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DIVISION MEMORANDUM

Date: October 21, 2009

From: Sally Seymour, MD
Deputy Director for Safety, Division of Pulmonary and Allergy Products

To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for an efficacy supplement for NDA# 21-395, for the approved product Spiriva HandiHaler (tiotropium bromide inhalation powder), for the reduction in exacerbations in patients with chronic obstructive pulmonary disease (COPD)

Introduction

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on November 19, 2009. As members of the PADAC you provide important expert scientific advice and recommendation to the US Food and Drug Administration (the Agency) on various regulatory decisions including new claims for drugs already marketed in the United States. The upcoming meeting is to discuss the supplemental NDA from Boehringer Ingelheim (BI) to add a labeling claim for the reduction in exacerbations in patients with chronic obstructive pulmonary disease (COPD) to the labeling for Spiriva HandiHaler (tiotropium bromide inhalation powder). The discussion will also include recent safety concerns with Spiriva HandiHaler including stroke, myocardial infarction, and cardiovascular death that have been cited in the public domain recently.

Spiriva HandiHaler is approved for the long term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. On November 17, 2008, BI submitted an efficacy supplement for Spiriva HandiHaler to add the following labeling claims to the product label: a) reduction in COPD exacerbations; b) description of long-term effects on lung function; c) reduction in mortality; and d) reduction in respiratory failure. Only one other medication, Advair Diskus, currently has a labeling claim and indication for a reduction in COPD exacerbations.

To support the proposed labeling claims, BI submitted the results of a 4-year, placebo-controlled, parallel group trial in approximately 6000 patients with moderate-severe COPD. The trial is called Understanding Potential Long-term Impacts on Function with Tiotropium or UPLIFT (Study 205.235). In addition, BI referenced another clinical trial with Spiriva HandiHaler, a VA study (Study 205.266) that had been previously submitted to the Agency. On July 22, 2009, BI amended the efficacy supplement to remove the mortality claim to maintain consistency with global labeling. According to BI, there was no new Spiriva HandiHaler data contributing to this decision.

This memorandum summarizes the contents of the Agency background material and the key issues and questions for discussion at the meeting. The focus is primarily on the COPD

exacerbation data and the safety issues of stroke, MI, and cardiovascular death, which are introduced in the next section. For completeness, the safety discussion will also include some data from a new inhalation solution formulation of tiotropium bromide that is under development, Spiriva Respimat.

The briefing package includes the following: clinical briefing document, statistical briefing document, epidemiology review, and reference articles. The materials prepared by the Agency contain findings and opinions based on reviews of information submitted by BI. These background materials represent preliminary findings, and do not represent the final position of the Agency. An important piece in our decision on this application will be the opinions and input that we receive from you at this meeting.

Background

Spiriva HandiHaler consists of tiotropium bromide in a dry powder formulation contained in capsules and administered with the HandiHaler inhalation device. Spiriva HandiHaler was approved on January 30, 2004, for the long term, once-daily, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Tiotropium bromide is a long acting anticholinergic and is a bronchodilator medication. A new inhalation solution formulation of tiotropium bromide, Spiriva Respimat, is under development and some safety information from that program will be included in this memo and briefing package. It is also important to note a related product, ipratropium bromide, which is a short acting anticholinergic that has been approved as a bronchodilator for patients with COPD since 1986. The safety profile of tiotropium is well-defined with known side effects related to the anticholinergic effects including dry mouth, constipation, and urinary retention. However, it is not unusual for safety signals to be identified post-marketing and recently several safety concerns with Spiriva HandiHaler have been raised as outlined below.

In November 2007, BI voluntarily submitted a document to the Agency that described a potential stroke safety signal with tiotropium. As part of routine safety monitoring, BI pooled safety data from clinical trials with tiotropium and noted a numerical increase in stroke adverse events. The pooled data included results from 29 controlled clinical trials – 25 with Spiriva HandiHaler and 4 with Spiriva Respimat, which reflected 13,544 patients contributing 4572 person years of exposure to tiotropium. Based upon BI's analysis, there was a numerical increase in the risk ratio for stroke of 1.37 (95% CI: 0.73, 2.56) with use of tiotropium. Although there is uncertainty of the risk, because of the seriousness of stroke and the Agency's commitment to inform the public about ongoing safety reviews, on March 18, 2008, the Agency released an Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler) that described the preliminary information regarding stroke¹.

In September 2008, a meta-analysis was published in the *Journal of the American Medical Association* evaluating cardiovascular risk of inhaled anticholinergics². The inhaled

¹<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm070651.htm>

² Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease – A systematic review and meta-analysis. *JAMA* 2008; 300(12): 1439-1450. Correction: *JAMA* 2009; 301(12): 1227-1230.

anticholinergics included in the analysis were tiotropium and ipratropium. The authors analyzed 17 randomized, controlled clinical trials for the primary combined outcome of cardiovascular death, myocardial infarction (MI), or stroke, and showed a relative risk of 1.58 (95% CI 1.21, 2.06) for inhaled anticholinergics compared to placebo and concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke.

Also of interest is the Lung Health Study, which the NIH initiated in 1986 to evaluate whether smoking intervention and use of inhaled bronchodilator (ipratropium bromide) could slow the rate of decline in FEV₁ in smokers. The Lung Health Study was a large, multicenter, randomized clinical trial, sponsored in 5887 smokers³. Patients were randomized to smoking intervention plus ipratropium, smoking intervention plus placebo, or usual care and were followed for years. One notable finding was a potential signal of an increase in cardiovascular deaths in the ipratropium group compared to the placebo group. However, there was no dose effect and the results were not adjusted for multiplicity. In addition, BI raised the issue that cardiovascular deaths were primarily noted in patients who were not compliant with study medication⁴. While the Lung Health Study was conducted with ipratropium, it is of interest because it is included in some of the published meta-analyses of inhaled anticholinergics.

As you review the briefing documents, you will hear more about the potential safety signals with tiotropium. Part of the focus of this meeting will be to discuss the potential safety signals. We ask that you weigh the strength of the evidence of the potential safety signals and whether the data from UPLIFT are adequate to address these signals.

Clinical/Statistical- Efficacy

BI proposes to add the following labeling claims to the Spiriva HandiHaler product label: a) reduction in COPD exacerbations; b) description of long-term effects on lung function; and c) reduction in respiratory failure. To support the proposed claims, BI submitted the results of a 4-year, placebo-controlled, parallel group trial in approximately 6000 patients with moderate-severe COPD. The trial is called Understanding Potential Long-term Impacts on Function with Tiotropium or UPLIFT (Study 205.235). In addition, BI referenced another clinical trial, a VA study (Study 205.266) that had been submitted and reviewed previously to support the COPD exacerbation claim. Due to the size and duration of the study, the focus of the efficacy discussion will be UPLIFT and the VA Study will be summarized briefly.

³ Anthonisen, MR, Connett JE, et al. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002; 166: 333-339.

⁴ Lanes S, Golisch W, Mikl J. Correspondence - Ipratropium and lung health study. *Am J Respir Crit Care Med* 2003; 167(5): 801-802.

Table 1 Summary of Clinical Program						
Study No.	Description	Subjects	Design	Dose	Duration	Endpoints
205.235 Multinational Jan 2003- Feb 2008	P4 efficacy trial – COPD exacerbations UPLIFT	5992 subjects with COPD	R, DB, PC	18 mcg Spiriva HandiHaler QD Placebo HandiHaler QD	4 years	-Rate of decline trough FEV1 - COPD exacerbations
205.266 United States Sept 2001- Feb 2003	P4 efficacy trial – COPD exacerbations VA Study	1829 subjects with COPD	R, DB, PC	18 mcg Spiriva HandiHaler QD Placebo HandiHaler QD	6 months	COPD exacerbations

UPLIFT Study Design

UPLIFT (Study 205.235) was a 4 year, randomized, double-blind, parallel group, placebo controlled trial to assess the rate of decline of lung function with Spiriva HandiHaler in patients with COPD. Patients were enrolled 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 $FEV_1 \leq 70\%$; 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 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) moderate to severe renal impairment. Unlike other clinical trials with Spiriva HandiHaler, many concomitant medications were allowed, including long-acting beta₂ adrenergic agonists, inhaled corticosteroids, chronic oxygen, and theophylline. The only medications not allowed during the treatment period were anticholinergic agents.

There were two co-primary endpoints: 1) the yearly rate of decline in trough FEV1 from day 30 (steady state) until completion of double-blind treatment and 2) the yearly rate in decline in FEV1 measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after inhalation of salbutamol) from day 30 (steady state) until completion of double-blind treatment. Pertinent secondary endpoints included time to first COPD exacerbation, number of COPD exacerbations, and other types of COPD exacerbation variables as well as yearly rate of decline in St. George's Respiratory Questionnaire (SGRQ). Safety endpoints included adverse events and all cause mortality.

BI seeks a labeling claim for reduction of exacerbations in the product label. There is no standard, well-accepted definition of COPD exacerbation⁵. In Study 205.235, COPD exacerbation was defined as an increase or new onset of more than one of the following of respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three days of more requiring treatment with antibiotics and/or systemic steroids.

Exacerbations were categorized as mild, moderate, and severe:

- mild – treated at home without visit to health care facility
- moderate – visit to outpatient facility or ER
- severe – hospital admission or ER visit greater than 24 hours

⁵ Cazzola M, MacNee W, et. al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008; 31: 416-418.

Clinic visits were held every 3 months, during which adverse events were recorded. PFTs were measured every 6 months. Patients recorded COPD exacerbations and hospitalizations. Study personnel reviewed the diaries during study visits and recorded exacerbations and hospitalizations on the case report form.

There were two protocol amendments that are important to note. There was an amendment to specify a Mortality Adjudication Committee (MAC) that centrally adjudicated all reported deaths. The committee had 3 members external to BI and not involved in the conduct of the study. In addition, BI amended the protocol for UPLIFT to collect vital status data for all prematurely discontinued patients.

VA Study Design

The VA Study (Study 205.266) was a phase 4, 6 month, randomized, double-blind, parallel group, placebo controlled trial in a Veteran's Affairs setting. The enrollment criteria were similar to UPLIFT. There were two co-primary endpoints: 1) the proportion of patients who experienced a COPD exacerbation and 2) the proportion of patients with a hospitalization associated with a COPD exacerbation during the 6 month period. In Study 205.266, 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 means ≥ 2 of the following (increase of symptom or new onset): cough, sputum, wheezing, dyspnea, or chest tightness. A change in treatment included antibiotics and/or systemic corticosteroids and/or hospitalization. Exacerbations were categorized as mild, moderate, and severe:

- mild – treatment with antibiotics, no visit to health care facility
- moderate – visit to outpatient facility or treatment with corticosteroids
- severe – hospital admission or ER visit greater than 24 hours

COPD Exacerbation Definition

The definition of COPD exacerbation used in the VA Study and UPLIFT are slightly different. Although there is no well-accepted definition of COPD exacerbation, the definition used in both clinical trials is reasonable as it includes both symptoms and treatment and is consistent with definitions in the literature. 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.

Efficacy Results

In general, patients enrolled in UPLIFT and the VA Study were primarily white males with a mean age around 65 to 68 years and a baseline pre-bronchodilator FEV₁ of approximately 1 liter (~36% to 39% predicted). The demographic profile was generally balanced between treatment groups in the two trials. There was a difference in patient disposition between treatment groups because the placebo group had a higher percentage of patients who discontinued (Spiriva HandiHaler 37%, placebo 45%), the primary reason being worsening of COPD.

UPLIFT

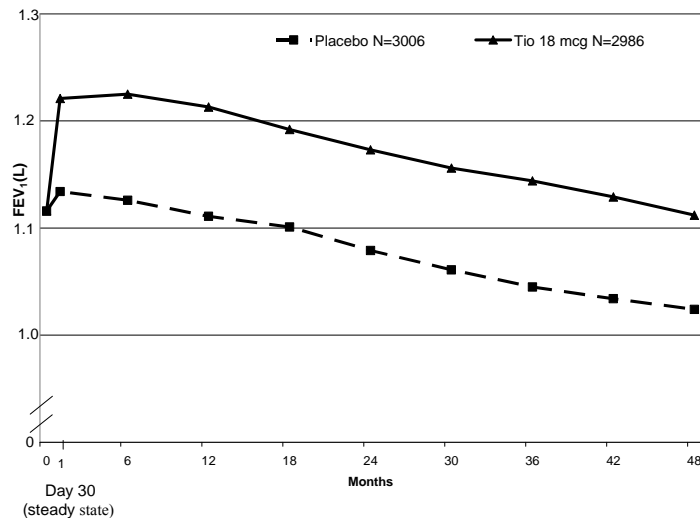
Long Term Effects on Lung Function

The results for the co-primary endpoints in UPLIFT are shown below in Table 2. As shown below, there was no significant difference in rate of decline of FEV₁ between the Spiriva HandiHaler and Placebo treatment groups.

Table 2 Rate of Decline in Pre- and Post- Bronchodilator FEV₁ in Study 205.235 (UPLIFT)				
Mean	Spiriva HandiHaler ml/year	Placebo ml/year	Difference ml/year	p value
Pre-Bronchodilator FEV ₁	30 n=2557	30 n=2413	0	0.95
Post-Bronchodilator FEV ₁	42 n=2554	40 n=2410	2	0.21

The pre-bronchodilator trough FEV₁ over time is shown in the following figure provided by the FDA's statistician, Dr. Joan Buenconsejo. Although there is no difference in the rate of decline, there is a difference in trough FEV₁ between treatment groups that is consistent over the 4 year period. The overall mean difference was 94 mL for pre-bronchodilator FEV₁ and 57 mL for post-bronchodilator FEV₁.

Figure 1 Mean Trough FEV₁ in UPLIFT (Study 205.235)



Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV₁ (observed mean) = 1.116. Patients with ≥ 3 acceptable PFTs after day 30 and non-missing baseline value were included in the analysis.

BI performed subgroup analyses based upon age, gender, smoking status, concomitant medication use, race, BMI, and GOLD stage. Based upon subgroup analysis of smokers (ex, sustained, intermittent) sustained smokers had the highest rate of decline of pre-bronchodilator FEV₁ (51 ml/yr) and sustained ex-smokers had the lowest rate of decline of FEV₁ (23 ml/yr).

BI noted that 72 and 74% of patients used LABA and ICS, respectively, and this may have confounded the effects of Spiriva HandiHaler.

BI proposes to describe the lung function (FEV₁) results of UPLIFT in the product label and state that the results for the co-primary endpoints were not significantly different between treatment groups and that the Spiriva HandiHaler group had sustained improvement in trough FEV₁ throughout the 4 years of the study. This claim regarding sustained improvement over 4 years of treatment is consistent with the current efficacy data described in the product label for a one year treatment period. Overall, the proposed description of the results for lung function is supported by the data submitted in this efficacy supplement.

COPD Exacerbations

The time to the first COPD exacerbation and time to first COPD exacerbation leading to hospitalization were identified by the Applicant as key secondary endpoints in UPLIFT. From a statistical standpoint, the primary endpoints did not win and with a step-down approach, secondary endpoints should not be considered. This deserves consideration when evaluating the support for the COPD exacerbation claim. However, COPD exacerbation is one of only several secondary efficacy variables in this large, long-term trial and there is independent data for COPD exacerbations in the VA Study (described below). In addition, the results for the secondary efficacy endpoints related to exacerbation are quite robust, thus, it may be reasonable to consider the COPD exacerbation claim.

The table below shows the pre-specified secondary efficacy endpoints of time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization (shaded). Based on the estimated hazard ratio (using Cox model), there is evidence that treatment with Spiriva HandiHaler reduced the risk of COPD exacerbation by 14% compared with placebo. Furthermore, based on Kaplan-Meier estimates, the median time to first COPD exacerbation in the Spiriva HandiHaler group is 16.7 months compared to 12.5 months in the placebo group. This implies a four-month delay in the time to first exacerbation in the tiotropium-treated patients compared to placebo-treated patients.

Table 3 Select COPD Exacerbation Endpoints in UPLIFT (Study 205.235)			
	Spiriva HandiHaler N=3006	Placebo N=2986	Ratio (p value)
Median time to first exacerbation (months)	16.7	12.5	0.86 (<0.0001)
Time to first exacerbation leading to hospitalization in 25% patients (months)	35.9	28.6	0.86 (0.0024)
Exacerbations per patient year*	0.73	0.85	0.86 (<0.0001)
Proportion of patients with exacerbations (%)	67	68	not calculated (0.35)
Proportion of patients hospitalized due to exacerbations (%)	25	27	not calculated (0.18)
*Poisson model with adjustment for overdispersion			

Other aspects of COPD exacerbation, including exacerbations per patient year, time to first exacerbation treated with steroids, time to first exacerbation treated with antibiotics, and number of exacerbation days, were all in favor of Spiriva HandiHaler. However, the number

of COPD exacerbations leading to hospitalization per patient year and number of days hospitalized due to exacerbation per patient year were not statistically significant.

VA Study

The following table shows the results for the co-primary endpoints (shaded) and some of the secondary endpoints related to COPD exacerbation. The co-primary endpoints were the proportion of patients who experienced a COPD exacerbation and the proportion of patients with a hospitalization associated with a COPD exacerbation during the 6 month period.

Table 4 COPD Exacerbation Endpoints in VA Study (Study 205.266)			
	Spiriva HandiHaler N=914	Placebo N=915	Odds Ratio (p value)
Proportion of patients with exacerbation (%)	28	32	0.81 (0.037)
Proportion of patients with hospitalizations due to exacerbation (%)	7.0	9.5	0.72 (0.056)
Median time to first COPD exacerbation (months)	NA	NA	0.83 (0.04)
Exacerbations per patient year*	0.71	0.88	0.81 (0.037)
Antibiotic days per patient year*	6.5	7.9	0.83 (0.105)
Corticosteroid days per patient year*	4.4	5.3	0.85 (0.375)
* adjusted for center and corrected for overdispersion			

The second co-primary endpoint was not statistically significant. In this study, sequential testing was conducted only on the ‘co-primary’ endpoints. Multiplicity correction was not pre-specified in the secondary endpoints. The secondary endpoints related to COPD exacerbation were numerically supportive but were not uniformly statistically significant as shown in the table above. It is important to address the analysis of the data for the number of COPD exacerbations, antibiotic days, and corticosteroid days. Ideally, analysis of this data should account for the follow up time and the between-patient variability in the data⁶. Correction for follow up time or exposure is important as there is differential discontinuation between the active and placebo groups. Correction for over dispersion in the data is important because some patients may have different rates of events. Because of this issue, the results shown above are corrected for over-dispersion.

In both studies, there are statistical issues with consideration of an exacerbation claim, which may preclude a single trial from supporting the claim. In accord with our regulations, the Agency usually requires more than one adequate and well-controlled study to provide independent substantiation of an efficacy claim. We ask that you consider whether the results of UPLIFT and the VA Study provide substantial evidence of efficacy to support a reduction in COPD exacerbation claim.

Clinical/Statistical- Safety

Since Spiriva HandiHaler is approved for patients with COPD, the safety of Spiriva HandiHaler in this population has been previously established. However, safety concerns

⁶ Suissa, S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2006; 173: 842-846.

regarding stroke, cardiovascular death, and MI have been raised recently as briefly described in the Background section. As UPLIFT is a large, 4 year, placebo controlled clinical trial in patients with COPD, the safety data are important to discuss, especially with regards to the aforementioned safety concerns. UPLIFT was amended to provide more complete information regarding mortality, so the mortality data will be a focus of discussion. In addition, some data from another tiotropium product under development, Spiriva Respimat program, will be incorporated in the safety discussion for completeness. Only a very brief summary of safety from the VA Study is included because the safety assessments were not as rigorous.

VA Study

In the VA Study (Study 205.266), limited safety monitoring was performed in that only serious adverse events (SAEs) were reported. Non-serious adverse events, laboratories, and ECGs were not collected. This limited safety monitoring is acceptable because Spiriva HandiHaler is an approved drug product for patients with COPD. A total of 1829 patients were randomized: 914 to Spiriva HandiHaler and 915 to placebo. There was a difference in discontinuation between Spiriva HandiHaler (16%) vs. placebo (27%), primarily secondary to adverse events and worsening of COPD. There were a few more deaths in the Spiriva HandiHaler group (22, 2.4%) compared to placebo (19, 2.1%); however, the cause of death was generally balanced and the rate was not adjusted for the difference in exposure. The most common SAEs were COPD exacerbation, pneumonia, bronchitis, myocardial infarction, and congestive heart failure. These SAEs were generally balanced with the exception of bronchitis which was more common in the Spiriva HandiHaler group (1.1%) compared to placebo (0.5%). These common SAEs are not unexpected in the COPD population. The safety data (SAEs) from Study 205.266 did not suggest any new safety signal for Spiriva HandiHaler.

UPLIFT

In UPLIFT, throughout the four year treatment period, patients were seen approximately every 3 months. Adverse event (AE) data was collected during the treatment period and up to 30 days following the treatment period. Of the 5993 randomized, more patients discontinued in the placebo group (45%) compared to the tiotropium group (37%). The main reason for discontinuation was adverse events, the most common being worsening of COPD. The difference in discontinuation led to a difference in exposure between treatment groups - mean of 1128 days in the tiotropium group and mean of 1033 days in the placebo group. In terms of pertinent protocol violations 3.8% of patients in each treatment group used anticholinergic medications for at least two consecutive visits, while 17% of patients in both treatment groups use a short acting inhaled anticholinergic at least once during the treatment period. This may reflect use during a COPD exacerbation.

Before discussing the safety data from UPLIFT, it is important to note that BI collected safety data for the 4 year (1440 Days) treatment period and up to 30 days following the end of treatment, for a total of 1470 Days. For safety analyses, BI specified using the 1470 Day safety data. Overall AE, SAE, and fatal AE results are shown in the table below, but these data do not take into account the difference in exposure between treatment groups.

