placebo group. This result is statistically significant for both tiotropium groups compared to placebo (p=0.002 and p=0.0008, respectively). The effect is smaller when not adjusted for treatment days, but is still present. There were fewer patients in the tiotropium groups with any exacerbations compared to the placebo group, with 37.2% of the tio R5 group, 36.9% of the tio R10 group, and 44.1% of the placebo group having at least 1 exacerbation. This difference is statistically significant at p=0.0031 and p=0.0028 for tio R5 and tio R10, respectively. A numerically lower exacerbation rate in the tiotropium groups compared to placebo was shown for both US and non-US sites. This difference did not reach statistical significance in the US sites, as the sample size was not powered to show this effect in subgroups.

Safety outcomes

Adverse events

Evaluation of the combined adverse events database for Protocols 205.254 and 205.255 reveals an overall dose-related increase in fatal adverse events in the tiotropium groups, with 12 (1.8%) in tio R5, 17 (2.5%), tio R10, and 5 (0.8%) placebo. Of these deaths, no cause was reported for 8 of them, 6 in the tio R10 group and 2 in the placebo group. A more detailed discussion of mortality is located in the Integrated Summary of Safety, Sections 7.1.1 and 7.2.9.1.

The most frequent AEs were COPD exacerbations, nasopharyngitis, upper respiratory tract infections, and dry mouth. Dry mouth was the most common drug related adverse event and was dose related.

There was an overall increase in cardiovascular events in the tiotropium groups, with 7.3% in the tiotropium groups and 5.5% in the placebo groups. This was largely driven by an increase in angina, arrhythmia, and congestive heart failure. Notably, there was no increase in myocardial infarction, atrial fibrillation, or ventricular tachycardia.

There was a dose-related increase in gastrointestinal disorders in the tiotropium groups, with 21.2% tio R5, 28.9% tio R10, and 14.9% of placebo. Dose-related increases in dyspepsia and dry mouth were responsible for the increase.

There was also evidence for dose-related urinary retention, as reflected by dose-related increases in urinary tract infections. Adverse events of urinary retention, urinary tract obstruction, urine flow decrease, and benign prostatic hypertrophy also occurred with increased frequency in the tiotropium groups.

For the respiratory system, a reduced incidence of COPD exacerbation and dyspnea was observed in the tiotropium groups compared to placebo; whereas cough, pneumonia, and nasopharyngitis were slightly increased.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. No particular stroke-related adverse event was definitively increased in the tiotropium groups. Combining terms of cerebral infarction, CVA, transient ischemic attack, and cerebrovascular insufficiency gives 3 events in the tio R5 group, 6 in the tio R10 group, and 3 in the placebo group.

Finally, there were also slight increases in hypertension and headache observed in the tiotropium groups compared to placebo.

Cardiac monitoring

Additional 12-lead ECG monitoring was performed pre-dose and at 5 minutes and 2 hours post-dose at the randomization visit (Visit 2) and at 16 and 40 weeks of treatment (Visits 5 and 8) in a subset of >300 patients from selected sites in protocols 205.254 and 205.255. In these same patients, 24-hour Holter monitoring was performed immediately prior to the randomization visit and at week 16 and 40. Both the ECGs and Holter studies in this subset of patients were centrally read.

Measured ECG parameters included heart rate, PR interval, QRS interval, QT interval, QTc. No clinically significant changes in any of these parameters were observed. Holter monitoring evaluated heart rate, ectopic activity (supraventricular premature beats and ventricular premature beats), and pauses. Again, no clinically significant changes were observed. Evaluation of shift tables for outliers also showed balance between the tiotropium and placebo groups.

Safety conclusions

Evaluation of the combined adverse events database for Protocols 205.254 and 205.255 reveals an overall dose-related increase in fatal adverse events in the tiotropium groups, with 12 (1.8%) in tio R5, 17 (2.5%), tio R10, and 5 (0.8%) placebo. Of these deaths, no cause was reported for 8 of them, 6 in the tio R10 group and 2 in the placebo group.

No new adverse event signals emerge on combination of data from Protocols 205.254 and 205.255. The most common adverse events were COPD exacerbations, nasopharyngitis, upper respiratory tract infection, and dry mouth. Evidence of dose-related increases in dry mouth, dyspepsia, and urinary tract infections occurred. There were small increases in cardiovascular events (angina, arrhythmia, and congestive heart failure), cough, pneumonia, nasopharyngitis, hypertension, and headache in the tiotropium groups compared to placebo. Adverse events of COPD exacerbation and dyspnea occurred more frequently in the placebo group.