Table 5 Adverse Events in UPLIFT (Study 205.235)*		
	Tiotropium n = 3006	Placebo n = 2986
Any AE	93%	92%
AE leading to discontinuation	21%	25%
Serious AEs	52%	50%
Fatal Events	13%	14%
*4 year treatment period (1440 days) + 30 day washout		

The most common AE was COPD exacerbation, which was more frequent in the placebo group. BI determined the rate ratio for Spiriva HandiHaler/placebo for AEs adjusting for exposure in patient years. For COPD exacerbation, the rate ratio was 0.84 (95% CI: 0.79, 0.89). The reduction in COPD exacerbation AEs is consistent with the efficacy data for COPD exacerbations. BI noted a decrease in respiratory failure with a rate ratio of 0.67 (95% CI: 0.51, 0.89) and seeks a labeling claim for a reduction in respiratory failure. However, because respiratory failure was not a pre-specified event with an agreed upon definition and respiratory failure is one of a multitude of safety endpoints evaluated, there are concerns with allowing a labeling claim for respiratory failure.

In terms of SAEs, respiratory system disorders were the most common SAEs, primarily COPD exacerbations, which favored Spiriva HandiHaler (rate ratio of 0.84, 95% CI: 0.76, 0.94). Dr. Michele noted that intestinal obstruction adverse events occurred with a rate ratio of 5.55 (95% CI: 1.24, 24.8) and for SAEs a rate ratio of 4.16 (95% CI: 0.90, 19.3). Intestinal obstruction may be related to the anticholinergic effects of tiotropium. Intestinal obstruction is listed in the current product label for Spiriva HandiHaler under the post-marketing adverse event section.

Stroke

In November 2007, BI voluntarily submitted a pooled analysis of 29 placebo controlled clinical studies with Spiriva HandiHaler (25 clinical trials) and Spiriva Respimat (4 clinical trials), which was performed as part of routine safety assessment. BI noted a numerical increase in risk of stroke (RR 1.37, 95% CI 0.73-2.56) in patients treated with tiotropium compared to placebo. This data reflected 13,544 patients contributing 4572 person years of exposure to tiotropium, but was not adjusted for multiplicity.

With the submission of UPLIFT, the safety database for Spiriva HandiHaler is doubled. Preferred terms for stroke were grouped similar to the grouping of terms for the pooled analysis and are discussed in detail in Dr. Michele's review. Adjusting for exposure in patient years, the hazard ratios for stroke adverse events in UPLIFT are as follows: stroke AEs 0.95 (95% CI 0.70, 1.29), stroke SAEs 0.97 (95% CI 0.69, 1.37), and fatal strokes (adjudicated) 0.85 (95% CI 0.39, 1.87). These data do not suggest an increase in stroke related adverse events with Spiriva HandiHaler compared to the placebo group, but the uncertainty of the confidence intervals is noted.

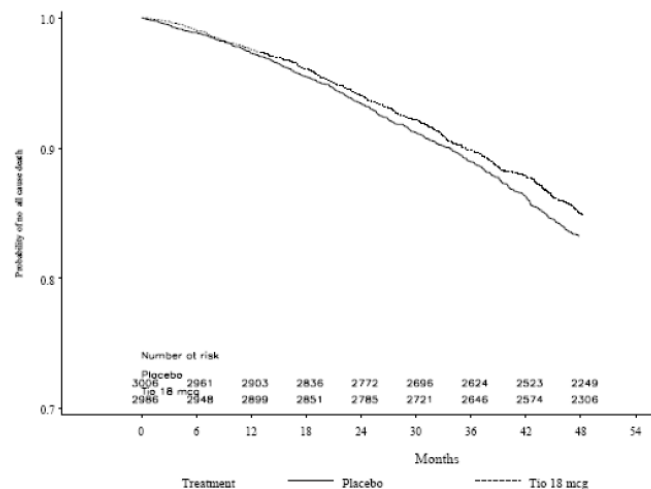
We ask you to consider the strength of the evidence of the potential safety signal and whether the data from UPLIFT are adequate to address the potential stroke signal identified in the 2007 pooled analysis.

Mortality

Because UPLIFT is a large, long term controlled clinical trial, the mortality data is of interest. Two protocol amendments specified obtaining vital status on patients who discontinued and established an independent adjudication committee. These amendments make the mortality data in UPLIFT more robust. Because of the collection of vital status data, there are several datasets for the mortality data. BI analyzed the fatal adverse event data in multiple ways – on treatment (deaths on treatment) vs. vital status (all deaths including discontinuation vital status data); and Day 1440 (4 years) vs. Day 1470 (4 years + 30 day washout) vs. all (no cut-off). BI was able to obtain vital status on 97-98% of patients.

The hazard ratio for fatal adverse events on treatment Day 1440 (4 years) is 0.83 (95% CI: 0.72, 0.95). The results for the other analysis of fatal adverse events (on treatment, vital status, Day 1440, Day 1470) were generally similar, e.g. Day 1470 Vital Status 0.89 (95% CI: 0.79, 1.02). Below is the Kaplan-Meier curve for the probability of no all cause mortality using the vital status data at Day 1470. The curves appear to separate around 12 months.

Figure 2 Kaplan Meier estimate of probability of no all cause mortality at Day 1470



The most common causes of death were COPD exacerbation, lung neoplasm, and unknown cause. Importantly, since BI seeks a labeling claim for COPD exacerbation, the rate ratio for death from COPD exacerbation was 0.79 (95% CI: 0.60, 1.02). For lung neoplasm and unknown cause the rate ratios were: 1.02 (95% CI: 0.73, 1.43) and 0.74 (95% CI: 0.46, 1.21), respectively. Cardiovascular deaths are of interest. The rate ratio for death due to cardiovascular disorders was 0.81 (95% CI 0.48, 1.36) and for death due to MI was 1.00 (95% CI 0.43, 2.30). The number needed to treat (NNT) was calculated by Dr. Joan Buenconsejo and depending upon the dataset used, the NNT with Spiriva HandiHaler over a 4 year period to prevent one death was between 63 (Vital Status, Day 1470) and 111 (treatment, all).

We ask you to comment on the mortality data from UPLIFT.

Cardiovascular death and myocardial infarction

As discussed in Section 2, in September 2008, a meta-analysis was published in *JAMA* evaluating cardiovascular risk associated with inhaled anticholinergics¹. For the primary combined outcome of cardiovascular death, myocardial infarction (MI), or stroke, the authors reported a relative risk of 1.58 (95% CI 1.21, 2.06) for tiotropium and ipratropium compared to placebo and concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke.

To evaluate this potential safety signal, the Office of Surveillance and Epidemiology (OSE) reviewed this meta-analysis as well as other relevant literature regarding the safety of tiotropium and ipratropium. In Dr. Simone Pinheiro's review, she noted limitations of the aforementioned meta-analysis, including study selection bias, and lack of discontinuation information and failure to use person-time data. Dr. Pinheiro also noted the limitations of other published observational studies^{7,8,9}. She noted that the Singh meta-analysis disagreed with the findings of other published meta-analyses^{10,11,12,13} and disagreed with the results of UPLIFT, all of which did not suggest an association between anticholinergics and cardiovascular events or mortality. Dr. Pinheiro concluded that the currently available data implicating tiotropium and ipratropium in increasing risk of cardiovascular death, myocardial infarction, and stroke is not compelling.

Because of the safety concern of MI and cardiovascular death, cardiac events in UPLIFT are of interest. The rate ratio for death due to cardiovascular disorder was 0.81 (95% CI 0.48, 1.36) and for death due to MI was 1.00 (95% CI 0.43, 2.30). Adjusting for exposure in patient years, overall cardiac SAEs were more common in the placebo group with a rate ratio of 0.84 (95% CI: 0.73, 0.98). In terms of SAEs, MI occurred with a rate ratio of 0.71 (95% CI: 0.52, 0.99) and angina occurred with a rate ratio of 1.44 (95% CI: 0.91, 2.26). The rate ratio for other events such as coronary artery disease (0.58, 95% CI: 0.33, 1.01) favored Spiriva HandiHaler. The AE data for cardiac events of interest showed similar findings.

⁷ Lee TA, Pickard AS, Au DH, Bartle B, Weiss KB. Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. *Ann Intern Med* 2008; 149(6): 380-90.

⁸ Macie C, Wooldrage K, Manfreda J, Anthonisen N. Cardiovascular morbidity and the use of inhaled bronchodilators. *Int J Chron Obstruct Pulmon Dis* 2008; 3(1): 163-9.

⁹ Ogale SS, Lee TA, Au DH, Boudreau DM, Sullivan SD. Cardiovascular Events Associated With Ipratropium Bromide in COPD. *Chest* 2009; prepublished online April 10, 2009.

¹⁰ Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety *Chest* 2006; 130(6): 1695-703.

¹¹ Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis *Thorax* 2006; 61(10): 854-62.

¹² Salpeter SR, Buckley NS. Systematic review of clinical outcomes in chronic obstructive pulmonary disease: beta-agonist use compared with anticholinergics and inhaled corticosteroids. *Clin Rev Allergy Immunol* 2006; 31(2-3): 219-30.

¹³ Wilt TJ, Niewoehner D, MacDonald R, Kane RL. Management of stable chronic obstructive pulmonary disease: a systematic review for a clinical practice guideline. *Ann Intern Med* 2007; 147(9): 639-53.

We ask you to consider the strength of the evidence of the potential safety signal and whether the data from UPLIFT are adequate to address the potential MI, cardiovascular death, and stroke signal suggested by the meta-analysis.

Spiriva Respimat

The data from UPLIFT suggests that there is a benefit of Spiriva HandiHaler on mortality and this is primarily driven by a decrease in deaths from COPD exacerbation. However, it is relevant to note a safety concern regarding mortality with another formulation of tiotropium under development, Spiriva Respimat. As mentioned in Section 2, Spiriva Respimat is a new formulation of tiotropium bromide, an inhalation solution, delivered via a novel inhaler, the Respimat. Inhalation products act locally in the lung and we consider Spiriva HandiHaler and Spiriva Respimat different products. Each product has a separate clinical development program to evaluate efficacy and safety.

BI has evaluated two doses of Spiriva Respimat in three, 48-week, double blind, placebo controlled, phase 3 clinical trials (Studies 205.254, 205.255, and 205.372) in patients with COPD. The nominal doses for Spiriva Respimat are 5mcg and 10mcg, which are different than Spiriva HandiHaler (18mcg) because of the difference in formulations/devices. Pharmacokinetic comparisons of the two formulations show that Spiriva Respimat 5mcg and Spiriva HandiHaler 18mcg have similar exposures.

The results of all 3 trials show that Spiriva Respimat both 5mcg and 10mcg are statistically superior to placebo for trough FEV₁ at 48 weeks. The trials also show a numerical imbalance in mortality favoring placebo. The results for fatal adverse events in the 48 week, Spiriva Respimat clinical trials are shown in the table below. At the suggestion of the Agency, BI retrospectively obtained vital status on patients who discontinued and the numerical imbalance may be partially explained by differences in discontinuation. However, the results are most striking in Study 205.255, in which there were no deaths in the placebo group. The causes of death were reviewed and are discussed in detail in Dr. Michele's review. The most common causes were unknown and neoplasm, primarily lung cancer, followed by COPD exacerbation and myocardial infarction. Based upon review of cause of death, there was no obvious pattern that could explain the imbalance.

Table 6 Fatal Adverse Events in 48 Week Clinical Trials with Spiriva 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 Vital Status	8 (2.5%)	8 (2.1%)	7 (2.3%)	1.1 (0.4, 3.0)	1.1 (0.4, 2.9)
Study 255 (n)	338	335	334		
Within Study	5 (1.6%)	8 (2.7%)	0 (0.0%)	undefined	undefined
With Vital Status	7 (1.8%)	10 (2.8%)	2 (0.6%)	3.4 (0.7, 16.5)	5.0 (1.1, 22.9)
Study 372 (n)	1952		1965		
Within Study	30 (1.5%)		19 (1.0%)	1.5 (0.9, 2.7)	NA
With Vital Status	52 (2.7%)		38 (1.9%)	1.4 (0.9, 2.1)	NA
*Kaplan Meier estimates at 48 weeks					
**Estimated by Cox proportional hazards regression with treatment as independent variable, stratified by study for pooled analysis					

While these data are from clinical trials with a completely different formulation of tiotropium, we included this information for a complete discussion. We ask you to comment on the Spiriva Respimat mortality data.

Summary

The purpose of the PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted by BI to support a labeling claim for the reduction in exacerbations in patients with COPD to the labeling for Spiriva HandiHaler (tiotropium bromide inhalation powder). This is an important discussion in light of recent safety concerns with Spiriva HandiHaler including stroke, myocardial infarction, and cardiovascular death.

At the PADAC meeting, BI will present an overview of the clinical program, which will be followed by the Agency's presentation of the efficacy and safety data. Please keep in mind the following questions that will be discussed and deliberated upon following the presentations and discussion.

Draft Questions

1. Please comment on the mortality data from Spiriva HandiHaler trial 205.235 (UPLIFT).
2. Please comment on the mortality data from the Spiriva Respimat Phase 3 trials (205.244, 205.245, and 205.372).
3. Do the data from trials 205.235 (UPLIFT) and 205.266 (VA study) provide substantial and convincing evidence to support the claim that Spiriva HandiHaler reduces COPD exacerbations? (voting question)
4. Do the data from trial 205.235 (UPLIFT) adequately address the potential safety signal of stroke events? (voting question)
 - If not, what additional data are needed?
5. Do the data from trial 205.235 (UPLIFT) adequately address the potential safety signal of adverse cardiovascular outcomes? (voting question)
 - If not, what additional data are needed?

Pulmonary-Allergy Drugs Advisory Committee Meeting

November 19, 2009

Clinical Briefing Document

**NDA# 21-395
Spiriva HandiHaler**

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1 EXECUTIVE SUMMARY

1.1 Brief Overview of Clinical Program

Spiriva HandiHaler (tiotropium bromide inhalation powder) 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. Tiotropium is a specific antagonist at muscarinic acetylcholine receptors, often called anticholinergic. The Applicant, Boehringer Ingelheim Pharmaceuticals, Inc., now seeks additional efficacy claims for Spiriva HandiHaler. Requested efficacy claims included in the clinical trials section of the label are: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure.

To support this application, BI submitted the results of a 4-year, placebo-controlled, parallel group trial enrolling nearly 6000 patients with moderate-severe COPD. The short title of this trial is UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium (Protocol 205.235). In addition, BI referenced trial 205.266 (VA Study), which had been previously submitted to the Agency (under S024) to support the COPD exacerbation claim. On July 22, 2009, BI withdrew the mortality claim to maintain consistency with global labeling. According to BI, there were no new Spiriva HandiHaler data contributing to this decision.

This clinical briefing document includes a review of the results of UPLIFT (Protocol 205.235) and the VA Study (Protocol 205.266). The safety portion of the briefing document will address recent safety concerns with Spiriva HandiHaler including stroke, myocardial infarction, and cardiovascular death that have been cited in the public domain recently. In addition, the safety review includes discussion of a mortality issue with a new formulation of tiotropium under development, Spiriva Respimat, an inhalation solution delivered via the Respimat device.

1.2 Efficacy

UPLIFT (Protocol 205.235) was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial to determine the effect of tiotropium 18 mcg capsule dry powder inhaler (tio HH18) on disease progression over 4 years in 5992 patients with COPD. The two co-primary endpoints were the yearly rate of decline in trough FEV1 from day 30 until completion of double blind treatment and the yearly rate of decline in FEV1 90 minutes after study drug and bronchodilator administration from day 30 until completion of double blind treatment. A number of secondary endpoints included other spirometry endpoints, COPD exacerbation-related endpoints, and the St. George Respiratory Questionnaire (SGRQ). For the purposes of the UPLIFT trial, a COPD exacerbation was defined as “an increase or new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three days or more requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous) steroids.” 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.

The UPLIFT trial showed no significant difference between treatment groups in the primary endpoints of rate of decline in pre- and post-bronchodilator FEV1. There was a loss of 30 ml per year of pre-bronchodilator FEV1 in both the placebo and tio HH18 groups and a loss of 42 (placebo) versus 40 ml (tio HH18) per year in post-bronchodilator FEV1. In a subgroup analysis, patients who were sustained quitters from smoking did experience a significant decrease in rate of decline in FEV1 compared to sustained smokers. This effect was observed across both treatment groups and provides internal validation for the trial.

For the key secondary endpoints of time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization, tiotropium showed a significant difference compared to placebo. For COPD exacerbations, patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p < 0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. Patients in the tio HH18 group also had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p = 0.0024$, RR 0.86, 95% CI 0.78, 0.95). The median time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group.

A significant improvement in most of the additional COPD exacerbation-related endpoints was also observed. These included the number of COPD exacerbations, time to first exacerbation treated with steroids, time to first exacerbation treated with antibiotics, number of exacerbations treated with steroids, number of exacerbation days, number of COPD exacerbations leading to hospitalization, and number of days hospitalized due to exacerbation per patient year.

Spirometry endpoints included trough FEV1, FVC, and SVC response and 90 minute FEV1 FVC, and SVC response. Endpoints were measured every six months throughout the four year treatment period. Consistent with the known bronchodilator properties of the drug, the tio HH18 group generally demonstrated a significant improvement ($p < 0.0001$) over placebo for all endpoints and time points tested. These data are supportive of the description of spirometry outcomes for the trial the Applicant proposes for the label.

The VA Study (Protocol 205.266) was a multicenter 6 month, randomized, double-blind, placebo controlled trial of tiotropium 18 mcg capsule dry powder inhaler (tio HH18) in COPD patients in a Veteran's Affairs setting. The enrollment criteria were similar to UPLIFT. There were two co-primary endpoints: 1) the proportion of patients who experienced a COPD exacerbation and 2) the proportion of patients with a hospitalization associated with a COPD exacerbation during the 6 month period. The definition of COPD exacerbation used in this clinical trial is also reasonable as it includes both symptoms and treatment and is consistent with definitions in the literature.

The results of the VA Study demonstrated that fewer patients in the tio HH18 group compared to placebo (27.9% versus 32.3%, $p = 0.037$) experienced a COPD exacerbation

over the 6 months of the trial. In addition, there were significantly fewer exacerbations per patient year in patients treated with tio HH18.

The evidence from the UPLIFT trial (Protocol 205.235), in conjunction with data from the VA trial (Protocol 205.266), is supportive of an exacerbation claim from a clinical perspective. Statistical issues related to multiplicity may complicate the claim.

1.3 Safety

The safety discussion for this application is complex because there are several potential safety signals that have recently been identified for Spiriva HandiHaler. These potential safety signals include stroke, myocardial infarction, and cardiovascular death. Because of its size, duration, and randomized, placebo-controlled design, the UPLIFT trial (Protocol 205.235) is particularly useful to address these potential safety signals. Therefore, the UPLIFT trial is the focus of this briefing document.

Mortality is an important outcome to address. The Applicant made protocol amendments to UPLIFT to provide more robust mortality data. Mortality was collected both on-treatment and for discontinued patients out to the time of their scheduled exit date from the study (vital status). Cause of death was adjudicated in a blinded fashion by an independent committee. While the Applicant has withdrawn their initial proposal for a mortality benefit claim, a detailed discussion of mortality is still warranted. In addition, when considering the mortality data from UPLIFT, it is of interest to briefly discuss an issue with the mortality data from a tiotropium product under development, Spiriva Respimat. Spiriva Respimat is a completely new inhalation solution formulation of tiotropium. The Applicant has conducted 3 one year clinical trials with Spiriva Respimat in patients with COPD that show a numerical imbalance in mortality, favoring placebo. There is no consistent cause of death. A review of the mortality data from the Spiriva Respimat program is included in the Appendix (Section 6.2) of this document.

In UPLIFT, the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792—411 (13.7%) in the placebo group and 381 (12.8%) in the tiotropium group. Vital status information was known for 98% of tio HH18 treated patients and 97% of placebo treated patients including discontinued patients out to at least 45 months post-randomization. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued. The risk ratio for death from any cause (tiotropium/placebo) on treatment was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data.

The primary cause of each death in the UPLIFT trial was adjudicated by an independent committee. The most common causes (adjudicated) of death both on-treatment and including vital status were COPD exacerbation, lung cancer, and death of unknown cause. Combining the preferred terms of sudden death, sudden cardiac death, and death of unknown cause, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

To support a labeling claim, the Agency typically requires replication of findings in two or more clinical trials. However, according to the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, reliance on a single study is possible in situations in which a trial has demonstrated a clinically meaningful effect on mortality or irreversible morbidity. In addition, the single study would typically be large multicenter center, with consistency across study subsets and statistically very persuasive findings. In support of a labeling claim for a mortality benefit, UPLIFT: 1) is a major study that more than doubles the size of the safety database, 2) has prespecified mortality endpoints and vital status data which were appropriately collected and adjudicated, and 3) demonstrates a salutary effect on mortality that is robust across multiple different analyses. In addition, the mortality benefit was driven by a reduction in fatal COPD exacerbations, suggesting a plausible mechanism of action. However, outstanding issues with regards to mortality with Spiriva Respimat and literature references to cardiovascular mortality require discussion.

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs were generally balanced between treatment groups, although COPD exacerbations were significantly reduced in the tio HH18 group compared to placebo [RR 0.86, 95% CI (0.76, 0.94), $p=0.0014$]. The Applicant seeks a labeling claim regarding a reduction in respiratory failure. While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Multiplicity is also an issue. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term “respiratory failure” is undefined and subject to investigator interpretation. There is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. A reduced number of patients in the tio HH18 group discontinued due to COPD exacerbations and dyspnea compared to the placebo group.

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. In addition, although the numbers were small, intestinal obstruction occurred significantly more frequently in the tio HH18 group and could represent an anticholinergic side effect related to constipation.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. In routine safety monitoring, the Applicant pooled the data from tiotropium trials and identified a potential

safety signal of stroke. The Agency released an Early Communication regarding this potential signal in March 2008. In UPLIFT, the risk ratios of stroke-related adverse events (AEs, SAEs, or fatal events) in the tio HH18 group relative to placebo were 0.95, 0.97, and 0.85, respectively.

Cardiovascular events are also adverse events of interest based on a potential safety signal observed in a 2008 meta-analysis literature report. There was no increase in adverse events of myocardial infarction in the tiotropium group compared to placebo, with a Risk Ratio of 0.71, 95% CI (0.52, 0.99). Overall, there was a borderline significant decrease in AEs in the cardiac SOC [RR 0.84, 95% CI (0.73, 0.98)], driven by a decrease in congestive heart failure and MI. Likewise, there was no increase in deaths due to cardiac disorders, sudden cardiac death, sudden death, or death due to unknown cause, although the confidence intervals for the risk ratio are wide.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Spiriva HandiHaler 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. 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.

As an anticholinergic, Spiriva HandiHaler has known safety concerns regarding worsening symptoms and signs associated with narrow-angle glaucoma, prostatic hyperplasia, and bladder-neck obstruction and should be used with caution in patients with any of these conditions. The most common adverse events occurring in patients in 1-year placebo and active controlled registration 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%).

2.2 Important Issues with Pharmacologically Related Products

Ipratropium bromide is a short-acting, anticholinergic bronchodilator that is also manufactured by Boehringer Ingelheim and is approved as a bronchodilator for the maintenance treatment of bronchospasm 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. 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%).

2.3 Other Relevant Background Information

In September 2008, the *Journal of the American Medical Association* published a meta-analysis by Singh, Loke, and Furberg evaluating cardiovascular risk of inhaled anticholinergics¹. After screening 103 published articles, the authors analyzed 17 literature reports of trials of tiotropium or ipratropium enrolling 14,783 patients for the primary combined outcome of cardiovascular death, myocardial infarction (MI), or stroke. Singh et al. reported a relative risk of 1.58 (95% CI 1.21, 2.06) for tiotropium compared to placebo and concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke. The effect was primarily demonstrated in the six studies of ≥ 6 months duration (total patients 7267). Of note, 3923 of these patients were drawn from the Lung Health Study, which compared ipratropium to placebo over 5 years. In the Lung Health Study, there was a known and reported imbalance in mortality favoring placebo.

On November 30, 2007, the Applicant submitted a document to FDA 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). 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. This communication was updated on October 7, 2008 with preliminary results from UPLIFT.

2.4 Comparison of Spiriva HandiHaler and Spiriva Respimat

Tiotropium bromide is available in the United States as a dry powder capsule for inhalation, Spiriva HandiHaler. Boehringer Ingelheim has also developed a second formulation of tiotropium bromide, Spiriva Respimat. Spiriva Respimat is an aqueous inhalation solution which was approved in Europe in 2007 at a dose of 5 mcg once daily. Spiriva Respimat is not approved in the United States. Data from three one year Spiriva Respimat trials are included in this briefing document for the discussion of mortality. The Applicant has evaluated two different doses of Spiriva Respimat in pivotal trials, 5 and 10 mcg once daily.

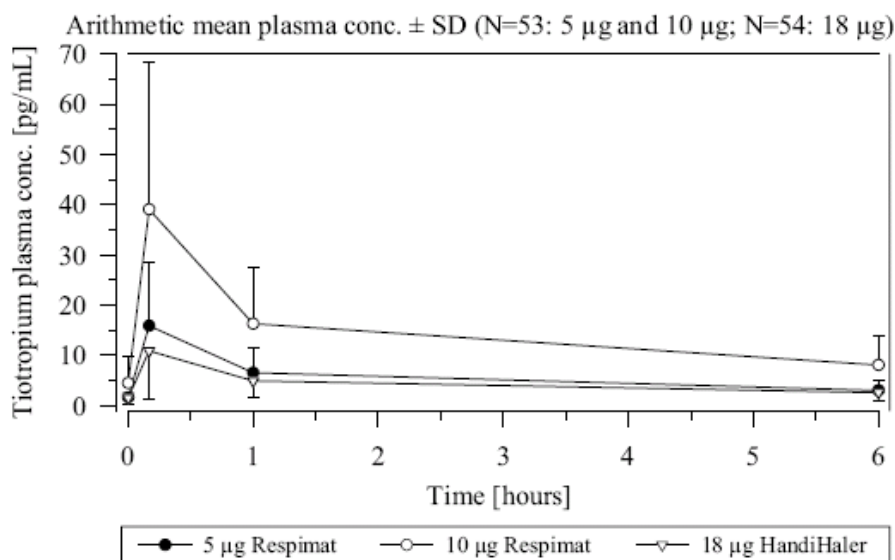
For inhalational pulmonary products, the FDA has generally considered efficacy to be primarily related to local effects. Therefore, efficacy data may not be directly transferrable from one device/formulation to another. Pharmacokinetic data in comparison with alternative formulations are useful as a benchmark but do not necessarily predict clinical dose ranging. Safety may be related to both systemic and local

effects. The extent to which safety data can be compared from one device/formulation to another is subject to discussion and interpretation.

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 for Spiriva Respimat 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.

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, although Spiriva Respimat 5mcg has a numerically higher C_{max}. Figure 1 shows the mean plasma concentration following dosing in Study 205.249. Similar results were obtained in Study 205.250.

Figure 1: Protocol 205.249 tiotropium mean plasma concentrations



BI Trial No.: 0205.0249

3 DATA SOURCES, REVIEW STRATEGY

3.1 Tables of Clinical Studies

Studies referenced in this NDA supplement are displayed in Table 1.

Table 1: Spiriva HandiHaler clinical studies submitted for this supplement

ID #	Study type	Study duration	Patient age	Treatment groups	N (ITT)	Study Year	Countries
205.266	efficacy for COPD exacerbations	6 mo	≥40 yrs	tio HH18 QD placebo	914 915	2003 [†]	US (VA)
205.235	Efficacy and safety COPD	4 years	≥40 yrs	tio HH18 QD placebo	2986 3006	2008	EU N America Africa Australia

[†]Year patient enrollment ended

tio HH18 = tiotropium HandiHaler 18 mcg

3.2 Review Strategy

The UPLIFT trial (Protocol 205.235) is the focus of this efficacy supplement (S029) briefing document. Where appropriate, data from the VA trial (Protocol 205.266), reviewed under a previous efficacy supplement (S024), are mentioned in the integrated summaries of safety and efficacy. Protocol 205.266 was a placebo controlled trial evaluating the effect of Spiriva HandiHaler on COPD exacerbations; thus, it provides evidence from a second trial to support the requested COPD exacerbation claim. The complete summary of the individual trial reports for the two trials are provided in Section 6.1.

Because the mortality data from Spiriva Respimat is relevant to discussion at the PADAC meeting, abbreviated reviews of relevant Spiriva Respimat studies are provided in Section 6.2.

3.3 Study Designs

3.3.1 Protocol 205.235 (UPLIFT)

The UPLIFT trial was a 4-year, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel group study comparing the rate of decline in forced expiratory volume in one second (FEV1) in patients with COPD receiving tiotropium HandiHaler 18 mcg (tio HH18) to those receiving placebo in addition to their usual care for COPD. Usual care included short- and long-acting inhaled beta-agonists, steroids, and theophyllines but excluded inhaled anticholinergics. Following an initial screening period of 14-30 days, qualifying patients were randomized to tiotropium or placebo. Patients were seen after 1 month of treatment, at 3 months, and then every 3 months until study drug termination at 4 years. At study drug termination, patients received open-label ipratropium for 30 days. The final visit occurred approximately 30 days post-treatment.

Reviewer comment:

The enrollment criteria for this trial represent a “real world” population of patients with COPD. In contrast to studies leading to approval of a COPD exacerbation claim for

Advair Diskus in which the patient population was enriched for exacerbation by inclusion of patients with a history of recent exacerbation, Protocol 205.235 did not exclude patients based on lack of exacerbation history.

3.3.2 Protocol 205.266 (VA Trial)

The VA trial was a 6-month, multicenter, randomized, double-blind, placebo-controlled, parallel group study assessing the proportion of patients experiencing an exacerbation and the proportion of patients hospitalized for an exacerbation in patients with moderate to severe COPD in a United States Veterans Affairs setting. Following an initial screening period, patients were randomized in a 1:1 fashion to tiotropium or placebo. Patients also received open label albuterol as a rescue medication and were permitted to stay on their usual care therapy, excluding anticholinergics. Patients had follow up visits at three months and 6 months, along with monthly telephone contacts to evaluate COPD exacerbations.

Reviewer comment:

Similar to the UPLIFT trial, the VA trial enrolled a “real world” patient population. Overall, the VA population tended to be sicker than other Spiriva trials, as the inclusion criteria permitted a higher dose of oral corticosteroids (<20 mg) and unrestricted use of oxygen.

4 INTEGRATED REVIEW OF EFFICACY

The Applicant proposes two efficacy claims—long term effects on lung function and reduction in COPD exacerbations. Each of these efficacy variables will be discussed separately. The lung function efficacy variables are discussed in Section 4.1 and the COPD exacerbations efficacy variables are discussed in Section 4.2. Mortality and respiratory failure are discussed under safety, as they were not pre-specified efficacy endpoints.

4.1 Effects on Lung Function

Boehringer Ingelheim (BI) proposes a labeling claim describing the results of the lung function endpoints in UPLIFT and describing the maintenance improvement in pulmonary function throughout the 4 year treatment period.

4.1.1 Methods

To support this application, BI submitted the UPLIFT trial, a 4-year randomized, double-blind, placebo controlled trial evaluating the efficacy of Spiriva HandiHaler in a population of patients with moderate to severe COPD.

4.1.2 General Discussion of Lung Function Endpoints

The primary endpoints for Study 205.235 (UPLIFT) were:

- The yearly rate of decline in trough FEV₁ from day 30 (steady state) until completion of double blind treatment. Trough FEV₁ is the pre-dose value measured approximately 24 hours after the previous dose of study drug.
- The yearly rate of decline in FEV₁ 90 minutes after study drug and ipratropium administration (including 30 minutes post albuterol) from day 30 (steady state) until completion of double blind treatment

Secondary endpoints related to lung function included:

- Yearly rate of decline in trough FVC and slow vital capacity (SVC)
- Yearly rate of decline in trough FVC and slow vital capacity (SVC) from day 30 until completion of double-blind treatment. Trough FVC and SVC are the pre dose values measured approximately 24 hours after the previous dose of study drug.
- Yearly rate of decline in FVC and SVC measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after albuterol) from day 30 until completion of double-blind treatment.
- Yearly rate of decline in FEV₁, FVC, and SVC prior to ipratropium and albuterol inhalation from day 1 until completion of the trial (30 days post study drug treatment).
- Yearly rate of decline in FEV₁, FVC, and SVC measured 90 minutes after inhalation of ipratropium (and 30 minutes after inhalation of albuterol) from day 1 until completion of the trial (30 days post study drug treatment).
- Estimated mean pre- and post-bronchodilator FEV₁, FVC, and SVC from day 30 until completion of double-blind treatment.

Trough FEV₁ was defined as the FEV₁ measured at the -5 minute time point at the end of the dosing interval 24 hours post drug administration. Trough FEV₁ response was defined as the change from baseline in trough FEV₁. Baseline FEV₁ was the pre-treatment FEV₁ value measured at Visit 2 in the morning 5 minutes prior to administration of the first dose of study medication.

FEV₁, FVC, and SVC measurements were obtained through pulmonary function testing at screening (Visit 1), baseline (Visit 2), after 30 days (Visit 3) and every 6 months thereafter until the end of the double-blind treatment period (Visits 5, 7, 9, 11, 13, 15, 17, and 19). PFTs were also performed at the final visit after being off study drug (on open-label ipratropium) for 30 days. PFTs were performed using standardized spirometry equipment provided by the Applicant and calibrated by study staff on all test days. A calibration log was maintained for the spirometry equipment. Equipment and techniques conformed to American Thoracic Society (ATS) criteria.

At screening (Visit 1), spirometry was performed at the 90-minute post-bronchodilator timepoint (after administration of 4 inhalations of ipratropium [80 mcg] and 4 inhalations of albuterol [400 mcg]). For this visit, washout of respiratory medications was not required. At the randomization visit (Visit 2) and the end of trial visit (30 days after completion of study medication), washout of restricted medications was required and spirometry was performed pre-bronchodilator and at the 90 minute post-bronchodilator timepoint (after administration of 4 inhalations of ipratropium [80 mcg] and 4 inhalations

of albuterol [400 mcg]). For visits at Day 30 (Visit 3) and then every 6 months until the end of treatment (Visits 5, 7, 9, 11, 13, 15, 17, and 19), washout of restricted medications was required and spirometry was performed pre-bronchodilator and at the 90 minute post-bronchodilator timepoint (after administration of study drug, 4 inhalations of ipratropium [80 mcg], and 4 inhalations of albuterol [400 mcg]).

Reviewer comment:

Additional details of the spirometry assessment are described in the detailed review of UPLIFT in the Appendix. FEV1 is an established endpoint for COPD trials. Methodology for pulmonary function testing and collection of spirometry data was appropriate in the UPLIFT trial.

4.1.3 Lung Function Efficacy Findings

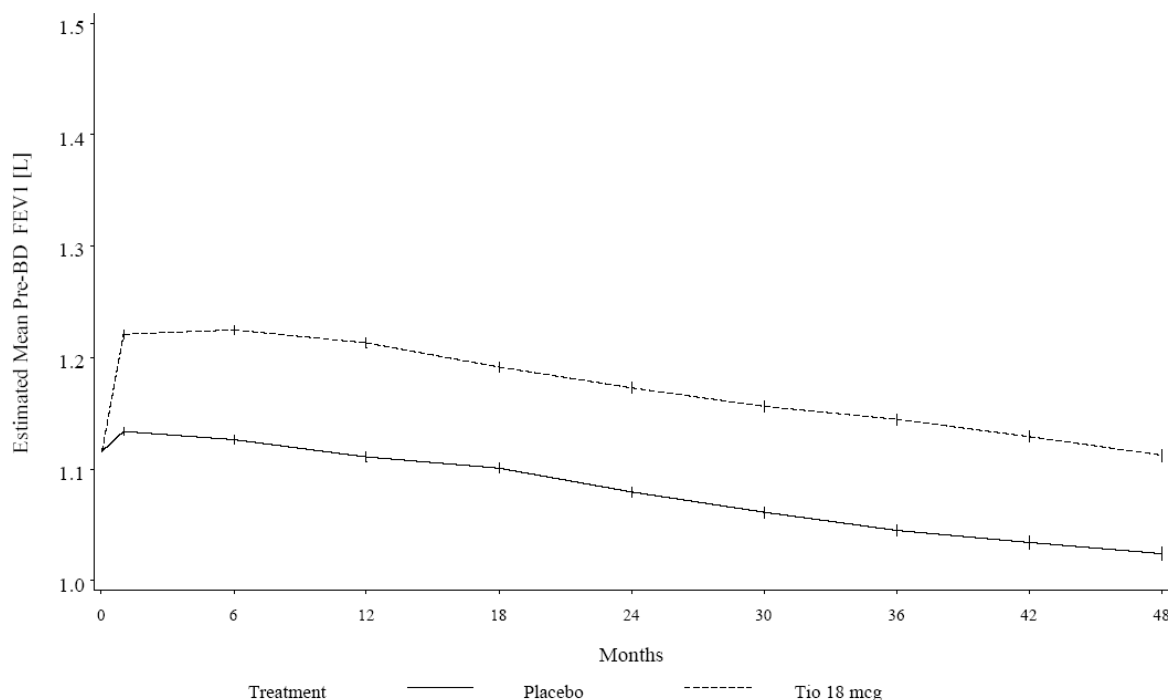
There were two co-primary endpoints for this study, rate of decline of pre- and post-bronchodilator FEV1 from Day 30 (steady state) until completion of double-blind treatment. The endpoints did not achieve statistical significance, thus the Applicant reported p-values as unadjusted for multiple comparisons.

There was no significant difference between treatment groups for rate of decline in either pre- or post-bronchodilator FEV1. The sponsor reports that sensitivity analyses including patients with at least one measurement and including center as a random effect also showed no significant treatment difference. Likewise, adjusting for baseline covariates of post-bronchodilator FEV1, age, sex, height and smoking status did not change significance. Pre-specified subgroups of age, gender, smoking status, baseline ICS use, baseline ICS/LABA combination use, baseline anticholinergic use, GOLD stage, race, region, reversibility, and BMI were evaluated. No significant treatment by subgroup interaction was detected. See Table 2 and Figure 2.

Table 2: Protocol 205.235 rate of decline in FEV1 (random effects model)

	Placebo		Tio HH18		Difference		
	N	Mean (SE) ml/yr	N	Mean (SE) ml/yr	Mean (SE) ml/yr	95%CI	p-value
Pre-BD	2413	30 (1)	2557	30 (1)	0 (2)	(-4, 4)	0.9524
Post-BD	2410	42 (1)	2554	40 (1)	2 (2)	(-6, 2)	0.2074

Figure 2: Protocol 205.235 mean pre-bronchodilator FEV1



Treated set with at least 3 measurements after and including Day 30. Estimated based on repeated measure ANOVA model. Model adjusted for baseline measurement. Day 1 (baseline) value is overall mean, not estimated from the mixed model.

An evaluation of the association between smoking status and rate of decline in FEV1 demonstrated that in both treatment groups, sustained smokers had the highest mean rate of decline in FEV1, sustained ex-smokers had the lowest rate, and intermittent smokers were in between. Smokers were distributed evenly between the groups, and rate of decline was comparable between treatment groups for all smoker subgroups. See Table 3, Figure 3, and Figure 4. The figures were generated by Dr. Joan Buenconsejo, FDA statistical reviewer.

Table 3: Protocol 205.235 rate of decline in FEV1 by smoking status

	Placebo		Tio HH18		Subgroup treatment interaction n p-value	Difference	
	N	Mean (SE) ml/yr	N	Mean (SE) ml/yr		Mean (SE) ml/yr	p-value
Pre-BD					0.8889		
Sustained ex-smoker	1438	23 (2)	1486	23 (2)		0 (2)	0.8465
Sustained smoker	303	51 (4)	313	51 (4)		0 (5)	0.9865
Intermittent smoker	672	36 (2)	758	35 (2)		2 (3)	0.6493
Post-BD					0.8424		
Sustained ex-smoker	1432	36 (2)	1484	36 (2)		3 (2)	0.1909
Sustained smoker	305	59 (4)	312	59 (4)		0 (5)	0.9807
Intermittent smoker	673	48 (3)	754	46 (2)		2 (3)	0.5731

Figure 3: Protocol 205.235 pre-bronchodilator FEV1 over time by smoking status

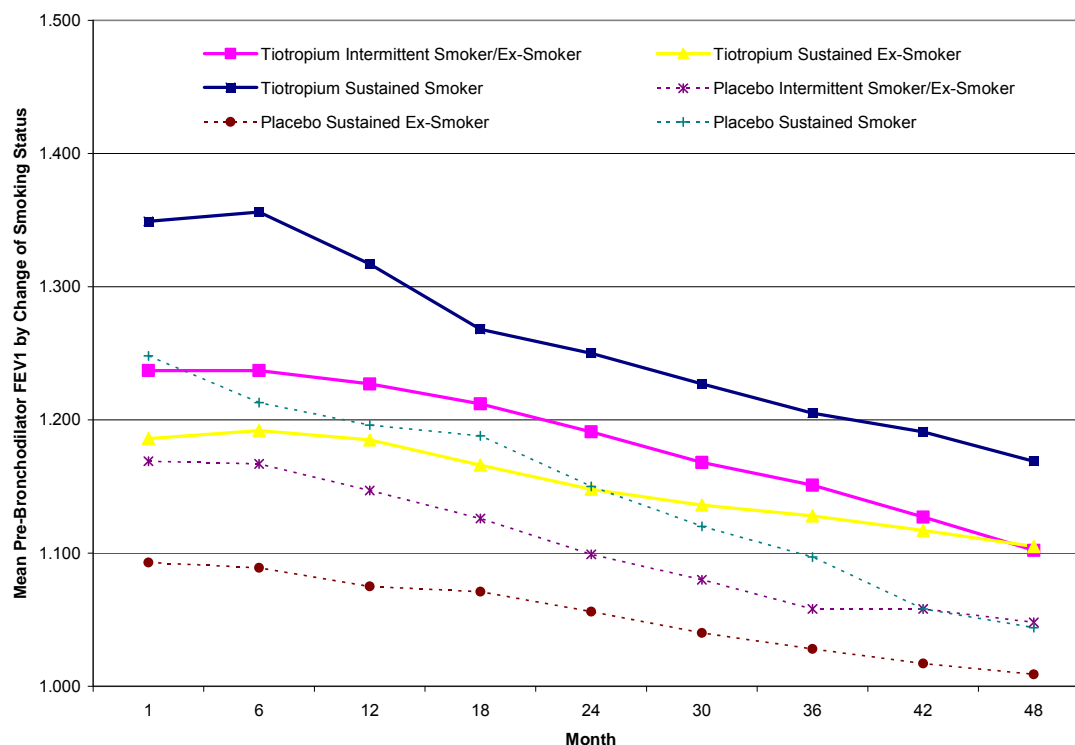
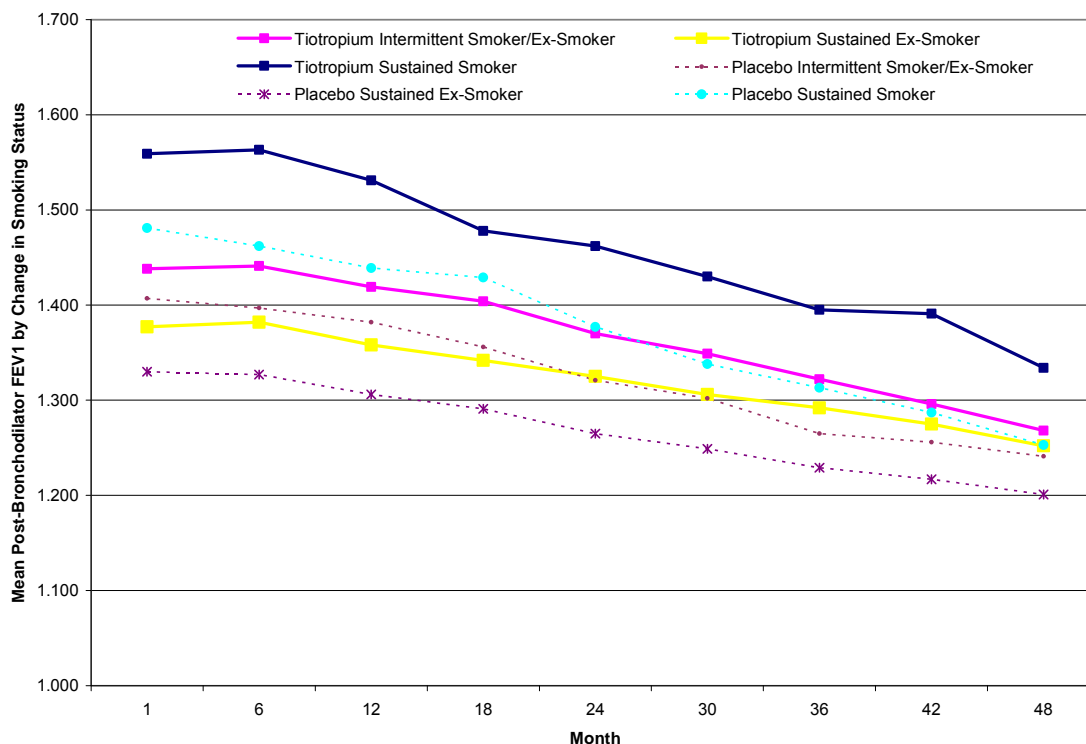


Figure 4: Protocol 205.235 post-bronchodilator FEV1 over time by smoking status



Reviewer comment:

This study failed on the primary endpoint, rate of decline of FEV1. However, it is important to note that the difference between treatment groups is maintained throughout the study, suggesting that tiotropium does not lose bronchodilator efficacy with prolonged use (see subsequent discussion of FEV1 at each timepoint). It is well-accepted in the COPD literature that sustained smoking causes a more rapid decline of lung function compared to patients who are able to quit smoking, in whom the rate of decline returns to similar slope as that of never smokers^{2, 3}. The UPLIFT trial demonstrates this fact nicely, providing internal validation for the FEV1 measurements in the study.