12-lead ECG monitoring in a subset of >300 patients from selected sites showed no clinically significant changes in heart rate, PR interval QRS interval, QT interval, and QTc in the tiotropium groups compared to placebo. Holter monitoring over 24 hours likewise showed no evidence of change in heart rate, ectopic activity, or pauses.

10.1.6.3 Discussion and conclusions

The primary endpoints of trough FEV_1 response and the SGRQ were analyzed only for the individual studies. However, a combined subgroup analysis of trough FEV_1 comparing US to non-US patients demonstrated significant improvement in trough FEV_1 in both regions.

The number of COPD exacerbations during the 48 week treatment period was the fourth co-primary endpoint. The mean COPD exacerbation rate per patient year for all patients in the study was 0.93 for the tio R5 group, 1.02 for the tio R10 group, and 1.91 for the placebo group. This result is statistically significant for both tiotropium groups compared to placebo (p=0.002 and p=0.0008, respectively). The effect is smaller when not adjusted for treatment days, but is still present. There were fewer patients in the tiotropium groups with any exacerbations compared to the placebo group, with 37.2% of the tio R5 group, 36.9% of the tio R10 group, and 44.1% of the placebo group having at least 1 exacerbation. This difference is statistically significant at p=0.0031 and p=0.0028 for tio R5 and tio R10, respectively. A numerically lower exacerbation rate in the tiotropium groups compared to placebo was shown for both US and non-US sites. This difference did not reach statistical significance in the US sites, as the sample size was not powered to show this effect in subgroups.

Evaluation of the combined adverse events database for Protocols 205.254 and 205.255 reveals an overall dose-related increase in fatal adverse events in the tiotropium groups, with 12 (1.8%) in tio R5, 17 (2.5%), tio R10, and 5 (0.8%) placebo. Of these deaths, no cause was reported for 8 of them, 6 in the tio R10 group and 2 in the placebo group.

No new adverse event signals emerge on combination of data from Protocols 205.254 and 205.255. The most common adverse events were COPD exacerbations, nasopharyngitis, upper respiratory tract infection, and dry mouth. Evidence of dose-related increases in dry mouth, dyspepsia, and urinary tract infections occurred. There were small increases in cardiovascular events (angina, arrhythmia, and congestive heart failure), cough, pneumonia, nasopharyngitis, hypertension, and headache in the tiotropium groups compared to placebo. Adverse events of COPD exacerbation and dyspnea occurred more frequently in the placebo group.

12-lead ECG monitoring in a subset of >300 patients from selected sites showed no clinically significant changes in heart rate, PR interval QRS interval, QT interval, and QTc in the tiotropium groups compared to placebo. Holter monitoring over 24 hours likewise showed no evidence of change in heart rate, ectopic activity, or pauses.

10.2 Line-by-Line Labeling Review

The labeling review is found under Section 9.4.

11 REFERENCES

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3. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone piorpionate or tiotropium bromide. Journal of Respiratory and Critical Care Medicine 2008; 177:19-26.

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5. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2007.
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6. Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St. George's Respiratory Questionnaire in bronchiectasis. American Journal of Respiratory and Critical Care Medicine 1997; 156:536-541.

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/s/

Theresa M Michele
7/31/2008 11:19:17 AM
MEDICAL OFFICER

Sally Seymour
7/31/2008 11:25:18 AM
MEDICAL OFFICER
I concur.

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION:	NDA 21-936	**TRADE NAME:**	Spiriva® Respimat
APPLICANT/SPONSOR:	Boehringer Ingelheim	**USAN NAME:**	Tiotropium bromide
MEDICAL OFFICER:	Theresa M. Michele, M.D.		
TEAM LEADER:	Charles E. Lee, M.D.	**CATEGORY:**	Anticholinergic bronchodilator
DATE:	December 20, 2007	**ROUTE:**	Inhaled

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
Nov 16, 2007	Nov 16, 2007	NDA 21-936, N-000	Electronic NDA submission

RELATED APPLICATIONS

Document Date	Application Type	Comments
June 28, 2002	IND 65,127	Initial IND
Dec 29, 2004	IND 65,127 and 46,687	General Correspondence regarding addition of dyspnea to the product label
April 20, 2005	IND 65,127	Pre-NDA meeting minutes
Oct 21, 2005	IND 65,127	Type C meeting minutes, pediatric indication for cystic fibrosis
June 2, 2006	IND 65,127	Drug Safety Oversight Board meeting minutes, mortality signal
Nov 30, 1994	IND 46,687	Tiotropium inhalation powder using HandiHaler
Dec 12, 2001	NDA 21-395	Tiotropium inhalation powder using HandiHaler