FEV1 endpoints

Mean pre- and post-bronchodilator FEV1 at each visit was estimated using a repeated measure ANOVA model with visit as a discrete variable and baseline value as a covariate. The tio HH18 group had a significantly higher pre- and post-bronchodilator FEV1 compared to placebo at all timepoints. Pre-bronchodilator FEV1 was a trough level performed after wash-out of appropriate pulmonary medications (see section on PFT measurements). For mean pre-bronchodilator FEV1, the estimated mean difference between tio HH18 and placebo groups ranged from 87 to 103 ml ($p < 0.0001$), with an overall mean difference of 94 ml. See Table 4. Post bronchodilator FEV1 was measured after four puffs of albuterol, four puffs of ipratropium and administration of study drug.

For post-bronchodilator FEV₁, the treatment difference ranged from 47 to 65 ml (p<0.0001), with an overall mean difference of 57 ml.

Table 4: Protocol 205.235 FEV₁

Test Day	Broncho-dilator	Placebo [L]	Tio HH18 [L]	Treatment difference [L]	p-value	95% CI
Day 1	Pre	1.116	1.116			
	Post	1.347	1.347			
Month 1	Pre	1.134	1.221	0.087	<0.0001	0.077, 0.098
	Post	1.372	1.418	0.047	<0.0001	0.037, 0.057
Month 6	Pre	1.126	1.225	0.099	<0.0001	0.087, 0.110
	Post	1.365	1.423	0.058	<0.0001	0.047, 0.069
Month 12	Pre	1.111	1.213	0.103	<0.0001	0.091, 0.115
	Post	1.345	1.398	0.054	<0.0001	0.042, 0.065
Month 18	Pre	1.101	1.192	0.091	<0.0001	0.078, 0.104
	Post	1.326	1.379	0.053	<0.0001	0.040, 0.066
Month 24	Pre	1.079	1.173	0.094	<0.0001	0.081, 0.107
	Post	1.294	1.356	0.062	<0.0001	0.049, 0.075
Month 30	Pre	1.061	1.156	0.095	<0.0001	0.081, 0.109
	Post	1.274	1.335	0.061	<0.0001	0.047, 0.075
Month 36	Pre	1.045	1.144	0.099	<0.0001	0.085, 0.114
	Post	1.250	1.315	0.065	<0.0001	0.051, 0.080
Month 42	Pre	1.034	1.129	0.095	<0.0001	0.080, 0.110
	Post	1.236	1.297	0.061	<0.0001	0.045, 0.076
Month 48	Pre	1.024	1.112	0.088	<0.0001	0.073, 0.103
	Post	1.219	1.268	0.049	<0.0001	0.033, 0.065
Overall mean	Pre	1.080	1.174	0.094	<0.0001	0.084, 0.105
	Post	1.298	1.354	0.057	<0.0001	0.046, 0.067

Pre-BD N=2363 placebo, N=2494 tio HH18; Post-BD N=2374 placebo, N=2516 tio HH18

Mean and 95% CI estimated using repeated measured ANOVA adjusted for D1 baseline overall mean value.

The FDA statistical reviewer for this application, Dr. Joan Buenconsejo, also evaluated FEV₁ in terms of a responder analysis. Responders were defined as an improvement of 15% from baseline in trough (pre-bronchodilator) FEV₁. Patients who discontinued from the study were considered non-responders. Using these criteria, at Month 1, 33% of patients in the tio HH18 group were responders compared to 16% in the placebo group. At Month 48, 16% of the tio HH18 group were responders compared to 9% of the placebo group. The proportion of responders in the tio HH18 group was also higher than placebo at all visits for post-bronchodilator FEV₁. See FDA statistical briefing document.

Reviewer comment:

Bronchodilatory effect of tio HH18 is slightly lower than that observed in the Spiriva HandiHaler Phase 3 program. For Spiriva HandiHaler Phase 3 pivotal trials the FEV₁ trough response was 0.110-0.130L. Overall, however, the results are comparable. The spirometry results from this study demonstrate bronchodilator efficacy in a more “real

world” patient population in which there was high use of concomitant respiratory medications. In addition, the results (trough FEV1 treatment difference of 0.09-0.10L) are similar to that observed in Spiriva HandiHaler Protocol 205.266, a Phase 3 trial conducted in a Veteran’s Affairs setting (NDA 21-395, S024), with similar “real world” inclusion criteria.

While the proportion of patients considered responders is relatively low, tio HH18 showed a significant and sustained improvement over placebo at all visits throughout the study. The UPLIFT trial did not have an inclusion criterion for bronchodilator responsiveness. Less than half of patients were considered responders to maximal bronchodilation (4 puffs of albuterol and 4 puffs of ipratropium). Counting missing data (including discontinued patients) as non-responders and evaluation at the end of the dosing interval also contributes to the relatively low percentage of patients with a 15% FEV1 response to therapy. As such, these numbers should not be construed to mean that only 1/6 of patients received benefit from tiotropium after 4 years of therapy. In addition, it is important to put this analysis into context of the study population, who had a baseline pre-bronchodilator FEV1 of only 1.096L. A 15% increase in this population is approximately 164ml, a very large bronchodilator improvement for COPD. Patients who did not demonstrate this large of an increase likely received some benefit. Overall, the responder analysis is supportive of a sustained bronchodilator effect compared to placebo over the course of the study.

FVC measurements

Mean pre- and post-bronchodilator FVC values were significantly increased in the tio HH18 group compared to placebo at all time points from Day 30 to Month 48, with treatment differences for pre-bronchodilator (trough) values ranging from 0.17-0.20 ($p<0.0001$). The overall mean pre-bronchodilator difference was 0.19L ($p<0.0001$). The differences for post-bronchodilator (peak) values ranged from 0.03-0.07L ($p=0.04$, $p<0.0001$), with an overall mean difference of 0.05L ($p<0.0001$).

SVC measurements

Mean pre-bronchodilator (trough) SVC values were significantly increased in the tio HH18 group compared to placebo at all time points from Day 30 to Month 48, with treatment differences ranging from 0.15 to 0.19L ($p<0.0001$). The overall mean pre-bronchodilator difference was 0.17L ($p<0.0001$). The mean post-bronchodilator (peak) SVC values were significantly increased in the tio HH18 group compared to placebo out to Month 36, becoming non significant at months 42 and 28. The differences ranged from 0.03-0.05L. The overall mean post-bronchodilator SVC difference was 0.035L ($p=0.0006$).

Lung function efficacy subgroup analysis

Subgroup analyses were performed for the primary endpoints of rate of decline in pre- and post-bronchodilator FEV1 from Day 30 until the end of treatment. The following subgroup parameters were investigated:

- Age (<55 , ≥ 55 - <65 , ≥ 65 - <75 , ≥ 75 years)
- Gender (male/female)
- Smoking status (active smoker/ex-smoker)

- Race (white/black/Asian)
- Baseline long-acting β -agonist use (yes/no)
- Baseline inhaled corticosteroid use (yes/no)
- Baseline LABA and ICS combination use (yes/no)
- Anticholinergic use (yes/no)
- GOLD stage (I or II/III/IV)
- Region (Asia/Eastern Europe/Latin America/USA/Western Europe)
- Reversibility (yes/no)
- Body mass index ($<20/ \geq 20$ - $<25/ \geq 25$ - $<30/ \geq 30$)

There were no subgroup by treatment interactions, i.e. the same treatment effect (no change in disease progression over time compared to placebo) was observed in each subgroup. As noted previously, current smokers in both treatment groups had a larger loss of lung function over time than did ex-smokers. In addition, younger patients and patients with more preserved lung function at baseline (GOLD Stage I/II) in both treatment groups had a greater loss in lung function over time. See the FDA statistical briefing document for a table of all subgroup analyses for both pre- and post-bronchodilator FEV1.

Reviewer comment:

It makes physiologic sense for younger patients (more likely to be GOLD Stage I/II) and patients with GOLD Stage I/II to lose more lung function (in ml) over time, as the starting point allows a greater loss. In patients with Stage IV disease (FEV1 at baseline of $<1L$), a loss of even a small amount may represent a clinically important decline. If the numbers were expressed as % predicted rather than absolute slope, a more linear curve would be expected (ref Fletcher, 1977).³ In addition, it is possible that smoking status may have confounded the age and GOLD stage evaluations, because younger patients with better lung function may be more likely to be active smokers.

4.1.4 Lung Function Efficacy Conclusions

The UPLIFT study showed no significant difference between treatment groups in the primary endpoints of rate of decline in pre- and post-bronchodilator FEV1. In a subgroup analysis, patients who were sustained quitters from smoking did experience a significant decrease in rate of decline in FEV1 compared to sustained smokers. This effect was observed across both treatment groups.

The Applicant offers two plausible explanations for the failure of the UPLIFT trial to demonstrate a difference in long-term rate of decline in FEV1, confounding by concomitant disease-modifying therapy and differential discontinuation biasing against tiotropium. While these effects may be real, the UPLIFT design overall was significantly strengthened by its “real world” approach to inclusion of multiple concomitant medications, similar to the situation encountered in the COPD population in the United States. Thus, one can conclude that in the setting of high-quality COPD care, the addition of tiotropium is unlikely to impact the natural history of disease.

Spirometry endpoints included trough FEV₁, FVC, and SVC response and 90 minute FEV₁ FVC, and SVC response. Endpoints were measured every six months throughout the four year treatment period. Consistent with the known bronchodilator properties of

the drug, the tio HH18 group generally demonstrated a significant improvement ($p < 0.0001$) over placebo for all endpoints and time points tested.

Based upon review of the pulmonary function data, the Applicant's proposed claim is generally supported. It is reasonable to describe UPLIFT in the product label and note that the primary endpoints were not significantly different. Regarding the sustained improvement in trough FEV1, this is consistent with the current indication and efficacy data in the product label and would also be reasonable to include in the description of the outcomes of UPLIFT in the product label.

4.2 Effects on COPD Exacerbations

Boehringer Ingelheim (BI) proposes a labeling claim related to COPD exacerbations in the product label.

4.2.1 Methods

To support this application, BI submitted the UPLIFT trial, a 4-year randomized, placebo controlled trial evaluating the efficacy of Spiriva HandiHaler in a population of patients with moderate to severe COPD. In addition, the Veterans Affairs trial mentioned in the proposed labeling (Protocol 205.266) is discussed briefly in this section and is provided in detail in Section 6.1.2.

4.2.2 General Discussion of COPD Exacerbation Endpoints

COPD exacerbations were recorded on an ongoing basis throughout the UPLIFT study. As an aid to recall, patients were given a Patient Daily Record book that was reviewed at each visit.

For the purposes of the UPLIFT trial, a COPD exacerbation was defined as "an increase or new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three days or more requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous) steroids." The onset of the COPD exacerbation was defined by the onset of the first recorded symptom. The end of the COPD exacerbation was recorded as defined by the investigator.

Exacerbation events were derived based on the adverse event (AE) records on the exacerbation AE CRF page. All events included on the exacerbation AE CRF were included in the efficacy analysis whether or not BI determined that they met all components of the protocol exacerbation definition. In addition to standard AE reporting, total days on antibiotics, total days on systemic steroid bursts, and number of hospitalized days (broken into regular ward and intensive care unit) were also collected for all COPD exacerbation events. Overlapping exacerbations were collapsed into one exacerbation. Two exacerbations were considered distinct events if there were at least 7 exacerbation-free days between the end of one event and the start of the next one.

Exacerbations were categorized as mild, moderate, and severe according to the following definitions:

- mild: treated at home without seeing a health care provider

- moderate: visit with a health care provider (e.g., home visit, visit to an outpatient facility or an emergency department) but not requiring admission to hospital
- severe: hospitalization (emergency room visits >24 hours were considered hospitalizations)

Reviewer comment:

The definition of COPD exacerbation 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 definition is essentially the same as the one used in the Spiriva HandiHaler VA study (Protocol 205.266), with only a slight variation in wording. 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 exists, although in general the definition used in this study is acceptable.

The Applicant initially proposed to combine events with one day or fewer between events, and look at combination of 7 days between events as a sensitivity analysis. The Applicant changed the SAP based on feedback from FDA. From a clinical perspective, recurrence of an event a few days after stopping therapy likely represents recurrence of an incompletely treated exacerbation rather than a new event. In previous Spiriva trials (including 205.266), sensitivity analysis evaluating combining events with one versus 7 days between events did not make a significant difference in overall outcome.

The definition of COPD exacerbation was essentially the same for Protocol 205.266 as in the UPLIFT trial. A slight difference was that the list of symptoms did not include sputum purulence, although increased sputum was included.

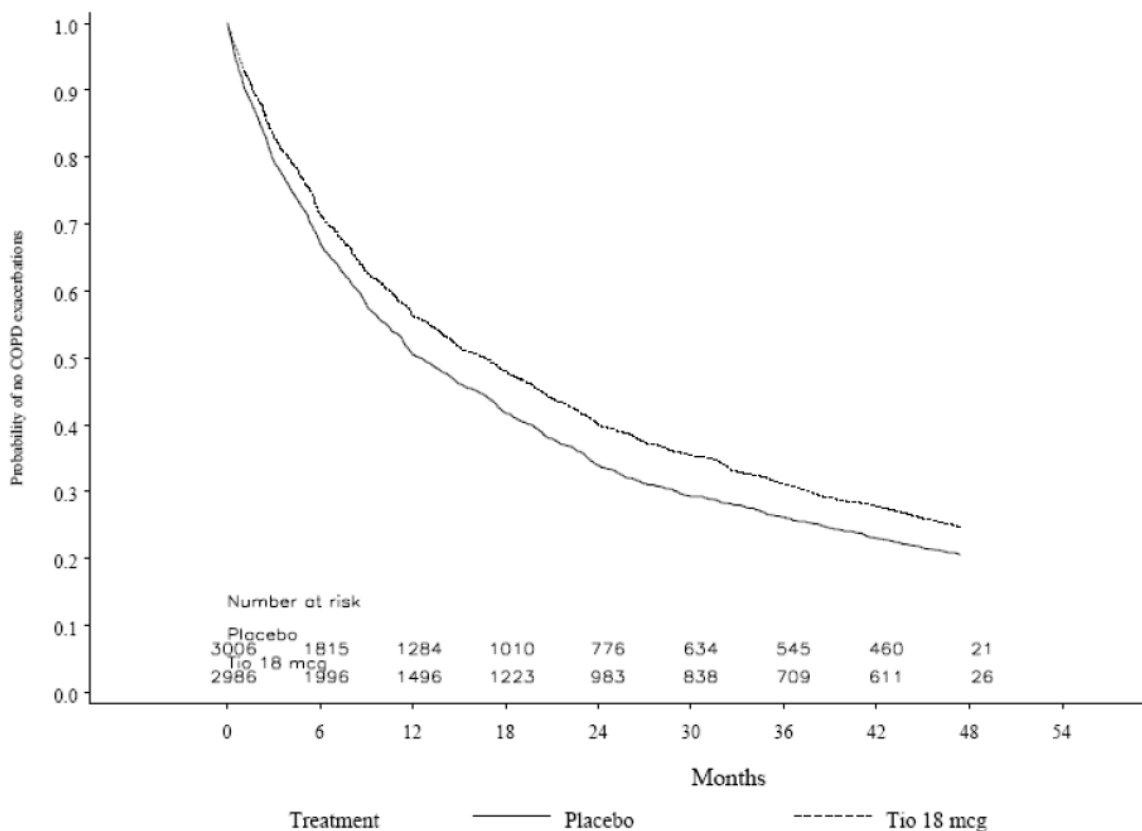
4.2.3 COPD Exacerbation related Efficacy Findings

Protocol 205.235 (UPLIFT) key secondary endpoints

There were two key secondary endpoints for Protocol 205.235, time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization.

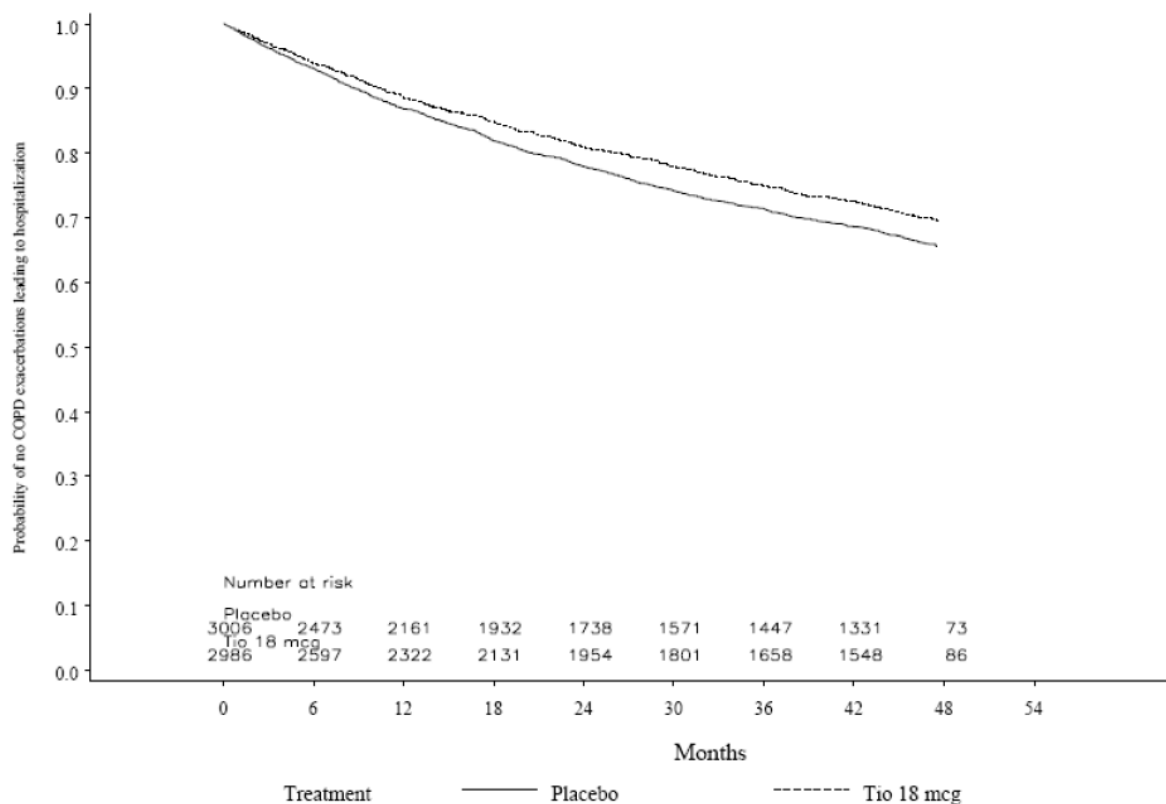
For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p < 0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. A Kaplan-Meier estimate of the probability of no exacerbation as provided by the Applicant is presented in Figure 5.

Figure 5: Study 205.235 Kaplan-Meier estimates of the probability of no exacerbation



The Applicant also reports that patients in the tio HH18 group had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p = 0.0024$, RR 0.86, 95% CI 0.78, 0.95). The median time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group. Since only 27% of the placebo group and 25% of the tio HH18 group experienced exacerbations leading to hospitalizations, the median time to first exacerbation was calculated based on the first 25% of patients with exacerbations. A Kaplan-Meier estimate of the probability of no exacerbation resulting in hospitalization as provided by the Applicant is presented in Figure 6.

Figure 6: Protocol 205.235 Kaplan-Meier estimates of the probability of no exacerbation leading to hospitalization



Reviewer comment:

Significance was not achieved for the co-primary endpoints; however, the key secondary endpoints showed a significant difference from placebo with an unadjusted p -value of <0.0001 . Strictly speaking, because the trial adjusted for multiplicity using a step-wise approach, i.e. allowing testing of secondary endpoints only if the primary endpoints were met, the trial could be considered “failed” for the secondary endpoints as well. Adjusting for multiplicity in a more-conventional way, a $p < 0.01$ would be considered to show statistical significance, which the trial met.

Clinically, the exacerbation endpoints are clinically important, and the failure of the study to show an improvement in disease progression does not detract from the finding of improvement in exacerbations, which was also replicated in a second, independent study (Protocol 205.266). If the exacerbation finding had been less robust, adjustments for multiplicity would pose a greater concern.

This same argument also applies to labeling claims regarding lung function, which from a statistical standpoint also represent secondary endpoints with a failed primary. In addition, it would be difficult to provide a description of the study in the label without discussing lung function. Regardless of efficacy, it is important to describe the UPLIFT in the product label due to the safety implications of such a large, long-term trial.

Protocol 205.266 (VA trial) COPD exacerbation endpoints

There were two co-primary endpoints for this study, proportion of patients experiencing a COPD exacerbation and the proportion of patients with a hospitalization associated with a COPD exacerbation during the 6-month period. Treatment response was defined to be the odds-ratio for tiotropium compared to placebo.

The percentage of patients with a COPD exacerbation meeting the protocol definition was significantly lower for tio HH18 compared to placebo ($p=0.04$), with an odds ratio of 0.806. A sensitivity analysis evaluating all events reported by the investigator as exacerbations whether or not meeting protocol definitions demonstrated similar results. The percentage of patients with a hospitalization due to COPD exacerbation was numerically lower in the tio HH18 group compared to placebo, but did not reach statistical significance ($p=0.06$), with an odds ratio of 0.718. See Table 5.

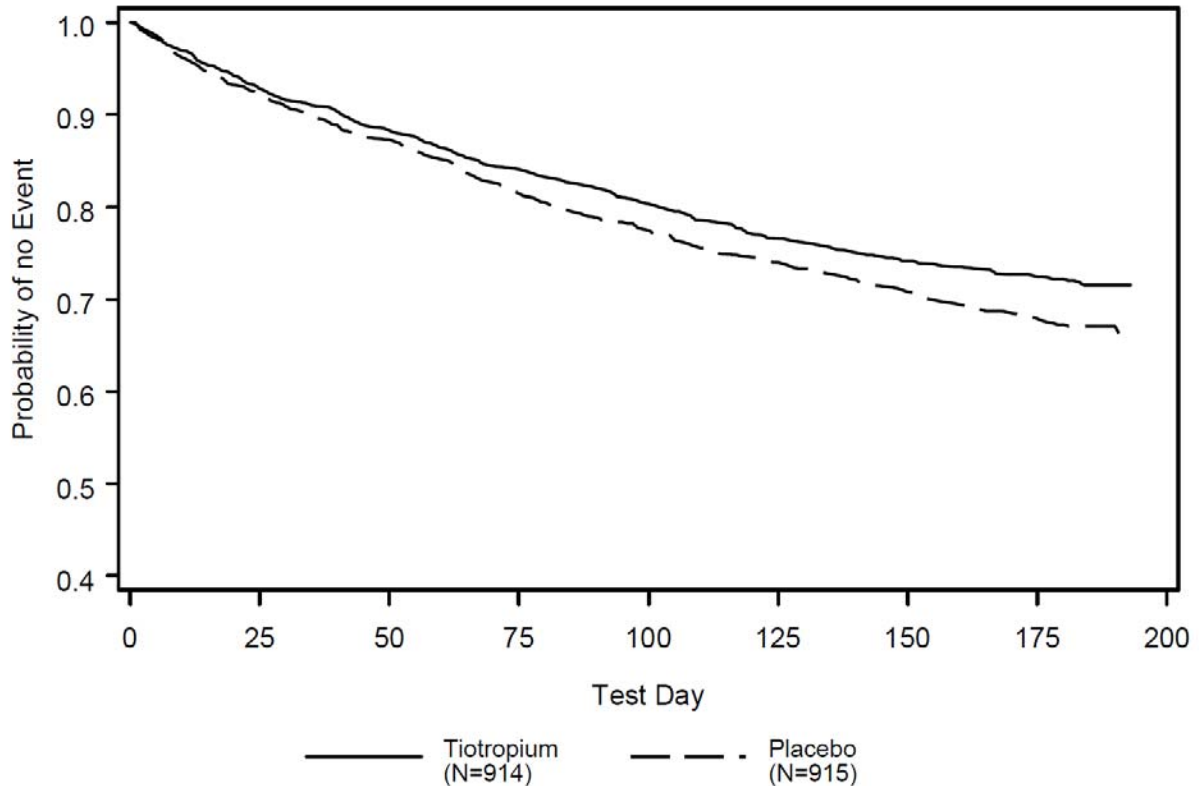
Table 5: Protocol 205.266 percentage of patients with COPD exacerbations

Endpoint (percent of patients)	Tio HH18 (N=914)	Placebo (N=915)	Odds ratio	p-value
Exacerbations meeting protocol definition	27.9	32.3	0.806	0.0368
Hospitalizations due to exacerbation	7	9.5	0.718	0.0557
All reported exacerbations	27.9	32.6	0.798	0.0287

Key secondary endpoints in Protocol 205.266 (VA trial) included time to first COPD exacerbation and time to first hospitalization associated with a COPD exacerbation.

For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p=0.04$, RR 0.834). Time to first exacerbation is not given for either group. A Kaplan-Meier estimate of the probability of no exacerbation as provided by the Applicant is presented in Figure 7: Study 205.266 Kaplan-Meier estimates of the probability of no exacerbation.

Figure 7: Study 205.266 Kaplan-Meier estimates of the probability of no exacerbation



The Applicant also reports that patients in the tio HH18 group had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p=0.05$, RR 0.723).

Protocol 205.235 (UPLIFT) other COPD exacerbation related endpoints

A number of additional endpoints related to COPD exacerbations were examined, including:

- number of COPD exacerbations
- time to first exacerbation treated with steroids
- time to first exacerbation treated with antibiotics
- number of patients with at least one COPD exacerbation
- number of exacerbations treated with steroids
- number of exacerbation days
- number of COPD exacerbations leading to hospitalization
- number of patients with at least one exacerbation leading to hospitalization
- number of days hospitalized due to exacerbation per patient year

The endpoints involving number of exacerbation events are calculated per person year, with a correction for overdispersion. Results as calculated by the Applicant are presented in Table 6. All recorded COPD events were included in the analysis. The Applicant reports that 98.8% of the recorded exacerbation events agreed with the protocol definition.

Table 6: Protocol 205.235 COPD related events endpoints

Endpoint	Placebo	Tio HH18	Risk Ratio	p-value
Exacerbations/pt year	0.85	0.73	0.86	<0.0001
Time to first exacerbation with steroids [median, month]	26.4	36.5	0.84	<0.0001
Time to first exacerbation with antibiotics [median, month]	16.2	19.8	0.87	<0.0001
Pts with exacerbations [%]	68	67	NC	0.3481
Exacerbations with steroids	0.52	0.44	0.84	<0.0001
Exacerbations with antibiotics	0.71	0.62	0.87	<0.0001
Exacerbation days [mean]	13.6	12.1	0.89	0.0011
Exacerbations with hospitalization	0.16	0.15	0.94	0.3413
Pts hospitalized due to exacerbation [%]	27	25	NC	0.1766
Days in hospital due to exacerbations [mean]	3.13	3.17	1.01	0.8624

All endpoints other than time to first event and percent of patients are reported as number of events per patient-year. Poisson regression analysis adjusted for overdispersion was used.

NC=not calculated

Reviewer comment:

These exacerbation endpoints are generally in favor of tiotropium. The number of exacerbations per patient year is consistent with that found in Study 205.266 (VA study, NDA 21-395, S-024), in which the number of exacerbations per patient year was 0.876 in the placebo group and 0.711 in the tio HH18 group, giving a risk ratio of 0.812. The percent of patients with exacerbations and hospitalized with exacerbations may be biased against tiotropium due to differential drop out from the placebo group.

This analysis correctly adjusts for overdispersion. The default Poisson regression technique assumes that all patients are homogenous with respect to their rate of exacerbation. The correction for overdispersion takes into account that for COPD, the majority of exacerbations occur in a small portion of patients while the rest of the population has no exacerbations.⁴ The method of calculation of exacerbation rate and correction for overdispersion is critical as different statistical methodologies may give very different results.

COPD exacerbation subgroup analysis

Subgroup analyses were conducted for the time to first exacerbation, time to first exacerbation leading to hospitalization, and number of exacerbations per patient year. The following subgroup parameters were investigated:

- Age (<55, ≥55-<65, ≥65-<75, ≥75 years)
- Gender (male/female)
- Smoking status (active smoker/ex-smoker)
- Race (white/black/Asian)
- Baseline long-acting β -agonist use (yes/no)
- Baseline inhaled corticosteroid use (yes/no)
- LABA and ICS combination use (yes/no)
- Baseline anticholinergic use (yes/no)
- GOLD stage (I or II/III/IV)
- Region (Asia/Eastern Europe/Latin America/USA/Western Europe)
- Reversibility (yes/no)
- Body mass index (<20/ ≥20-<25/ ≥25-<30/ ≥30)

There were no significant subgroup by treatment interactions. Patients with GOLD stage I/II disease overall had fewer exacerbations with a longer time to the first exacerbation, as would be expected for milder disease. For patients with GOLD stage IV disease, the time to first COPD exacerbation was not improved with Spiriva as it was in other subgroups. However, this may have been a statistical anomaly as the numbers were relatively small and the time to first COPD exacerbation requiring hospitalization and number of exacerbations per year were improved in this subgroup. All other subgroups were relatively homogeneous with respect to COPD exacerbation treatment effect. See Table 7 for the subgroup analysis of number of patients with exacerbations and median time to first exacerbation. See the statistical background document for the subgroup analyses of COPD exacerbations leading to hospitalization (number of patients and median time to first exacerbation for 25% of patients) and estimated rate of exacerbations per patient-year.

Table 7: Protocol 205.235 subgroup analysis of COPD exacerbation: number (%) of patients with an exacerbation and median time to first exacerbation (in months)

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	2049/3006 (68%) 13 months	2001/2986 (67%) 17 months	0.86 (0.81, 0.91)	
Sex: Female	539/784 (69%) 10 months	496/735 (68%) 15 months	0.83 (0.74, 0.94)	
Male	1510/2222 (68%) 13 months	1505/2251 (67%) 17 months	0.87 (0.81, 0.93)	0.5632
Gold Stage: I/II	883/1356 (65%) 17 months	824/1386 (60%) 23 months	0.82 (0.75, 0.90)	
III	942/1331 (71%) 10 months	944 /1304 (72%) 13 months	0.87 (0.79, 0.95)	

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	2049/3006 (68%) 13 months	2001/2986 (67%) 17 months	0.86 (0.81, 0.91)	
IV	188/271 (69%) 9 months	200/250 (80%) 10 months	0.99 (0.81, 1.21)	0.2341
Baseline Smoking Status: Ex-Smoker	1458/2108 (69%) 12 months	1437/2112 (68%) 16 months	0.86 (0.80, 0.93)	
Smoker	591/898 (66%) 14 months	564/874 (65%) 18 months	0.85 (0.76, 0.95)	0.8680
Reversibility: Yes	1036/1513 (69%) 13 months	1021/1520 (67%) 17 months	0.86 (0.79, 0.94)	
No	946/1393 (68%) 12 months	913/1357 (67%) 16 months	0.86 (0.79, 0.94)	0.9854
Baseline ICS: Yes	1338/1860 (72%) 10 months	1302/1840 (71%) 13 months	0.85 (0.79, 0.92)	
No	711/1146 (62%) 18 months	699/1146 (61%) 23 months	0.86 (0.78, 0.96)	0.8068
Baseline LABA: Yes	1302/1808 (72%) 11 months	1275/1796 (71%) 13 months	0.85 (0.79, 0.92)	
No	747/1198 (62%) 17 months	726/1190 (61%) 22 months	0.87 (0.78, 0.96)	0.7171
Baseline ICS/LABA: Yes	1066/1462 (73%) 10 months	1052/1464 (72%) 12 months	0.86 (0.79, 0.93)	
No	983/1544 (64%) 17 months	949/1522 (62%) 21 months	0.86 (0.78, 0.94)	0.9146
Race: White	1845/2697 (68%) 12 months	1817/2691 (68%) 16 months	0.87 (0.81, 0.92)	
Black	36/53 (68%) 18 months	19/38 (50%) 41 months	0.48 (0.28, 0.85)	
Asian	118/185 (64%) 13 months	119/192 (62%) 18 months	0.81 (0.63, 1.05)	0.2310
Region: Asia	114/178 (64%) 13 months	113/184 (61%) 18 months	0.81 (0.62, 1.05)	
E. Europe	402/597 (67%) 20 months	367/590 (62%) 21 months	0.88 (0.76, 1.01)	
Latin America	163/207 (79%) 9 months	142/198 (72%) 15 months	0.78 (0.63, 0.98)	

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	2049/3006 (68%) 13 months	2001/2986 (67%) 17 months	0.86 (0.81, 0.91)	
USA	489/767 (64%) 12 months	477/767 (62%) 18 months	0.80 (0.71, 0.91)	
W. Europe	881/1257 (70%) 11 months	902/1247 (72%) 13 months	0.90 (0.82, 0.99)	0.5122
Age: <55	254/382 (67%) 12 months	248/384 (65%) 18 months	0.83 (0.70, 0.99)	
55 –<65	716/1055 (68%) 14 months	714/1054 (68%) 17 months	0.90 (0.81, 0.99)	
65 –<75	825/1198 (69%) 13 months	810/1208 (67%) 17 months	0.86 (0.78, 0.95)	
≥ 75	254/371 (69%) 9 months	229/340 (67%) 13 months	0.76 (0.64, 0.91)	0.4440
BMI: <20	263/352 (75%) 10 months	216/297 (73%) 13 months	0.76 (0.64, 0.91)	
20 –<25	673/1024 (66%) 12 months	709/1074 (66%) 16 months	0.86 (0.78, 0.96)	
25 –<30	704/1033 (68%) 14 months	705/1039 (68%) 17 months	0.91 (0.82, 1.01)	
≥ 30	407/597 (68%) 13 months	371/576 (64%) 19 months	0.82 (0.71, 0.94)	0.4118
Baseline Anticholinergic: Yes	922/1350 (68%) 11 months	950/1366 (70%) 14 months	0.87 (0.79, 0.95)	
No	1127/1656 (68%) 15 months	1051/1620 (65%) 18 months	0.85 (0.78, 0.92)	0.7960

*Hazard ratio based on Cox model with treatment, baseline covariate and baseline covariate by treatment interaction;
p-value was obtained using log-rank test.

Reviewer comment:

The subgroup analysis notes baseline anticholinergic use in 45% of the study population. This should not be construed to mean that these patients remained on anticholinergics, which were prohibited during the trial. The rate of protocol violations for anticholinergic use was approximately 3.8%.

4.2.4 COPD Exacerbation Efficacy Conclusions

For the key secondary endpoints in Protocol 205.235 (UPLIFT) of time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization, tiotropium showed a significant difference compared to placebo. For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p < 0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months

in the tio HH18 group. Patients in the tio HH18 group also had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p=0.0024$, RR 0.86, 95% CI 0.78, 0.95). The median time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group.

A significant improvement in most of the additional COPD exacerbation-related endpoints was also observed. These included the number of COPD exacerbations, time to first exacerbation treated with steroids, time to first exacerbation treated with antibiotics, number of exacerbations treated with steroids, number of exacerbation days, number of COPD exacerbations leading to hospitalization, and number of days hospitalized due to exacerbation per patient year. In conjunction with supportive evidence from Protocol 205.266 (VA study, submitted under NDA 21-395, S-024), these data are clinically supportive of an exacerbation claim. Statistical issues of multiplicity may require discussion.

5 INTEGRATED REVIEW OF SAFETY

5.1 Methods

Safety review included Protocol 205.235 (UPLIFT) as well as an analysis of pooled data from 30 clinical trials conducted with tiotropium (HandiHaler and Respimat). Safety endpoints for the UPLIFT trial included all adverse events, including serious adverse events, all cause mortality, and respiratory mortality. Other than the pooled data, data presented in the Integrated Review of Safety are from the analysis of UPLIFT data. A review of the safety data from the VA study was also performed and is included in the Study 205.266 review in the Appendix. In Protocol 205.266 (VA trial) only serious adverse events were recorded (not all adverse events), so the safety data are limited.

All adverse events, serious and non-serious, were collected in an ongoing fashion throughout the trial (Protocol 205.235) until the end of the double-blind treatment period. At each study visit, all AEs regardless of causality were recorded after review of the Patient Daily Record and discussion with the patient. In addition, all serious adverse events that occurred within 30 days of the last dose of study drug were reported. Adverse events were followed until resolution, until follow up was agreed adequate by the monitor and investigator, or until a patient was lost to follow up. Elective procedures planned prior to signing informed consent were not considered adverse events. Adverse events were monitored by an independent Data Safety Monitoring Board (DSMB).

A protocol amendment allowed for long-term assessment of outcome for patients prematurely discontinued from UPLIFT. Vital status, including cause of death, if known, was collected every 6 months beginning November 15, 2005 for each discontinued patient until completion of the planned observation period (4 years). Vital status was recorded on a separate CRF that captured the following variables: 1) patient's vital status (alive, deceased, or unknown), 2) date of death, 3) cause of death, 4) source of information, 5) additional information regarding the circumstances, 6) if the patient's status was unknown, the date the patient was last known to be alive, and 7) the investigator's signature and date. At the time the amendment was instituted,

approximately 1,500 of the 6,000 patients enrolled in the UPLIFT trial had prematurely discontinued from participation.

5.2 Demographics

The mean age of the patients in Protocol 205.235 was 64.5 years (range 40-88 years). The majority of the trial population (74.6%) was male and 89.9% were white. The mean duration of COPD was 9.8 years. All patients were current (29.6%) or ex-smokers (70.4%), with a mean smoking history of 48.7 pack years. The mean pre-bronchodilator FEV₁ was 1.096L with a mean percent predicted of 39.4%. The mean pre-bronchodilator FEV₁/FVC was 42.3%. The overall demographic profile was generally balanced across the treatment groups. Pulmonary function data at baseline were generally comparable. Demographic and disease characteristics are provided in Table 8, and baseline PFT variables are provided in Table 9.

Table 8: Protocol 205.235 patient demographic and disease characteristics

	Placebo	Tio HH18	Total
Number of patients	3006	2986	5992
Gender [N (%)]			
Male	2222 (73.9)	2251 (75.4)	4473 (74.6)
Female	784 (26.1)	735 (24.6)	1519 (25.4)
Race [N (%)]			
White	2697 (89.7)	2691 (90.1)	5388 (89.9)
Black	53 (1.8)	38 (1.3)	91 (1.5)
Asian	185 (6.2)	192 (6.4)	377 (6.3)
Missing	71 (2.4)	64 (2.2)	136 (2.3)
Age [years]			
Mean	64.5	64.5	64.5
SD	8.5	8.4	8.5
Min	40.0	40.0	40.0
Max	88.0	88.0	88.0
Smoking history [N (%)]			
Ex smoker	2108 (70.1)	2112 (70.7)	4220 (70.4)
Smoker	898 (29.9)	874 (29.3)	1772 (29.6)
Smoking history [pack years]			
Mean	48.4	49	48.7
SD	27.9	28.0	27.9
Min	10.0	10.0	10.0
Max	285.0	225.0	285.0
Duration of COPD [years]			
Mean	9.7	9.9	9.8
SD	7.4	7.6	7.5
Min	0.0	0.08	0.0
Max	53.0	55.0	55.0
Gold stage [N (%)]			
Stage I	1 (0.0)	2 (0.1)	3 (0.1)
Stage II	1355 (45.1)	1384 (46.3)	2739 (45.7)
Stage III	1331 (44.3)	1304 (43.7)	2635 (44.0)
Stage IV	271 (9.0)	250 (8.4)	521 (8.7)
missing	48 (1.6)	46 (1.5)	94 (1.6)

Table 9: Protocol 205.235 baseline PFT data

	Tio HH18	Placebo	Total
Number of patients	3006	2986	5992
Pre-bronchodilator FEV₁ [L]			
Mean	1.092	1.101	1.096
SD	0.40	0.40	0.40
Min	0.29	0.28	0.28
Max	2.71	2.64	2.71
Pre-bronchodilator % predicted normal FEV₁			
Mean	39.3	39.5	39.4
SD	11.9	12.0	12.0
Min	9.0	11.0	9.0
Max	76.0	73.0	76.0
Pre-bronchodilator FVC [L]			
Mean	2.63	2.63	2.63
SD	0.83	0.81	0.82
Min	0.64	0.67	0.64
Max	6.70	6.13	6.70
Pre-bronchodilator FEV₁ / FVC [%]			
Mean	42.1	42.4	42.3
SD	10.5	10.5	10.5
Min	15.0	14.0	14.0
Max	76.0	75.0	76.0

Data were Obtained from Visit 2, Randomization Visit.