REVIEW SUMMARY:

This NDA is an application for an inhalation spray formulation of tiotropium bromide. The applicant is Boehringer Ingelheim Pharmaceuticals, Inc. The drug is a long-acting anticholineric being developed for treatment of COPD The product is intended for use with the Respimat inhaler at a dose of 5 mcg (2 inhalations) once daily. The proposed indication, once-daily maintenance treatment of brochospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, is the same as that of another tiotropium formulation, Spiriva HandiHaler. The application is a combination paper and electronic submission.

Tiotropium Respimat was developed as a new inhalational product with a stand-alone clinical program. The applicant's drug development program included 4 pivotal clinical efficacy and safety studies, 4 supportive clinical efficacy and safety studies, and 2 PK/PD studies. The pivotal trials consisted of 2 sets of replicative studies each analyzed separately as well as with combined data. The study reports are appropriately indexed and organized to allow review. The applicant has provided an Integrated Summary of Safety, Integrated Summary of Efficacy, copies of proposed labeling, and appropriate case report forms and case report tabulations. A brief review of the proposed labeling reveals that a new claim for preventing COPD exacerbations is present which will need to be supported. A potential safety signal of excess mortality in the tiotropium-treated groups was observed in the two replicative 48 week trials. This will be the subject of detailed clinical review, including a safety consult and an Advisory Committee meeting.

The submission is adequate to allow for clinical review. The submission is filable. Additional information regarding tiotropium safety data will be requested from the sponsor.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	**FILABLE**___X____	**NOT FILABLE**_____	
	APPROVAL_____	**APPROVABLE**_____	**NOT APPROVABLE**_____
OTHER ACTION:	**COMMENTS FOR SPONSOR**_____X_		

1. GENERAL INFORMATION

Tiotropium bromide dry powder inhaler (HandiHaler inhalation device, 18 mcg tiotropium) was approved on January 30, 2004 (NDA 21-395) for the long-term, once-daily maintenance treatment of brochospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The applicant, Boehringer Ingelheim Pharmaceuticals, Inc., seeks to develop tiotropium bromide as an inhalation spray delivered via the Respimat device. The proposed indication for Spiriva Respimat is the same as for the Handihaler. The proposed dose is two inhalations once daily for a total dose of 5 mcg (2.5 mcg/actuation). Tiotropium is a specific antagonist at muscarinic acetylcholine receptors, often called anticholinergic.

The product is contained in a plastic container that is crimped into an aluminum cylinder forming a cartridge. The inhalation solution is a sterile aqueous solution of tiotropium bromide monohydrate and two excipients, benzalkonium chloride (BAC) and edetate disodium (EDTA). The pH of the solution is adjusted with hydrocholoric acid (b) (4). The Respimat is a hand-held, pocket-sized, multi-dose, oral inhalation device that generates a slow-moving aerosol cloud of medication from the aqueous solution. The Respimat cartridge allows 60 actuations (30 doses, following priming). The solution is expelled mechanically rather than by a propellant gas. The delivery device provides both a dose indication and a locking mechanism after the declared number of doses to prevent tail-off of dosing. [Module 2, Section 2.2, page 1]

The application is provided both electronically and in paper.

2. CLINICAL DEVELOPMENT PROGRAM

Tiotropium Respimat was developed as a new inhalational drug product with a stand-alone clinical program. A total of 2050 COPD patients were treated with tiotropium in the clinical program for tiotropium Respimat. There were 1064 patients from this total who received the 5 mcg dose of tiotropium proposed for marketing in this application. Of these 670 patients were treated for up to 48 weeks. [Module 2, Section 2.5., page 8]

There were 10 clinical trials conducted with tiotropium Respimat that are included in the original NDA submission. These studies are briefly described below. [Module 2, Section 2.5, page 10]

There were 4 clinical efficacy and safety studies considered by the applicant to be pivotal in their drug development program. These trials are grouped into two replicative protocols.

- 205.251 and 205.252: 12-week comparison of the safety and efficacy of tiotropium Respimat (5 mcg and 10 mcg) to ipatropium bromide (active comparator) and placebo in patients with COPD
- 205.254 and 205.255: 48 week comparison of the safety and efficacy of tiotropium Respimat (5 mcg and 10 mcg) to placebo in patients with COPD; additional vital status information on prematurely withdrawn patients is listed under protocol 205.392

Reviewer comment:

The pivotal clinical studies will be reviewed in depth in the NDA clinical review. Of note, a mortality signal was observed in the 48-week studies in favor of placebo. This issue was discussed at an advisory board meeting of the Drug Safety Oversight Committee and also with the sponsor at a Type A meeting. It was determined in these meetings that no safety signal existed for Spiriva Handihaler (a marketed product) and additional follow up data should be gathered on patients with early discontinuations from the 205.254 and 205.255 trials to determine if differential discontinuation may have been a confounding factor. Potential mortality signals will be specifically addressed in the NDA review, and a consult to the internal safety review team will be placed. In addition, an Advisory Committee meeting will be convened to address this issue.

There were 4 supportive clinical efficacy and safety studies in the applicant's drug development program. Two of these were replicative trials. In addition, in the 4-month NDA Safety Update, the applicant plans to submit clinical study reports for 3 additional trials completed with tiotropium Respimat as part of other programs and the final follow up data from the 48 week studies (205.392). In addition, a study conducted solely with tiotropium Handihaler in a Veteran's Affairs setting is being used to support an efficacy claim for reduced exacerbations. Supportive clinical efficacy and safety studies submitted with the NDA include:

- 205.127: 3-week dose ranging pharmacokinetic trial to investigate 5 doses of tiotropium Respimat (1.25, 2.5, 5.0, 10.0, and 20.0 mcg) versus tiotropium Handihaler (active control) and placebo in patients with COPD
- 205.248: single dose safety and tolerability study of tiotropium Respimat in patients with asthma
- 205.249 and 205.250: 4-week crossover non-inferiority and pharmacokinetic trial of tiotropium Respimat (5 and 10 mcg) versus Handihaler (18 mcg) versus placebo in patients with COPD
- 205.266: 6-month parallel group study of tiotropium Handihaler (18 mcg) versus placebo assessing exacerbations and hospitalizations in patients with COPD in a Verterans Affairs setting

Studies to be provided in the 4-month NDA Safety Update:

- 1205.4 and 1205.6: Phase 2 dose ranging studies for BEA 2180 using tiotropium Respimat 5 mcg as active comparator in patients with COPD
- 205.291: Phase 2 crossover trial conducted in Japan for efficacy and safety of tiotropium Respimat (5 mcg) versus Handihaler (18 mcg) in patients with COPD

Reviewer comment:

The supporting clinical efficacy and safety studies will receive abbreviated reviews in the NDA clinical review.

There were 2 PK and PD studies in the applicant's drug development program:

- 205.112: 14-day placebo-controlled study to establish the safety, tolerability, and PK of multiple increasing doses of tiotropium Respimat (10, 20, and 40 mcg) in healthy subjects
- 205.138: single dose placebo-controlled study to establish the safety and tolerability of ocular administration of tiotropium (0.02, 0.04, 0.08, 0.16, 0.28, 0.40 mcg) in healthy subjects

Reviewer comment:

The ocular safety study will receive a focused review. In addition, the safety data from the 2 PK studies will be reviewed as part of the NDA clinical review of the Integrated Safety Summary.

3. FOREIGN MARKETING AND REGULATORY HISTORY

The HandiHaler formulation of tiotropium bromide was approved on January 30, 2004 for the chronic treatment of bronchospasm associated with COPD, and is marketed worldwide.

The applicant's opening IND for the Respimat was submitted on June 28, 2002 (IND 65,127). A type C meeting was held with the sponsor on December 29, 2004 to discuss the possibility of a labeled indication for relief of dyspnea in COPD patients. Although the sponsor addressed many of the concerned raised by the DPAP Advisory Committee meeting held on September 6, 2002, the self-administered computerized Mahler Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) the Division advised the applicant that this instrument could not be utilized to support a dyspnea indication due to fundamental inherent weaknesses of the instrument. A pre-NDA was held with the sponsor in April 2005.

In March 2004, the applicant submitted a Type A meeting request regarding a potential mortality signal in the tiotropium Respimat 48 week trials. Because there was a marketed product containing the same drug product (tiotropium HandiHaler), this issue was reviewed by the Drug Safety Oversight Board on June 15, 2006. The committee concluded that "the potential safety signal for Spiriva Respimat is weak because the signal is present in one of two very similar studies (study 225) and the rate of death in the placebo group of study 225 was zero, a very unusual finding in a COPD population. The difference in mortality seen in study 225 is likely due to this unusually low mortality rate in the placebo group. The causes of death show no sensible pattern and the HandiHaler data are reassuring."