Reviewer comment:

The demographics in this study are highly consistent with those across the Phase 3 programs for Spiriva HandiHaler.

5.3 Extent of exposure (dose/duration)

A total of 5992 COPD patients were randomized and received at least one dose of study drug. The planned exposure for each patient was 1440 days (approximately 48 months). One eligible patient withdrew at the randomization visit, prior to receiving study drug. One additional patient was randomized twice in error (once to each treatment group).

Mean exposure to study drug for all patients was 1080 days. Significantly fewer ($p < 0.0001$) patients in the tio HH18 group prematurely discontinued than in the placebo group [1080 (36.2%) versus 1341(44.6%)]. The highest percentage of discontinuations occurred in the first year of treatment. A summary of patient exposure is provided in Table 10.

Table 10: Protocol 205.235 summary of treatment exposure

	Placebo N=3006 n (%)	Tio HH18 N=2986 n (%)	Total N=5992 n (%)
Total treated			
Exposure (months)			
≥ 1	2867 (95.4)	2915 (97.6)	5782 (96.5)
≥ 3	2740 (91.2)	2816 (94.3)	5556 (92.7)
≥ 6	2618 (87.1)	2726 (91.3)	5344 (89.2)
≥ 9	2513 (83.6)	2634 (88.2)	5147 (85.9)
≥ 12	2418 (80.4)	2565 (85.9)	4983 (83.2)
≥ 15	2344 (78.0)	2496 (83.6)	4840 (80.8)
≥ 18	2249 (74.8)	2432 (81.4)	4681 (78.1)
≥ 21	2161 (71.9)	2363 (79.1)	4524 (75.5)
≥ 24	2090 (69.5)	2293 (76.8)	4383 (73.1)
≥ 27	2013 (67.0)	2236 (74.9)	4249 (70.9)
≥ 30	1947 (64.8)	2177 (72.9)	4124 (68.8)
≥ 33	1891 (62.9)	2117 (70.9)	4008 (66.9)
≥ 36	1831 (60.9)	2060 (69.0)	3891 (64.9)
≥ 39	1779 (59.2)	2001 (67.0)	3780 (63.1)
≥ 42	1723 (57.3)	1970 (66.0)	3693 (61.6)
≥ 45	1665 (55.4)	1904 (63.8)	3569 (59.6)
Treatment Exposure (days)			
Mean	1032.7	1128.1	1080.3
Min	1	1	1
Max	1550	1655	1655

Protocol violations

There were a total of 440 patients with protocol violations in this study; 7.5% (223 patients) of the tioHH18 group and 7.2% (217 patients) of the placebo group. The most common protocol violations were due to use of anticholinergics on at least 2 consecutive visits (112 patients in the tiotropium group and 115 in the placebo group. Of the 60 patients with post-bronchodilator FEV1 >70% of predicted or post-bronchodilator FEV1>70% of FVC at either Visit 1 or 2, the majority had post-bronchodilator FEV1% of predicted or post-bronchodilator FEV1% of FVC values ranging from 71-75%. See Table 11.

Table 11: Protocol 205.235 protocol violations

Protocol violation	Tio HH18 N=3006 n (%)	Placebo N=2986 n (%)	Total N=5992 n (%)
Total with protocol violation	217 (7.2)	223 (7.5)	440 (7.3)
Entrance criteria not met			
Known active tuberculosis	0	1 (0.0)	1 (0.0)
History of excluded pulmonary disease	10 (0.3)	7 (0.2)	17 (0.3)
History of thoracotomy with resection	1 (0.0)	4 (0.1)	5 (0.1)
Respiratory infection/COPD exacerbation	26 (0.9)	29 (1.0)	55 (0.9)
Unstable respiratory medication use	7 (0.2)	10 (0.3)	17 (0.3)
Known narrow angle glaucoma	1 (0.0)	3 (0.1)	4 (0.1)
Symptomatic prostatic hyperplasia	0	1 (0.0)	1 (0.0)
Malignancy in last 5 years	5 (0.2)	2 (0.1)	7 (0.1)
Anticholinergic drug hypersensitivity	0	1 (0.0)	1 (0.0)
Involved in other trials	0	1 (0.0)	1 (0.0)
FEV1>70% or FEV1/FVC>70%	28 (0.9)	32 (1.1)	60 (1.0)
Informed consent signed late	2 (0.1)	2 (0.1)	4 (0.1)
Improper medication wash out	39 (1.3)	43 (1.4)	82 (1.4)
Incorrect trial medication taken	1 (0.0)	0	1 (0.0)
Anticholinergic use for ≥2 consecutive visits	115 (3.8)	112 (3.8)	227 (3.8)

Reviewer comment:

Protocol violations were generally balanced between the treatment groups. The rate of protocol violations is consistent with those seen across the Spiriva Phase 3 programs. The persistent use of anticholinergics was noted in only a small percentage of patients, which was similar between treatment groups. This is unlikely to affect the results of the study.

Treatment compliance

Medication compliance was determined by counting returned capsules of study medication. Compliance was defined as the percentage of capsules taken over the planned total. As a patient should take one capsule per day, compliance of the patient was calculated as number of capsules used divided by the number of days that the patient was on treatment. More patients in the tio HH18 group than in the placebo group had compliance of >80%. See Table 12.

Table 12: Protocol 205.235 treatment compliance

Compliance	Placebo N=3006 N (%)	Tio HH18 N=2986 N (%)	Total N=5992 N (%)
0 - < 50%	212 (7.1)	138 (4.6)	350 (5.8)
50% - <80%	425 (14.1)	347 (11.6)	772 (12.9)
80% - <120%	2331 (77.5)	2467 (82.6)	4798 (80.1)
≥ 120%	8 (0.3)	7 (0.2)	15 (0.3)
incomplete	5 (0.2)	6 (0.2)	11 (0.2)
missing	25 (0.8)	21 (0.7)	46 (0.8)

Reviewer comment:

Compliance for this study overall was good, although lower than in the Phase 3 Spiriva programs. This is to be expected, because the UPLIFT protocol had a duration of 4 years, during which compliance might be expected to decrease. It is also relevant that patients in the Spiriva group had improved compliance compared to the placebo group, suggesting that patients may have felt benefit from the drug.

5.4 Deaths

The UPLIFT Mortality Adjudication Committee adjudicated all the causes of death. Several terms were pre-specified on the worksheets used by the UPLIFT Mortality Adjudication Committee: stroke, COPD (with pneumonia, without pneumonia, or pneumonia not specified), pneumonia, pulmonary embolism, congestive heart failure, myocardial infarction, lung cancer, breast cancer, colorectal cancer, sudden cardiac death, sudden death, and death of unknown cause.

Vital status was collected on all patients who prematurely discontinued from the trial extending to 4 years post-randomization. The primary cause of each death was adjudicated by an independent committee. Time to death was defined as time to the end date of the fatal AE (date of death). The primary analysis evaluated deaths with a cut off date of 1440 days (4 years); however, evaluations with a cut off date of 1470 days (4 years plus 30 days) and no cut off date were also conducted. The Applicant also presents fatal events in two ways: 1) deaths on treatment and 2) deaths including post-discontinuation vital status. The adjudicated cause of death is presented as the primary analysis, but investigator-reported cause of death is also presented. Both on-treatment deaths and deaths collected as vital status on discontinued patients were adjudicated as to cause.

Overall, the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tio HH18 group. The risk ratio for death from any cause (tiotropium/placebo) was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data. See Table 13.

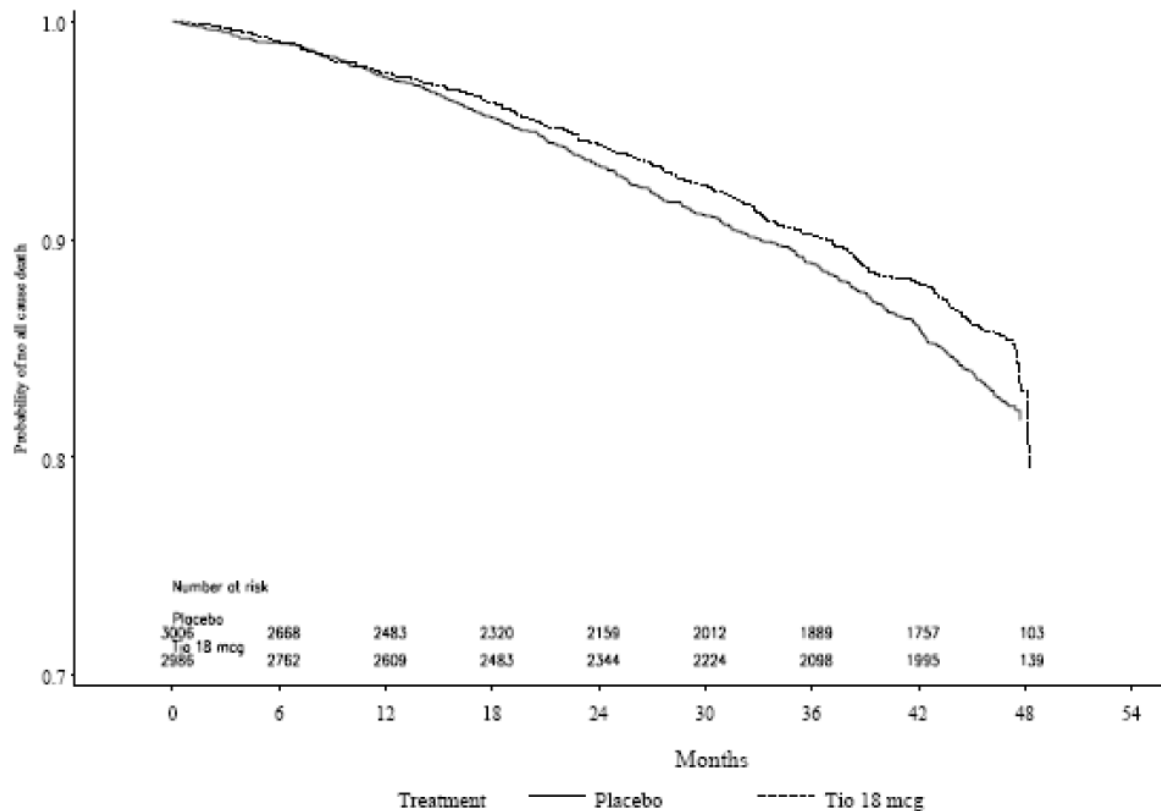
Table 13: Protocol 205.235 fatal event summary

	Placebo N (%)	Tio HH18 N (%)	Rate difference	Risk Ratio	Risk Ratio Tio HH18 vs. Placebo 95% CI	p-value
On treatment (Day 1440)	400 (13.3)	361 (12.1)	1.2%	0.83	0.72, 0.95	0.010
On treatment (Day 1470)	402 (13.4)	374 (12.5)	0.9%	0.85	0.74, 0.98	0.024
On treatment (all)	411 (13.7)	381 (12.8)	0.9%	0.84	0.73, 0.97	0.016
Vital status (Day 1440)	491 (16.3)	430 (14.4)	1.9%	0.87	0.76, 0.99	0.034
Vital status (Day 1470)	495 (16.5)	446 (14.9)	1.6%	0.89	0.79, 1.02	0.086
Vital status (all)	514 (17.1)	467 (15.6)	1.5%	0.89	0.78, 1.00	0.058

On-treatment mortality

A Kaplan-Meier estimate of the probability of no death on treatment as presented by the Applicant is given in Figure 8. The curves show separation after 12 months out to 48 months.

Figure 8: Protocol 205.235 Kaplan-Meier estimates of probability of no all cause mortality [adjudicated on treatment deaths censored at Day 1470]



Reviewer comment:

The sudden drop off in the tio HH18 group at 48 months is due to the small number of patients left at risk at this time point (103 in the tio HH18 group), i.e. only a few patients remained in the trial past the protocol-specified study end date.

The most common causes (adjudicated) of death on-treatment were COPD exacerbation, lung cancer, and death of unknown cause. See Table 14. There were 271 patients who died of lower respiratory causes by Day 1470, 140 (4.7%) in the placebo group and 131 (4.4%) in the tio HH18 group [RR=0.85, 95% CI (0.67, 1.08)]. Forty-nine patients died of cardiac causes, 25 (0.8%) in the placebo group and 24 (0.8%) in the tio HH18 group [RR=0.88, 95% CI (0.50, 1.55)]. The preferred terms of sudden death, sudden cardiac death, and death of unknown cause are coded by MedDRA under the General Disorders System Organ Class; however, these terms are often considered cardiac events. Combining these three preferred terms, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

Table 14: Protocol 205.235 on-treatment adjudicated cause of death occurring in ≥ 10 patients in either treatment group

Cause of death	Placebo N (%)	Tio HH18 N (%)	Risk Ratio	p-value (95% CI)
	[n=3006]	[n=2986]		
COPD exacerbation	121 (4.0)	103 (3.4)	0.79	0.07 (0.60, 1.02)
Lung cancer	66 (2.2)	73 (2.4)	1.02	0.89 (0.73, 1.43)
Death (unknown cause)	36 (1.2)	29 (1.0)	0.74	0.23 (0.46, 1.21)
Sudden cardiac death	23 (0.8)	15 (0.5)	0.60	0.13 (0.31, 1.15)
Pneumonia	18 (0.6)	27 (0.9)	1.39	0.28 (0.76, 2.52)
Congestive heart failure	14 (0.5)	15 (0.5)	0.99	0.98 (0.48, 2.05)
Sudden death	12 (0.4)	14 (0.5)	1.08	0.85 (0.50, 2.33)
Cerebrovascular accident	13 (0.4)	12 (0.4)	0.85	0.69 (0.39, 1.87)

Reviewer comment:

Evaluating the mortality benefit by cause of death, nearly 40% of the benefit observed with tiotropium is driven by a reduction in fatal COPD exacerbations. This is consistent with the mechanism of action of the drug as a bronchodilator improving pulmonary function, as well as the efficacy benefit of reduction in COPD exacerbations seen in Protocols 205.235 and 205.266. Approximately one third of the benefit was attributable to a reduction in death of unknown cause and sudden cardiac death. Although mortality falling into these categories is generally considered to be related to cardiovascular

disease, in a population with moderate to severe COPD, one could postulate that some of these deaths may actually be attributed to hypoxia or respiratory failure precipitating death of unknown cause or a cardiac event.

The small increase in deaths attributed to pneumonia is not expected in a COPD population. A subgroup analysis of concomitant medication use in patients who died of pneumonia demonstrated that the increase was only found in patients who were taking ICS, LABAs or both at baseline. This finding suggests that the difference in pneumonia deaths may be confounded by ICS/LABA use, although the numbers are too small to draw any definitive conclusions. Of note, most patients taking one of these concomitant medications were taking a combination drug, with relatively few using LABAs alone. See Table 15.

Table 15: Protocol 205.235 subgroup analysis of pneumonia deaths

	Placebo		Tio HH18		Risk Ratio (95% CI)
	N (Pt-Year at risk)	N (%)	N (Pt-Year at risk)	N (%)	
Overall	3006 (8740)	18 (0.2)	2986 (9453)	27 (0.3)	1.39 (0.76, 2.52)
Baseline ICS	1860 (5335)	10 (0.2)	1840 (5797)	19 (0.3)	1.75 (0.81, 3.76)
No ICS	1146 (3411)	8 (0.2)	1146 (3663)	8 (0.2)	0.93 (0.35, 2.48)
Baseline LABA	1808 (5214)	8 (0.2)	1796 (5695)	17 (0.3)	1.95 (0.84, 4.51)
No LABA	1198 (3532)	10 (0.3)	1190 (3765)	10 (0.3)	0.94 (0.39, 2.25)
Baseline ICS/LABA	1462 (4197)	7 (0.2)	1464 (4610)	15 (0.3)	1.95 (0.80, 4.78)
No ICS/LABA	1544 (4549)	11 (0.2)	1522 (4850)	12 (0.2)	1.02 (0.45, 2.32)

Deaths were counted as on treatment (all), adjudicated.

Vital status mortality

Vital status information was known for 98% of tiotropium treated patients and 97% of placebo treated patients out to at least 45 months post-randomization. There were a total of 921 deaths, including vital status, for the full 4 year protocol defined study period (1440 days). There were 941 deaths for the period of 4 years plus 30 days (1470 days). See Table 45. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued.

The causes of death for deaths determined via collection of vital status were also adjudicated by an independent committee. Similar to on-treatment causes of death, the most frequent causes of death in the group including vital status were COPD exacerbation, lung cancer, and death of unknown cause.

Number needed to treat

As calculated by Dr. Joan Buenconsejo, FDA statistical reviewer, the number of patients that need to be treated with tiotropium over a four year period to prevent one death varies between 63 and 111 depending on what mortality grouping (on treatment versus vital

status and cut-off day) and method of calculation is used. See Table 16. This number compares favorably with other treatments that have known mortality benefits. For example, statins are associated with a NNT of 33-167 over a 5 year treatment period for all cause mortality depending on the drug and the patient population in which they are used.⁵

Table 16: Protocol 205.235 number needed to treat for mortality

	Placebo N=3006	Tiotropium N=2986	Risk Difference	NNT
FATAL AE - dataset				
On-Treatment (all)	411 (13.7)	381 (12.8)	0.009	111
Vital Status (1470 cut-off)	495 (16.5)	446 (14.9)	0.016	63

NNT=number needed to treat over 4 year period to prevent 1 death

Subgroup analysis of mortality

The Applicant conducted subgroup analyses for time to all cause death and on-treatment death. The following subgroup parameters were investigated:

- Age (<55, ≥55-<65, ≥65-<75, ≥75 years)
- Gender (male/female)
- Smoking status (active smoker/ex-smoker)
- Race (white/black/Asian)
- Baseline long-acting β-agonist use (yes/no)
- Baseline inhaled corticosteroid use (yes/no)
- Baseline LABA and ICS combination use (yes/no)
- GOLD stage (I or II/III/IV)
- Region (Asia/Eastern Europe/Latin America/USA/Western Europe)
- Reversibility (yes/no)
- Body mass index (<20/ ≥20-<25/ ≥25-<30/ ≥30)

For time to all cause death, there were two significant subgroup by treatment interactions, smoking status (p=0.0472) and body mass index (BMI) (p=0.0130). These same two subgroup interactions were also borderline significant for on treatment death, with p values of 0.0613 and 0.0782 respectively. For smoking status, ex-smokers obtained greater mortality benefit than current smokers. This seems plausible, as any potential drug effect could be overwhelmed by the detrimental effects of smoking. For BMI, the greatest mortality benefit was observed in the ≥25-<30 subgroup. Again, this seems medically plausible, as cachexia is generally a marker for worse disease in COPD patients, and obese patients have alternative mechanisms of respiratory mortality, such as obesity-hypoventilation. No treatment by subgroup interaction was observed for region; however, it is notable that the mortality benefit was driven by patients in Latin America, Asia, and Western Europe, with no benefit observed in the United States. This may be due to regional differences in standard of care and treatment for COPD, due to other confounders such as smoking status, or due to random chance since the subgroup interaction was not significant.

As with any subgroup analysis, the results must be interpreted cautiously, as the study was not powered to support such analyses. See Table 17 and Figure 9. The results presented are those of the sponsor. Dr. Joan Buenconsejo (statistical reviewer) verified these results.