On December 4, 2007 the Division denied a submission by the sponsor to issue a pediatric Written Request for tiotropium Respimat (b) (4) .

As of November 2, 2007, registration dossiers for tiotropium Respimat have been submitted to 31 countries. The Decentralized Procedure in the European Union was successfully completed no July 24, 2007 with a positive opinion in all 25 participating countries. So far 10 European countries have issued national approval documents, the earliest of which occurred on August 20, 2007. In addition, applications are under regulatory review in Australia, Canada, Switzerland, South Africa Japan, and Turkey. Tiotropium Respimat has not been withdrawn from the market for any reason nor have any applications been withdrawn for any reason.

4. ITEMS REQUIRED FOR FILING (21 CFR 314.50)

The following items pertinent to a clinical review are included in the submission:

- Application form (FDA 356h) [Paper Module 1, Section 1.1.2] [356h.pdf]
- Index [Paper Module 2, Vol 1.1] [summary\summarytoc.pdf, clinstat\clintoc.pdf, hpbio\hpbiotoc.pdf, crf\crftoc.pdf, crt\datatoc.pdf]
- Summary [Paper Module 2, Vol 1.1, Sections 2.2 and 2.5] [summary\introduction.pdf, summary\clinicaloverview.pdf]
- Clinical technical section
  - Clinical study reports
    - Reports of human pharmacokinetic studies [Paper Module 5, Vol 1.1] [*see hpbio\hpbiotoc.pdf]*
    - Reports of human pharmacodynamic studies [Paper Module 5, Vol 1.2] [*see hpbio\hpbiotoc.pdf*]
    - Reports of efficacy and safety studies [Paper Module 5, Vol 1.3-1.19] [*see clinstat\clintoc.pdf*]
    - Reports of analyses of data from more than one study [Paper Module 5, Vol 1.20-1.25] [*see clinstat\clintoc.pdf*]
    - Report of Respimat device handling studies [Paper Module 5, Vol 1.2] [*see hpbio\hupharm.pdf*]
  - Other pertinent data
      - Handihaler post-marketing safety data October 2003-June 2005 (PSUR) [Paper Module 5, Vol 1.25] [clinstat\copd\u05-3295.pdf]
      - Handihaler clinical trial data summary of safety through May 2006 [referenced in submission, available in EDR May 31, 2006 document date]
  - Integrated summary of efficacy [Paper Module 2, Vol 1.2, Section 2.7.3] [summary\clinical\efficacysum.pdf]
  - Integrated summary of safety
    - Integrated summary of safety [Paper Module 2, Vol 1.2, Section 2.7.4] [Summary\clinical\safetysum.pdf]
    - Abuse and overdose information [Paper Module 2, Vol 1.2, Section 2.7.4, page 122] [Summary\clinical\safetysum.pdf]
    - Risk/benefit analysis
    - Good Clinical Practice certification [Paper Module 2, Vol 1.1, Section 2.5, page 11] [summary\clinicaloverview.pdf]
  - Debarment certification [Paper Module 1, Vol 1.1, Section 1.33] [other\debar.pdf]
  - Pediatric use [Paper Module 1, Vol 1.1, Section 1.9.1] [other\pediwaiver.pdf]

- Labeling [Paper Module 1, Vol 1.1, Section 1.14.1.2 and 1.14.1.3] [labeling\annotatedpi.pdf, labeling\spl\spirivarespimat.xml, labeling\proposed.doc]
- Case report forms [crf\crftoc.pdf, crt\datatoc.pdf]
- Financial disclosure [Paper Module 1, Vol 1.1, Section 1.3.4] [other\financial.pdf]

Reviewer comment:

The applicant has requested a waiver of pediatric studies on the grounds that COPD is a disease of adults. (b) (4) *; however, the Division denied a request to issue a Pediatric Written Request* (b) (4) (b) (4)

Although tiotropium Respimat was recently approved in 10 European countries, it is unlikely that any meaningful marketing data are available in so short a time. However, any available data at the time of the 4 month safety update will be requested.

No literature review is presented. Although pertinent literature was reviewed as part of the Handihaler NDA, literature from the interim period (December 2001 to present) will be requested.

Because of the potential mortality signal, available data from the Handihaler program will be reviewed. This will include a Periodic Safety Update Report (October 2003-June 2005) provided as part of this NDA and an additional summary of death safety data submitted to the Respimat IND on May 31, 2006. However, no data from May 2006-present were submitted. A summary of safety data from Handihaler clinical trials with a cut off date of November 2007 will be requested, including any data regarding cardiovascular adverse events. In addition, a large, Phase 4, 4-year clinical trial (UPLIFT) comparing tiotropium Respimat with Advair (salmeterol/fluticasone propionate) is nearing completion. Any available data from this trial will be requested.

5. CLINICAL STUDIES

There were 4 clinical efficacy and safety studies considered by the applicant to be pivotal in their drug development program. The clinical review of this application will focus on these studies, which will be reviewed in depth. In addition, the in-depth review will include combined data from the two 12-week studies, combined data from the two 48-week studies, and additional follow up safety data from subjects discontinued from the 48-week studies. The study reports are appropriately indexed to allow review.

Brief descriptions of each clinical study provided in the submission are listed in Section 2. Clinical development program. More detailed summaries of the pivotal trials are provided in Sections 5.1. and 5.2.

5.1. Pivotal 12 week efficacy and safety studies

5.1.1. Study 205.251

Study 205.251 was a 12 week randomized, double-blind, placebo and active controlled parallel group efficacy and safety comparison of two doses (5 mcg and 10 mcg) of tiotropium Respimat (tio R) in subjects with COPD. Both placebo and ipatropium bromide (36 mcg QID) control groups were included. The study was conducted in 39 different centers in 4 countries (Germany, Italy, Switzerland, and South Africa). A total of 361 male and female subjects with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 88 in the tio R 5 group, 93 in the tio R 10 group, 89 in the ipratropium group, and 91 in the placebo group. Of these, 320 (88.6%) completed the study. Efficacy endpoints included FEV_1 (trough, AUC, peak, onset and duration of response, percent responders), FVC (trough, $AUC_{0\text{-}6h}$, peak), twice daily peak expiratory flow rates (PEFR), rescue medication use, COPD symptoms, and global evaluations. Safety endpoints included adverse events, vital signs, laboratory evaluations, ECG testing and physical examinations. Significant improvements compared to placebo were observed for both doses of tiotropium and ipratropium for FEV_1, FVC, and rescue salbutamol use. Both tio R 5 and tio R 10 were superior to ipatropium for trough FEV_1, and were superior to placebo for PEFR. Small improvements in COPD symptom scores and physician global evaluations were observed. A total of 7.5% of subjects (27) were discontinued due to an adverse event, most commonly COPD exacerbation. Overall, 5.3% of subjects had serious adverse events, most commonly in the iprotropium group (9.0%), followed by tioR10 (5.4%), placebo (4.4%), and tio R 5 (2.3%). One death occurred in the tio R 10 group due to a COPD exacerbation with respiratory failure. [Module 5, Volume 1.6, Study report 205.251, page 5-9]

5.1.2. Study 205.252

Study 205.252 had identical design to Study 205.251. The study was conducted in 25 different centers in the United States and Canada. A total of 358 male and female subjects with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 92 in the tio R 5 group, 87 in the tio R 10 group, 89 in the ipratropium group, and 90 in the placebo group. Of these, 312 (87.2%) completed the study. Significant improvements compared to placebo were observed for both doses of tiotropium and ipratropium for FEV_1, FVC, PEFR, and rescue salbutamol use. There were no treatment differences in COPD symptoms or the physician's global evaluation. Both tio R 5 and tio R 10 were superior to ipatropium for trough FEV_1 and PEFR. A total of 9.5% of subjects (34) were discontinued due to an adverse event, most commonly COPD exacerbation. Overall, 4.7% of subjects had serious adverse events, most commonly in the iprotropium group (10.1%), followed by tioR10 (5.7%), tio R 5 (2.2%), and placebo (1.1%). Three deaths occurred, one in the tio R 10 group due to a cardiac arrest in the setting of hospitalization for COPD exacerbation, one in the ipratropium group due to metastatic pancreatic carcinoma, and one in the placebo group due to complications related to a lung neoplasm. [Module 5, Volume 1.9, Study report 205.252, page 4-9]