Table 17: Protocol 205.235 subgroup analysis of on-treatment deaths (all)

	Placebo N (# of deaths)	Tiotropium N (# of deaths)	Subgroup interaction p-value	Risk Ratio (95% CI)	p-value*
Overall	3006 (411)	2764 (381)		0.84 (0.73, 0.97)	0.016
Gender: Male	2222 (335)	2251 (310)	0.8610	0.84 (0.72, 0.98)	0.0253
Female	784 (76)	735 (71)		0.84 (0.61, 1.16)	0.2946
Gold Stage: I/II	1356 (134)	1386 (119)	0.8363	0.83 (0.65, 1.07)	0.1525
III	1331 (204)	1304 (200)		0.86 (0.71, 1.05)	0.1333
IV	271 (66)	250 (57)		0.76 (0.53, 1.09)	0.1325
Smoking Status: Ex-Smoker	2108 (299)	2112 (256)	0.0613	0.77 (0.65, 0.91)	0.0024
Smoker	898 (112)	874 (125)		1.04 (0.80, 1.34)	0.7847
Reversibility: No	1393 (227)	1357 (210)	0.9145	0.84 (0.70, 1.01)	0.0666
Yes	1513 (171)	1520 (157)		0.84 (0.68, 1.05)	0.1270
Baseline ICS: No	1146 (169)	1146 (158)	0.7180	0.87 (0.70, 1.08)	0.2151
Yes	1860 (242)	1840 (223)		0.83 (0.69, 0.99)	0.0399
Baseline LABA: No	1198 (178)	1190 (168)	0.7252	0.87 (0.70, 1.08)	0.2003
Yes	1808 (233)	1796 (213)		0.82 (0.68, 0.99)	0.0403

	Placebo N (# of deaths)	Tiotropium N (# of deaths)	Subgroup interaction p-value	Risk Ratio (95% CI)	p-value*
Overall	3006 (411)	2764 (381)		0.84 (0.73, 0.97)	0.016
Baseline ICS/LABA: No	1544 (233)	1522 (211)	0.9098	0.84 (0.70, 1.01)	0.0640
Yes	1462 (178)	1464 (170)		0.85 (0.69, 1.05)	0.1323
Race [†] : White	2697 (353)	2691 (339)	0.3248	0.87 (0.75, 1.01)	0.0686
Black	53 (5)	38 (2)		0.42 (0.08, 2.19)	0.3068
Asian	185 (42)	192 (30)		0.63 (0.40, 1.01)	0.0545
Region: Asia	178 (39)	184 (29)	0.3975	0.66 (0.41, 1.07)	0.0950
E. Europe	597 (86)	590 (86)		0.96 (0.71, 1.30)	0.7872
Latin Amer.	207 (52)	198 (35)		0.66 (0.43, 1.02)	0.0594
USA	767 (86)	767 (93)		0.97 (0.72, 1.30)	0.8264
W. Europe	1257 (148)	1247 (138)		0.83 (0.65, 1.04)	0.1060
Age: <55	382 (26)	384 (24)	0.3348	0.82 (0.47, 1.43)	0.4873
55 –<65	1055 (108)	1054 (96)		0.79 (0.60, 1.04)	0.0966
65 –<75	1198 (191)	1208 (194)		0.95 (0.78, 1.17)	0.6507
≥ 75	371 (86)	340 (67)		0.69 (0.50, 0.95)	0.0237
BMI: <20	352 (72)	297 (75)	0.0782	1.06 (0.77, 1.47)	0.7111
20 –<25	1024 (131)	1074 (140)		0.90 (0.71, 1.14)	0.3714
25 –<30	1033 (145)	1039 (103)		0.65 (0.51, 0.84)	0.0009
≥ 30	597 (63)	576 (63)		0.95 (0.67, 1.35)	0.7866

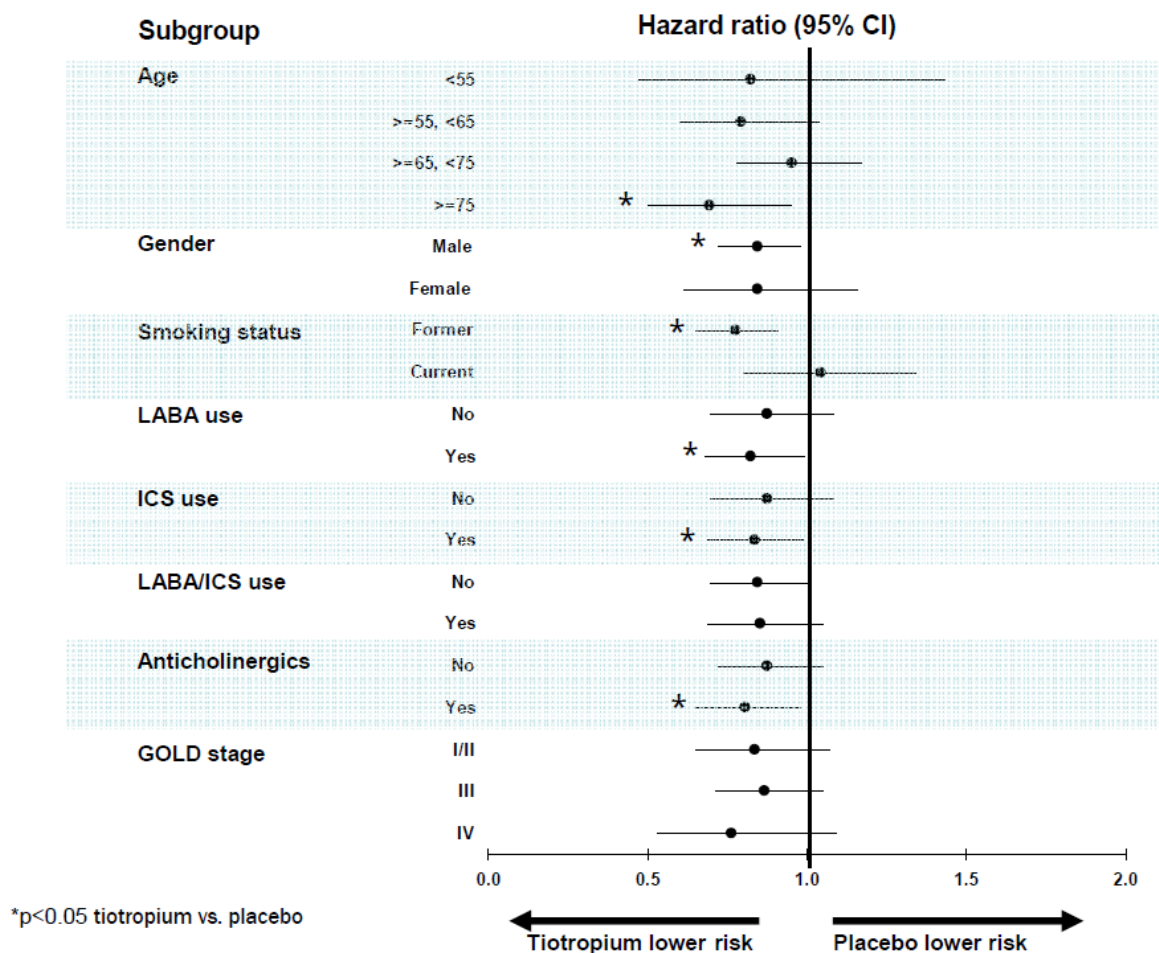
	Placebo N (# of deaths)	Tiotropium N (# of deaths)	Subgroup interaction p-value	Risk Ratio (95% CI)	p-value*
Overall	3006 (411)	2764 (381)		0.84 (0.73, 0.97)	0.016
Baseline			0.6153		
Anticholinergic: No	1656 (221)	1620 (199)		0.87 (0.72, 1.05)	0.0348
Yes	1350 (190)	1366 (182)		0.80 (0.65, 0.98)	0.1465

*Hazard ratio based on Cox model with treatment, baseline covariate and baseline covariate by treatment interaction; p-value was obtained using log-rank test. †Numbers do not add up to total due to missing data.

Reviewer comment:

As was noted in the efficacy review, the subgroup analysis notes baseline anticholinergic use in 45% of the study population. This should not be construed to mean that these patients remained on anticholinergics, which were prohibited during the trial. The rate of protocol violations for anticholinergic use was approximately 3.8%.

Figure 9: Protocol 205.235 mortality subgroup analysis Forest plot



Reviewer comment:

The Applicant initially requested a claim for mortality.

Since UPLIFT is a major study that doubles the size of the safety database for tio HH18, it is reasonable to describe major findings such as reduction in mortality in the product label. The persistence of the effect across many different analyses strengthens the evidence for a mortality benefit as does a plausible mechanism. However, a number of factors come into consideration for this claim:

- Mortality is a major claim which requires a substantive body of evidence. To support a labeling claim, the Agency typically requires replication of findings in two or more clinical trials. However, according to the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, reliance on a single study is possible in situations in which a trial has demonstrated a clinically meaningful effect on mortality or irreversible morbidity. In addition, the single study would typically be large multicenter center, such as UPLIFT, with consistency across study subsets and statistically very persuasive findings.*
- A small numerical imbalance in mortality in favor of the placebo group was observed in 3 one-year Phase 3 studies of Spiriva Respimat. Although Spiriva Respimat is a different drug product, it contains the same drug substance as Spiriva HandiHaler, thus the safety issue regarding mortality warrants discussion. A summary of the Spiriva Respimat data is included in the Appendix. These data complicate interpretation of the mortality data from UPLIFT.*
- A recent meta-analysis by Singh, et al.¹ concludes that anticholinergic medications including tiotropium increase long-term cardiovascular mortality. Dr. Simone Pinheiro of the Office of Surveillance and Epidemiology reviewed the relevant literature, including this meta-analysis. Dr. Pinheiro concluded that the currently available data implicating tiotropium and ipratropium in increasing risk of cardiovascular death, myocardial infarction, and stroke is not compelling. Refer to the Office of Surveillance and Epidemiology briefing document for details.*

5.5 Serious Adverse Events

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs occurring in more than 1% in either treatment group are given in Table 18. SAEs were generally balanced between treatment groups.

Table 18: Protocol 205.235 serious adverse events occurring in $\geq 1\%$ of patients in either treatment group (as reported by Applicant)

MedDRA System Organ Class MedDRA Preferred Term	Placebo N (%)	Tio HH18 N (%)	Total N (%)
Total Treated N (%)	3006 (100)	2986 (100)	5992 (100)
Total with serious adverse events	1509 (50.2)	1540 (51.6)	3049 (50.9)
Cardiac disorders	350 (11.6)	322 (10.8)	672 (11.2)
Angina#	31 (1.0)	48 (1.6)	79 (1.3)
Atrial fibrillation#	67 (2.2)	69 (2.3)	136 (2.3)
Cardiac failure	42 (1.4)	57 (1.9)	99 (1.7)
Cardiac failure congestive	42 (1.4)	27 (0.9)	69 (1.2)
Coronary artery disease	32 (1.1)	20 (0.7)	52 (0.9)
Myocardial infarction#	84 (2.8)	65 (2.2)	149 (2.5)
Neoplasms	170 (5.7)	197 (6.6)	367 (6.1)
Prostate cancer	22 (0.7)	31 (1.0)	53 (0.9)
Respiratory system disorders* (Lower)	985 (32.8)	911 (30.5)	1896 (31.6)
Acute respiratory failure	31 (1.0)	29 (1.0)	60 (1.0)
Bronchitis#	27 (0.9)	35 (1.2)	62 (1.0)
COPD exacerbation#	742 (24.7)	688 (23.0)	1430 (23.9)
Dyspnea#	54 (1.8)	36 (1.2)	90 (1.5)
Pneumonia#	290 (9.6)	296 (9.9)	586 (9.8)
Respiratory failure	113 (3.8)	85 (2.8)	198 (3.3)
Respiratory system disorders* (Other)	156 (5.2)	170 (5.7)	326 (5.4)
Lung neoplasm malignant	34 (1.1)	40 (1.3)	74 (1.2)
Pulmonary embolism	29 (1.0)	25 (0.8)	54 (0.9)

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.

Reviewer comment:

Based on the SAE data, the Applicant is requesting a claim for reduction in respiratory failure. While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term “respiratory failure” is undefined and subject to investigator interpretation. In addition, multiplicity is a concern since many adverse event variables were evaluated in the safety analysis and the effect is only marginally significant. Inclusion of the term respiratory failure may be appropriate as part of adverse event reporting for the study; however, there is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

5.6 Dropouts and Other Significant Adverse Events

5.6.1 Adverse Events Leading to Discontinuation

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. Fewer patients in the tio HH18 group discontinued due to a lower respiratory AE compared to patients in the placebo group [291 (9.7%) versus 412 (13.7%), respectively]. This was driven by a reduced number of patients in the tio HH18 group with COPD exacerbations and dyspnea. See Table 19.

Table 19: Protocol 205.235 adverse events leading to discontinuation occurring in ≥ 10 patients overall

MedDRA System Organ Class MedDRA Preferred Term	Placebo N (%)	Tio HH18 N (%)	Total N (%)
Total Treated N (%)	3006 (100)	2986 (100)	5992 (100)
Total with AEs leading to discontinuation	735 (24.5)	618 (20.7)	1353 (22.6)
Cardiac disorders	81 (2.7)	70 (2.3)	151 (2.5)
Atrial fibrillation#	7 (0.2)	7 (0.2)	14 (0.2)
Cardiac failure	7 (0.2)	13 (0.4)	20 (0.3)
Cardiac failure congestive	6 (0.2)	5 (0.2)	11 (0.2)
Myocardial infarction#	21 (0.7)	15 (0.5)	36 (0.6)
Gastrointestinal disorders	32 (1.1)	29 (1.0)	61 (1.0)
Dry mouth#	4 (0.1)	9 (0.3)	13 (0.2)
General disorders	38 (1.3)	47 (1.6)	85 (1.4)
Death	12 (0.4)	19 (0.6)	31 (0.5)
Sudden death	11 (0.4)	9 (0.3)	20 (0.3)
Nervous system disorders	38 (1.3)	39 (1.3)	77 (1.3)
Cerebrovascular accident	8 (0.3)	11 (0.4)	19 (0.3)
Respiratory system disorders* (Lower)	412 (13.7)	291 (9.7)	703 (11.7)
Acute respiratory failure	10 (0.3)	8 (0.3)	18 (0.3)
COPD exacerbation#	209 (7.0)	152 (5.1)	361 (6.0)
Dyspnea#	118 (3.9)	54 (1.8)	172 (2.9)
Pneumonia#	51 (1.7)	48 (1.6)	99 (1.7)
Respiratory failure	31 (1.0)	21 (0.7)	52 (0.9)
Respiratory system disorders* (Other)	82 (2.7)	89 (3.0)	171 (2.9)
Bronchial carcinoma	5 (0.2)	11 (0.4)	16 (0.3)
Lung neoplasm	5 (0.2)	8 (0.3)	13 (0.2)
Lung neoplasm malignant	19 (0.6)	21 (0.7)	40 (0.7)
Non-small cell lung cancer	7 (0.2)	5 (0.2)	12 (0.2)
Non-small cell lung cancer, malignant	4 (0.1)	6 (0.2)	10 (0.2)
Pulmonary embolism	9 (0.3)	5 (0.2)	14 (0.2)
Small cell lung cancer, stage unspecified	3 (0.1)	7 (0.2)	10 (0.2)

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.

5.6.2 Adverse Events of Stroke

Stroke is an adverse event of interest in the Spiriva HandiHaler program due to a potential increase in adverse events of stroke noted in a pooled analysis of 29 placebo-controlled studies with tiotropium. In 2007, the Applicant submitted the results of a pooled analysis of tiotropium clinical trial data, and identified stroke as occurring at higher rates in patients receiving tiotropium compared with patients receiving placebo (RR 1.37, 95% CI 0.73-2.56). An Early Communication was issued by FDA for Spiriva HandiHaler on March 18, 2008. This pooled trial population presented information on 13,544 patients from 29 clinical trials, contributing 4,571 person-years of exposure to tiotropium and 3,065 person-years of exposure to placebo. This population included 25 trials from the Spiriva HandiHaler program and 4 trials from the Spiriva Respimat program (205.251, 205.252, 205.254, and 205.255). The analysis also investigated a large number of other adverse events without correction for multiplicity. Because of the potential stroke signal, a detailed discussion of stroke AEs and methodology are warranted.

MedDRA permits classification of terms related to stroke under either the “nervous system disorders” system organ class (SOC) or the “vascular disorders” SOC. In Protocol 205.235, the Applicant classified all stroke preferred terms under nervous system disorders. While the terms are broken out separately in the adverse event tables, BI includes a number of terms in the analysis of “stroke” adverse events. Preferred terms were chosen from the Standardized MedDRA Queries (SMQ) for central nervous system hemorrhage and cerebrovascular accident (MedDRA version 11), which is collapsed into a single SMQ of central nervous system hemorrhages and cerebrovascular conditions in MedDRA version 12.0. Because the SMQs for stroke are very broad and include terms that are not true strokes, inclusion of all terms in the SMQ could generate noise and dilute out any potential signal. For example, BI did not include the preferred terms of “angiogram cerebral abnormal” and “cerebral aneurysm ruptured syphilitic” in the collapsed term of stroke. Overall, the list of preferred terms classified as stroke by BI is a conservative and appropriate choice. See Table 20 for terms that comprise the definition of stroke.

For the purposes of adjudication of fatal stroke events, the UPLIFT Mortality Adjudication Charter specifies that all stroke-related events will be classified as “stroke,” through the use of mortality adjudication worksheets. Therefore, this term in the adjudicated cause of death was pre-specified and grouped as considered appropriate by the adjudicators.

Table 20: Protocol 205.235 combined stroke definition

Preferred terms	Broad SMQ Stroke [†]	BI Custom Stroke
Amaurosis fugax	X	X
Angiogram cerebral abnormal	X	
Aphasia	X	
Balint's syndrome	X	
Basal ganglia hemorrhage	X	X
Basal ganglia infarction	X	
Basilar artery occlusion	X	X
Basilar artery stenosis	X	
Basilar artery thrombosis	X	X

Preferred terms	Broad SMQ Stroke [†]	BI Custom Stroke
Brain stem hemorrhage	X	X
Brain stem infarction	X	X
Brain stem ischemia	X	X
Brain stem stroke	X	
Brain stem thrombosis	X	X
Capsular warning syndrome	X	
Carotid aneurysm rupture	X	X
Carotid arterial embolus	X	X
Carotid arteriosclerosis	X	
Carotid artery aneurysm	X	
Carotid artery bypass	X	
Carotid artery disease	X	
Carotid artery dissection	X	
Carotid artery insufficiency	X	
Carotid artery occlusion	X	X
Carotid artery stenosis	X	X
Carotid artery stent insertion	X	
Carotid artery thrombosis	X	X
Carotid endarterectomy	X	
Central pain syndrome	X	
Cerebellar artery occlusion	X	X
Cerebellar artery thrombosis	X	X
Cerebellar embolism	X	X
Cerebellar hematoma	X	X
Cerebellar hemorrhage	X	X
Cerebellar infarction	X	X
Cerebellar ischemia	X	
Cerebral aneurysm ruptured syphilitic	X	
Cerebral arteriosclerosis	X	
Cerebral arteriovenous malformation hemorrhagic	X	X
Cerebral artery embolism	X	X
Cerebral artery occlusion	X	X
Cerebral artery stenosis	X	
Cerebral artery thrombosis	X	X
Cerebral hematoma	X	X
Cerebral hemorrhage	X	X
Cerebral hemorrhage fetal	X	X
Cerebral hemorrhage neonatal	X	X
Cerebral infarction	X	X
Cerebral infarction fetal	X	X
Cerebral ischemia	X	X
Cerebral revascularization synangiosis	X	
Cerebral thrombosis	X	X
Cerebral vasoconstriction	X	
Cerebral venous thrombosis	X	
Cerebrovascular accident	X	X
Cerebrovascular accident prophylaxis	X	
Cerebrovascular disorder	X	
Cerebrovascular insufficiency	X	
Cerebrovascular spasm	X	
Cerebrovascular stenosis	X	
Charcot-Bouchard microaneurysms	X	

Preferred terms	Broad SMQ Stroke [†]	BI Custom Stroke
Diplegia	X	
Dysarthria	X	
Embolic cerebral infarction	X	X
Embolic stroke	X	X
Fetal cerebrovascular disorder	X	
Hematomyelia	X	
Hemiparesis	X	
Hemiplegia	X	
Hemorrhage intracranial	X	X
Hemorrhagic cerebral infarction	X	X
Hemorrhagic stroke	X	X
Hemorrhagic transformation stroke	X	X
Intracerebral aneurysm operation	X	
Intracerebral hematoma evacuation	X	
Intracranial aneurysm	X	
Intracranial hematoma	X	X
Intracranial tumor hemorrhage		X
Intraoperative cerebral artery occlusion		X
Intraventricular hemorrhage	X	X
Intraventricular hemorrhage neonatal	X	X
Ischemic cerebral infarction	X	X
Ischemic stroke	X	X
Lacunar infarction	X	X
Lateral medullary syndrome	X	X
Meningorrhagia	X	
Millard-Gubler syndrome	X	
Monoparesis	X	
Monoplegia	X	
Moyamoya disease	X	
Paralysis	X	
Paralysis flaccid	X	
Paraparesis	X	
Paraplegia	X	
Paresis	X	
Pituitary hemorrhage		X
Pituitary infarction		X
Postprocedural stroke	X	X
Precerebral artery occlusion	X	X
Putamen hemorrhage	X	X
Quadriparesis	X	
Quadriplegia	X	
Red blood cells CSF positive	X	
Reversible ischemic neurologic deficit	X	X
Ruptured cerebral aneurysm	X	X
Spastic paralysis	X	
Spastic paraplegia	X	
Spinal artery embolism	X	
Spinal cord hemorrhage	X	
Spinal epidural hemorrhage	X	
Spinal hematoma	X	
Stroke in evolution	X	X
Subarachnoid hemorrhage	X	X

Preferred terms	Broad SMQ Stroke [†]	BI Custom Stroke
Subarachnoid hemorrhage neonatal	X	X
Subdural hemorrhage	X	
Subdural hemorrhage neonatal	X	
Thalamic infarction	X	X
Thalamus hemorrhage	X	X
Thrombotic cerebral infarction	X	X
Thrombotic stroke	X	X
Transient ischemic attack	X	X
Vascular encephalopathy	X	
Vertebral artery occlusion	X	X
Vertebral artery stenosis	X	
Vertebral artery thrombosis	X	X
Vertebrobasilar insufficiency	X	
Visual midline shift syndrome	X	
Wallenberg syndrome	X	

[†]Taken from MedDRA version 12.0, SMQ term "Central nervous systems hemorrhages and cerebrovascular conditions"

The results of UPLIFT show that stroke-related adverse events, SAEs, and fatal stroke events were not significantly increased in the tiotropium groups compared to placebo. See Table 21. There were no specific treatment by subgroup interactions for stroke adverse events other than as related to small numbers. However, the overall incidence of stroke events in both treatment groups did increase with age, as would be expected.

Table 21: Protocol 205.235 stroke adverse events

	Tio HH18 N=2986		Placebo N=3006		Risk Ratio (95% CI)
	N	Rate/100 pt yrs	N	Rate/100 pt yrs	
AE	82	0.88	80	0.93	0.95 (0.70, 1.29)
SAE	66	0.70	63	0.73	0.97 (0.69, 1.37)
Fatal (on treatment)	12	0.13	13	0.15	0.85 (0.39, 1.87)
Fatal (vital status, D1470)	14	0.13	17	0.15	0.82 (0.40, 1.66)

Reviewer comment:

The UPLIFT trial does not show a specific signal for stroke events. The Risk Ratio for adverse events of stroke is less than one, and the upper bound of the confidence interval is less than 1.3, suggesting that if there is any adverse drug effect, it is minimal. Because stroke was a pre-specified term for the adjudication of cause of death, readers can have confidence that fatal strokes were appropriately classified and are not "hiding" under some other preferred term. Serious adverse events and fatal adverse events of stroke are subgroups and as expected, have slightly wider confidence intervals, although the conclusions are the same.