5.2. Pivotal 48 week efficacy and safety studies

5.2.1. Study 205.254

Study 205.254 was a randomized, double-blind, placebo controlled, parallel group efficacy and safety comparison of one year treatment of two doses of tiotropium Respimat (5 and 10 mg) in subjects with COPD. The study was conducted in 77 different centers in 14 countries (Europe and North America). A total of 983 male and female subjects with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 332 in the tio R 5 group, 332 in the tio R 10 group, and 319 in the placebo group. Of these, 782 (79.6%) completed the study. Study endpoints included FEV_1 (trough, $AUC_{0\text{-}3h}$, peak), health-related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ), Malher Transition Dyspnea Index (TDI), COPD exacerbations, FVC (trough, AUC, peak), twice daily peak expiratory flow rates (PEFR), rescue medication use, COPD symptoms, global evaluations, and COPD hospitalizations. Trough FEV_1 after 48 weeks of treatment and the SGRQ after 48 weeks of treatment were co-primary endpoints. TDI and COPD exacerbations were also prespecified as 3rd and 4th co-primary endpoints for combined data from Studies 205.254 and 205.255. Safety endpoints included adverse events, vital signs, laboratory evaluations, ECGs, Holter testing, and physical examinations. Both doses of tio R showed significant improvements compared to placebo in the co-primary endpoints. Secondary endpoints of FEV_1 on other test days, SGRQ on other test days, TDI, PEFR, rescue medication use, daily symptom scores (wheezing and shortness of breath), physician's global evaluation, and patient's global rating were improved compared to placebo. Dry mouth was the most common adverse event and the incidence was dose-related, 5.4% in the tio R 5 group and 14.8% in the tio R 10 group. A total of 11.2% of subjects (111) were discontinued due to an adverse event, most commonly COPD exacerbation, and 152 subjects reported serious adverse events. Both discontinuations due to adverse events and serious adverse events occurred less frequently in the active treatment groups. Twenty deaths occurred in the study (7 in the tio R 5 group, 8 in the tio R 10 group, and 5 in the placebo group).

5.2.2. Study 205.255

Study 205.255 had an identical design to Study 205.254. The study was conducted in 79 different centers in 15 countries (Europe, North America, Africa, and Australia). A total of 1007 male and female subjects with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 338 in the tio R 5 group, 335 in the tio R 10 group, and 334 in the placebo group. Of these, 752 (74.7%) completed the study. Both doses of tio R showed significant improvements compared to placebo in the co-primary endpoints. Secondary endpoints of FEV_1 on other test days, SGRQ on other test days, TDI, PEFR, rescue medication use, daily symptom scores (shortness of breath), physician's global evaluation, and patient's global rating were improved compared to placebo. Dry mouth was the most common adverse event and the incidence was dose-related, 8.9% in the tio R 5 group and 14.3% in the tio R 10 group. A total of 15.3% of subjects (154) were discontinued due to an adverse event, most commonly COPD exacerbation, and 191 subjects reported serious adverse events. Both discontinuations due to adverse events and serious adverse events occurred less frequently in the active treatment groups. Fourteen deaths occurred in the study (5 in the tio R 5 group, 9 in the tio R 10 group, and none in the placebo group). [Module 5, Volume 1.14, Study Report 205.255, pages 3-7]

6. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission. [Module 1, Volume 1, Section 1.14] A brief review of the proposed labeling was performed. In general, wording of the proposed label is identical to that of Spiriva Handihaler, an approved product, with substitution of appropriate Respimat data. Labeling comments are noted below.

1. The Clinical Studies section includes a COPD exacerbations claim. The sponsor states that the proposed claim is supported by combined data from the 48-week studies (205.254 and 205.255) in addition to the VA study conducted with the Handihaler (205.266). Support for this claim will be a review issue that will also be discussed at the Advisory Board meeting.
2. The Adverse Reactions Section does not mention death.

7. DSI REVIEW AND AUDIT

A request for DSI consultation will be submitted. The consultation request will include the following sites identified for inspection:

1. Eugen Shmelev, MD (Site #07402, Study 205.254)
   City Clincial Hospital N11
   6 Dvintsev Str
   127018 Moscow, Russia

This site was the second highest enroller for the pivotal 48 week Study 205.254, with 48 subjects. In addition, this site had the largest number of unexplained deaths in the study (4 deaths, 3 of which were unexplained). All deaths occurred in tiotropium Respimat groups.

2. K Scott Miller, MD (Site #12, Study 205.252; Site #01512, Study 205.255)
   Lowcountry Lung and Critical Care PA
   9150-B Medcom St.
   Charleston, SC 29406-7108

This site was the high enroller for the pivotal 12 week Study 205.252, with 27 subjects. In addition, this site was also the highest US enroller for the pivotal 48 week Study 205.255, with 27 subjects.

8. SUMMARY

This NDA is an application for an inhalation spray formulation of tiotropium bromide. The applicant is Boehringer Ingelheim Pharmaceuticals, Inc. The drug is a long-acting anticholineric being developed for treatment of COPD The product is intended for use with the Respimat inhaler at a dose of 5 mcg (2 inhalations) once daily. The proposed indication, once-daily maintenance treatment of brochospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, is the same as that of another tiotropium formulation, Spiriva Handihaler. The application is a combination paper and electronic submission.

Tiotropium Respimat was developed as a new inhalational product with a stand-alone clinical program. The applicant's drug development program included 4 pivotal clinical efficacy and

safety studies, 4 supportive clinical efficacy and safety studies, and 2 PK/PD studies. The pivotal trials consisted of 2 sets of replicative studies each analyzed separately as well as with combined data. The study reports are appropriately indexed and organized to allow review. The applicant has provided an Integrated Summary of Safety, Integrated Summary of Efficacy, copies of proposed labeling, and appropriate case report forms and case report tabulations. A brief review of the proposed labeling reveals that a new claim for preventing COPD exacerbations is present which will need to be supported. A potential safety signal of excess mortality in the tiotropium-treated groups was observed in the two replicative 48-week trials. This will be the subject of detailed clinical review, including a safety consult and a Scientific Advisory Board meeting.

The submission is adequate to allow for clinical review. The submission is filable. Additional information regarding tiotropium safety data will be requested from the sponsor.

9. REVIEW TIMELINE

The schedule for review is provided in Table 1. Write-up will be concomitant with the review process. Clinical review will focus initially on the pivotal clinical studies, followed by supportive clinical studies, integrated summary of efficacy, integrated summary of safety, and additional safety data from the Handihaler program. The review will culminate with the proposed label. The initial draft review will be complete by June 11, 2008, and the review will be finalized July 16, two months in advance of the action date.

Table 1: Review timeline for NDA 21-936

Milestone	Target date for completion
Pivotal 12 week study 205.251	January 22, 2008
Pivotal 12 week study 205.252	February 5, 2008
Combined data sets from 205.251 and 205.252	February 12, 2008
Pivotal 48 week study 205.254	February 26, 2008
Pivotal 48 week study 205.255	March 12, 2008
Combined data sets from 205.254 and 205.255	March 19, 2008
Supportive clinical studies 205.127, 205.248, 205.249, and 205.250	April 4, 2007
Clinical pharmacology study 205.138	April 9, 2007
Midcycle review	April 16, 2008
Studies provided in 4 month update 1205.4, 1205.6, and 205.291	April 23, 2008
Integrated Summary of Efficacy	May 7, 2008
Integrated Summary of Safety	May 21, 2008
Handihaler safety data and literature review	May 31, 2008
Label review	June 4, 2008
Initial draft review complete	June 11, 2008
Advisory Committee meeting	June—date to be determined
Final draft review complete	July 9, 2008
Final review complete	July 16, 2008
Sponsor teleconference	July 29, 2008
Division goal date	September 2, 2008
PDUFA Action date (10 months)	September 16, 2008

10. COMMENTS FOR THE SPONSOR

The following comments are to be communicated to the sponsor.

Please supply the following information for utilization in the review process of your application:

- *Any post-marketing safety data for tiotropium Respimat available at the time of the 4 month safety update*
- *Literature review for tiotropium from the time of the tiotropium Handihaler NDA (December 2001) to the present*
- *Any available PSUR documents containing information from July 2005 to the present*
- *Summary of tiotropium Handihaler safety data from controlled clinical trials with a cut off date of July 2007 or later. Specific emphasis should be placed on mortality and cardiovascular adverse events. In addition, please provide a complete clinical study report for any trials focusing on cardiac outcomes.*
- *Any available data from the UPLIFT trial.*

Reviewed by:

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Theresa M. Michele, M.D.
Medical Officer, Division of Pulmonary and Allergy Products

_____
Charles E. Lee, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Products

cc: Original NDA
HFD-570/Division File
HFD-570/Lee/Medical Team Leader
HFD-570/Chowdhury/Director
HFD-570/Michele/Medical Reviewer
HFD-715/Davi/Biometrics Reviewer
HFD-570/Pei/Pharmacology-Toxicology Reviewer
ONDQA/Peri/CMC Reviewer
OCP/Suarez/Clinical Pharmacology Reviewer
HFD-570/Raggio/CS

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/s/

Theresa M Michele
1/16/2008 11:30:52 AM
MEDICAL OFFICER

Charles Lee
1/16/2008 02:25:18 PM
MEDICAL OFFICER
I concur.