5.6.3 Major Adverse Cardiac Events

In 2008 a meta-analysis was published noting that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke¹. Stroke was addressed above. In this section, cardiovascular death and MI will be addressed.

In UPLIFT, there were pre-specified definitions of MI and sudden cardiac death utilized the the adjudication committee. Sudden cardiac death was defined as unexplained death occurring within one hour of an abrupt change of a person's clinical state without other obvious cause. Sudden death was defined as death occurring more than one and less than 24 hours of last being observed alive and without evidence of a deteriorating medical condition. There was no increase in deaths due to cardiac disorders, sudden cardiac death, sudden death, or death due to unknown cause, although confidence intervals were wide. See Table 14.

There was no increase in adverse events of myocardial infarction in the tiotropium group compared to placebo (see Table 18), with a Risk Ratio of 0.71, 95% CI (0.52, 0.99). Overall, there was a borderline significant decrease in AEs in the cardiac SOC [RR 0.84, 95% CI (0.73, 0.98)], driven by a decrease in congestive heart failure and MI.

There was no treatment by subgroup interactions for cardiovascular adverse events. Combined cardiac ischemic events (angina/ischemia/MI) for both treatment groups were increased in current smokers compared to non-smokers and were also mildly increased in patients with ICS use. This result was not seen in combined ICS/LABA use, so the increase in cardiac ischemic events with ICS use likely represents a spurious result due to multiple comparisons and low numbers. Adverse events of congestive heart failure were increased in both treatment groups with age and with increasing GOLD stage, both of which could be plausible medically.

Reviewer's Comment:

Because myocardial infarction and sudden cardiac death were pre-specified terms for the adjudication of cause of death, readers can have confidence that these events were appropriately classified and are not "hiding" under some other preferred term.

5.7 Common Adverse Events

Adverse events were classified according to the MedDRA version 11.0. 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 in theory 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.

Non-serious adverse events were reported in almost all patients in both groups (92.3% of placebo patients and 92.6% of tio HH18 patients), an expected finding given the length of the study and the severity of disease in this patient population. In order to account for

differential drop out, the Applicant also reported AEs as exposure adjusted rates (number of patients experiencing an event divided by the person-years at risk).

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. Other known anticholinergic side effects also occurred with greater frequency in the tiotropium group although not significantly so. These included constipation, benign prostatic hypertrophy, dizziness, sinusitis, nasopharyngitis, cough, and urinary tract infection. See Table 22.

Table 22: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs occurring in >3% of either treatment group

	Placebo N=3006		Tio HH18 N=2986		Tio HH18/ placebo Rate Ratio (95% CI)
	N (%)	Incidence Rate	N (%)	Incidence Rate	
Total with AE	2774 (92.3)		2764 (92.6)		
COPD exacerbation#	1986 (66.1)	45.5	1934 (64.8)	38.1	0.84 (0.79, 0.89)
Pneumonia#	418 (13.9)	5.14	433 (14.5)	4.94	0.96 (0.84, 1.10)
Dyspnea#	443 (14.7)	5.49	364 (12.2)	4.09	0.75 (0.65, 0.86)
Nasopharyngitis	324 (10.8)	4.06	373 (12.5)	4.33	1.07 (0.92, 1.24)
Upper respiratory tract infection#	290 (9.6)	3.57	298 (10.0)	3.38	0.95 (0.81, 1.11)
Hypertension	284 (9.4)	3.45	275 (9.2)	3.08	0.89 (0.75, 1.05)
Bronchitis#	233 (7.8)	2.82	232 (7.8)	2.57	0.91 (0.76, 1.10)
Cough	213 (7.1)	2.57	238 (8.0)	2.64	1.03 (0.86, 1.24)
Back pain	188 (6.3)	2.25	198 (6.6)	2.18	0.97 (0.79, 1.18)
Urinary tract infection#	169 (5.6)	2.00	190 (6.4)	2.08	1.04 (0.85, 1.28)
Sinusitis#	160 (5.3)	1.90	194 (6.5)	2.14	1.12 (0.91, 1.39)
Influenza	158 (5.3)	1.87	158 (5.3)	1.73	0.92 (0.74, 1.15)
Headache	136 (4.5)	1.61	171 (5.7)	1.88	1.17 (0.94, 1.47)
Edema#	130 (4.3)	1.52	145 (4.9)	1.57	1.03 (0.82, 1.31)
Constipation	111 (3.7)	1.29	151 (5.1)	1.63	1.26 (0.99, 1.61)
Diarrhea	122 (4.1)	1.43	138 (4.6)	1.5	1.04 (0.82, 1.33)
Cataract	123 (4.1)	1.45	120 (4.0)	1.3	0.90 (0.70, 1.15)
Atrial fibrillation#	113 (3.8)	1.32	119 (4.0)	1.28	0.97 (0.75, 1.26)
Dry mouth#	80 (2.7)	0.93	152 (5.1)	1.68	1.80 (1.37, 2.36)
Depression	98 (3.3)	1.14	131 (4.4)	1.42	1.25 (0.96, 1.62)
Insomnia	91 (3.0)	1.06	131 (4.4)	1.42	1.34 (1.02, 1.75)
Arthralgia	94 (3.1)	1.10	125 (4.2)	1.36	1.24 (0.95, 1.62)
Benign prostatic hyperplasia	96 (3.2)	1.12	122 (4.1)	1.32	1.18 (0.90, 1.54)
Rhinitis	112 (3.7)	1.32	101 (3.4)	1.09	0.83 (0.63, 1.08)
Abdominal pain#	96 (3.2)	1.12	113 (3.8)	1.22	1.09 (0.83, 1.43)
Respiratory failure	120 (4.0)	1.39	88 (2.9)	0.94	0.67 (0.51, 0.89)
Hypercholesterolemia	97 (3.2)	1.13	104 (3.5)	1.12	0.99 (0.75, 1.31)
Nausea	94 (3.1)	1.09	93 (3.1)	1.00	0.91 (0.69, 1.22)
Dizziness	81 (2.7)	0.94	103 (3.4)	1.11	1.18 (0.88, 1.58)

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.

Reviewer comment:

The adverse events observed in the UPLIFT trial are consistent with the known adverse event profile of Spiriva HandiHaler. The findings of significant reductions in COPD

exacerbation, dyspnea, and respiratory failure are supportive of the efficacy findings in the trial. No particular cardiac signals were identified.

5.8 Less Common Adverse Events

All AEs with a risk ratio ≥ 3 in the tio HH18 group compared to placebo are presented in Table 23. Analysis of these events reveals that while the risk ratio may be high, the number of patients with each event is very low and in most cases there is no biologic plausibility for a causal relationship. The risk ratio reached statistical significance for only one event, intestinal obstruction. Events that could be secondary to anticholinergic effects include atrial tachycardia, tachyarrhythmia, intestinal obstruction, and prostate infection. Supraventricular tachyarrhythmic events in general did not appear to be increased overall in the tio HH18 group, with atrial fibrillation occurring in 113 (3.8%) patients in the placebo group and 119 (4.0%) patients in the tio HH18 group [RR 0.97, 95% CI (0.75, 1.26)] and tachycardia occurring in 43 (1.4%) patients in the placebo group and 40 (1.3%) patients in the tio HH18 group [RR 0.86, 95%CI (0.56, 1.32)].

Table 23: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs with a risk ratio of ≥ 3

	Placebo N=3006		Tio HH18 N=2986		Tio HH18/ placebo Rate Ratio (95% CI)
	N (%)	Incidence Rate	N (%)	Incidence Rate	
Total with AE	2774 (92.3)		2764 (92.6)		
Atrial tachycardia	1 (0.0)	0.01	8 (0.3)	0.08	7.39 (0.92, 59.1)
Tachyarrhythmia	2 (0.1)	0.02	8 (0.3)	0.08	3.70 (0.79, 17.4)
Tricuspid valve incompetence	1 (0.0)	0.01	6 (0.2)	0.06	5.54 (0.67, 46.1)
Epigastric discomfort	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Intestinal obstruction*	2 (0.1)	0.02	12 (0.4)	0.13	5.55 (1.24, 24.8)
Large intestinal perforation	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Peritonitis	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Tongue disorder	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Ulcer	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Bile duct stone	2 (0.1)	0.02	8 (0.3)	0.08	3.70 (0.79, 17.4)
Abscess	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Appendicitis	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Osteomyelitis	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Prostate infection	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Foreign body trauma	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Tendon rupture	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Ulna fracture	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
INR increased	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Vitamin B12 deficiency	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Costochondritis	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Lumbar spinal stenosis	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Musculoskeletal discomfort	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Intercostal myalgia	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Non-Hodgkin's lymphoma	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Esophageal carcinoma	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Neurosis	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Restlessness	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Urethral stenosis	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Metastases to lung	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Small cell lung cancer, metastatic	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Rash generalized	1 (0.0)	0.01	6 (0.2)	0.06	5.55 (0.67, 46.1)
Skin disorder	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)

*p=0.02

Reviewer comment:

Intestinal obstruction is included in the postmarketing section of the Spiriva HandiHaler label and could be consistent with the known anticholinergic side effect of constipation.

5.9 Malignancy

Inhalational carcinogenicity studies in animals did not suggest carcinogenic potential for tiotropium. In Protocol 205.235, a total of 464 patients overall had SAEs of neoplasm including benign, malignant, and unspecified as well as cysts and polyps. Events excluded neoplasms of the respiratory system, which were categorized under the respiratory SOC. These included 245 patients (8.2%) in the tio HH18 group, and 219 (7.3%) patients in the placebo group. Accounting for discontinuations, the Relative Risk per 100 patient years was 1.04 [95% CI 0.86, 1.25] for tio HH18 versus placebo. The most common neoplasms reported overall were prostate cancer, basal cell carcinoma, colon cancer, bladder cancer, and metastases to the liver, all of which were balanced between treatment groups. There were 37 fatal cancers in the tio HH18 group and 45 in the placebo group (adjudicated, on-treatment population). 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 SOC of “respiratory, other.” When the reviewer combined preferred terms into a single “lung cancer” category, there were 263 patients with AEs of lung cancer, 140 (4.7%) in the tio HH18 group and 123 (4.1%) in the placebo group, making lung cancer the single most prevalent neoplasm reported in Protocol 205.235. Due to differential discontinuations, the AE numbers are comparable between groups. There were 79 fatal respiratory neoplasms in the tio HH18 group and 68 in the placebo group (adjudicated, on-treatment population). These included laryngeal cancer, lung cancer, mediastinum neoplasm, pharyngeal cancer, and pleural mesothelioma. The majority were classified by the Mortality Adjudication Committee as lung cancer, with 73 tio HH18 group and 66 in the placebo group [RR 1.02 (95% CI 0.73, 1.43)]. 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 lung cancer related preferred terms in the respiratory (other) category to determine total lung cancer events. Addition of events in this fashion may result in overestimation of effect if a single patient experienced more than one lung-cancer AE in this category. The preferred terms that were combined into the reviewer-specified “lung cancer” category are: large cell carcinoma of the respiratory track stage unspecified, lung adenocarcinoma, lung adenocarcinoma metastatic, lung adenocarcinoma recurrent, lung cancer metastatic, lung carcinoma cell type unspecified recurrent, lung carcinoma cell type unspecified Stage 0, lung carcinoma cell type unspecified Stage III, lung neoplasm, lung neoplasm malignant, lung squamous cell carcinoma Stage III, lung squamous cell carcinoma Stage IV, lung squamous cell carcinoma metastatic, non-small cell lung cancer, non-small cell lung cancer metastatic, small cell lung cancer extensive stage, small cell lung cancer limited stage, small cell lung cancer metastatic, and small cell lung cancer stage unspecified.

5.10 Postmarketing Experience

One adverse event of interest that was specifically captured in post marketing experience is the accidental oral ingestion of Spiriva HandiHaler capsules. During the 2008 reporting period, there were 1560 reported oral ingestions of Spiriva capsules, for an incidence rate of approximately 0.20 accidental ingestions per 1000 prescriptions written. Of these reported oral ingestions, only 7 reported associated SAEs. These events included coronary blockage, infection in the feet secondary to diabetes, pneumonia (pre-existing), CPK increased and muscle rigidity, overdose (patient was hospitalized because she swallowed two capsules), and one report of ingestion of Spiriva capsule as the SAE. There were also 25 non-serious associated AEs, many of which were reported as “drug ineffective.” Because tiotropium has very poor oral absorption, adverse events other than “drug ineffective” are not anticipated.

FDA issued a Public Health Advisory on February 29, 2009 regarding correct use of Spiriva HandiHaler and swallowing of capsules. In addition, labeling changes to address this issue were approved in 2009.

5.11 Pooled Analysis

As part of this NDA, Boehringer Ingelheim submitted pooled analyses of adverse event data from 30 clinical trials. These trials consisted of 26 Spiriva HandiHaler trials and 4 Spiriva Respimat trials. The criteria used for selection of these trials are as follows:

- Randomized, placebo controlled, parallel group design
- COPD patient population
- Duration of at least 4 weeks of treatment intervention
- Spiriva HandiHaler 18 mcg or Spiriva Respimat 5 or 10 mcg

A variety of different analyses were performed, including the following combination of trials:

- UPLIFT alone
- HandiHaler trials excluding UPLIFT (25 trials)
- Respimat trials (4 trials)
- UPLIFT + HandiHaler trials
- UPLIFT + HandiHaler + Respimat
- 4 Respimat trials, 5 versus 10 mcg Respimat

The following subgroups were analyzed for the 30 combined trials:

- Age (<60, 60 - <70, ≥70)
- Gender
- GOLD Stage (I/II, III, IV)

- Cardiac disorders flag
- Coronary artery disease flag
- Renal disorder flag
- Atherosclerotic disease flag
- Anticholinergics use flag
- LABA use flag
- ICS use flag
- Other steroids use flag
- Statins use flag (defined by ATC-4 code HMG CoA Reductase Inhibitors)

In the pooled analysis, BI uses the combined terms of “cardiovascular death” and “cardiovascular endpoint.” These terms were defined as follows. The term “cardiovascular death” includes deaths due to:

- cardiac disorders SOC
- vascular disorders SOC
- BI expanded MI term
- BI stroke term (see Table 20)
- sudden death
- cardiac death
- sudden cardiac death

The term “cardiovascular endpoint” includes AEs of:

- fatal AEs in the cardiac disorders SOC
- fatal AEs in the vascular disorders SOC
- BI expanded MI term (fatal and non-fatal)
- BI expanded stroke term (fatal and non-fatal, see Table 20)
- sudden death
- cardiac death
- sudden cardiac death

In the original pooled analysis of 29 clinical trials (excluding UPLIFT), a numerical increased risk of stroke events with tiotropium, specifically Spiriva HandiHaler, was observed [Risk Ratio 1.36, 95% CI (0.73, 1.56)].

Based on patient-years of exposure in patients with COPD participating in placebo-controlled trials, the UPLIFT study more than quadruples (4.37 times larger) the safety database for Spiriva HandiHaler, and more than triples (3.35 times larger) the safety database for tiotropium as a whole. See Table 24 for patient years of exposure.

Table 24: Patient-years of exposure across the tiotropium program

Database	Placebo	Tiotropium
HandiHaler trials (25)	2079	2736
Respimat trials (4)	517	1188
UPLIFT	8499	9222
UPLIFT + HandiHaler trials	10578	11958
All 30 trials	11095	13146

As might be expected for a pooled analysis when including a trial of large size, the UPLIFT data dominate the pooled analysis. Combining UPLIFT with the HandiHaler studies or with the 29 studies eliminates the potential stroke signal previously observed. In addition, no cardiovascular signals were observed. See Table 25.

Table 25: Pooled analysis results for major adverse cardiac events

	MI		Stroke		Cardiovascular death	
	Risk Ratio	95% CI	Risk Ratio	95% CI	Risk Ratio	95% CI
HandiHaler trials	1.285	0.687, 2.401	1.957	0.942, 4.066	NP	NP
Respimat trials	0.376	0.117, 1.213	0.873	0.298, 2.555	NP	NP
HandiHaler + Respimat trials	NP	NP	NP	NP	0.973	0.542, 1.747
UPLIFT	0.713	0.516, 0.985	0.968	0.685, 1.367	0.730	0.560, 0.951
UPLIFT + HandiHaler trials	0.820	0.619, 1.086	1.045	0.791, 1.380	NP	NP
All 30 trials	0.788	0.789, 1.353	1.033	0.789, 1.353	0.767	0.603, 0.976

MI=myocardial infarction, NP=not provided in this supplement

The subgroup analysis was systematically reviewed for interactions with MI and stroke. No treatment by subgroup interactions were observed for either of these events. In both treatment groups, however, the incidence of MI and stroke were increased with a history of cardiac disorder, history of coronary artery disease, history of atherosclerotic disease, and history of statin use. These are all expected correlations. Presumably, statin use is serving as a marker for hypercholesterolemia, which was not measured in these studies, rather than statins causing MI and stroke. Incidentally, lower respiratory infections and pneumonia were increased in both treatment groups in patients using inhaled corticosteroids and other steroids.

Reviewer comment:

Because UPLIFT is such a large study, the pooled analysis does not add significantly to the understanding of adverse events for tiotropium.

5.12 Literature

In September 2008, JAMA published a meta-analysis by Singh, et al. entitled “Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis.”¹ This article has received wide press.

The Singh, et al. meta-analysis identified trials from the literature that had the following inclusion criteria: 1) randomized controlled trial with more than 30 days of follow up, 2) trial participants with a diagnosis of COPD of any severity, 3) inhaled anticholinergic (short or long-acting) versus control (active or placebo), and 4) trial reported on the incidence of serious cardiovascular adverse events, including MI, stroke, or cardiovascular death. Of 703 potentially relevant trials, the analysis included only 17. Twelve of the trials included tiotropium (all Spiriva HandiHaler), and four included ipratropium. Of the tiotropium trials, two were replicate studies of others in the analysis, which resulted in double counting of over 1000 patients, and one included open-label tiotropium. The primary endpoint of the meta-analysis was pre-specified as a composite of nonfatal MI, nonfatal stroke (including transient ischemic attack), and cardiovascular death (including sudden death). The authors note that cardiovascular events were determined from the SAE reporting in the trial and were not uniformly defined across the studies, nor were patient-level data evaluated to further define events in the meta-analysis.

Initial results were reported in September 2008,¹ and revised results were published in March 2009.⁶ These results demonstrated a significant increase in the risk of myocardial infarction (MI) and cardiovascular death. Stroke and all cause mortality were not significantly increased. See Table 26. The increase in MI and cardiovascular death was primarily found in long-term trials (>6 months), and was driven by the Lung Health Study.² The Lung Health Study was a large NIH-sponsored multicenter clinical trial of smoking intervention and inhaled bronchodilator (ipratropium) use in middle-aged smokers with mild-moderate COPD. With 5-years of follow up, a small increase in cardiovascular mortality was reported in the ipratropium group compared to placebo. On further analysis, this increase was attributed to a statistical anomaly due to non-compliance.⁷

Table 26: Singh, et al. anticholinergic meta-analysis results

Outcome	No of RCTs	Inhaled anticholinergic n/N	Controls n/N	RR (95% CI)	p-value
As reported September 2008					
CV death	12	57/6156	31/6220	1.80 (1.17-2.77)	0.008
MI	11	68/5430	43/5168	1.53 (1.05-2.23)	0.03
Stroke	7	25/4548	18/4703	1.46 (0.81-2.62)	0.20
All cause mortality	17	149/7472	115/7311	1.26 (0.99-1.61)	0.06
As reported March 2009					
CV death	12	56/5668	28/5615	1.92 (1.23-3.00)	0.004
MI	13	68/5430	43/5123	1.52 (1.04-2.22)	0.03
Stroke	9	25/4548	18/4703	1.46 (0.81-2.62)	0.20
All cause mortality	17	146/6984	108/6661	1.29 (1.00-1.65)	0.05

RCT=randomized controlled trials, RR=risk ratio, CV=cardiovascular, MI=myocardial infarction

A number of methodological issues exist with the Singh meta-analysis, including double counting of trials, use of open-label data, and results driven by a single large trial (Lung Health Study). These are examined in detail in a review of published literature of meta-analyses and cohort studies by Dr. Simone Pinheiro of the Office of Safety and Epidemiology. (See OSE Briefing document, NDA 21-395). In brief, other issues include:

- Study selection: Only trials reporting AEs were included. Sixty-nine trials were excluded from the analysis because cardiovascular AEs were not reported in the publication. This is particularly important as none of the trials were originally designed to evaluate risk of cardiovascular adverse events. Studies with an imbalance in the number of adverse events may be both more likely to provide information on adverse events and to be included in the meta-analysis. This could have resulted in a biased selection of studies which could explain, at least in part, the associations observed in Singh et al.
- Meta-analysis combined data from both ipratropium and tiotropium: While these two compounds belong to the same class and may share many of the same side effects, the short-versus long-acting nature of the drugs could have significant implications for systemic effects such as cardiovascular events.

- Meta-analysis combined data from placebo and active controlled trials: The nature and design of these two types of trials are fundamentally different, and the active controls may have side effects of their own.
- Meta-analysis did not account for differential discontinuation rates: As there are generally more patients who discontinue from placebo than from active treatment, this may bias against the drug as patients who tolerate placebo tend to be healthier than those who discontinue, particularly in long-term follow up.
- No patient-level data were utilized: The fact that randomized studies were included in the meta-analysis does not mean that comparisons between trials are randomized comparisons. Therefore, risk factors such as smoking status, BMI, COPD severity, and LABA use could confound the analyses if they differ across trials and are associated with the outcomes of interest.

Reviewer comment:

While the Singh, et al. article raises issues with regards to cardiovascular mortality and MI with tiotropium, these issues are addressed with randomized, placebo-controlled data from the UPLIFT trial. According to Dr. Pinheiro, other studies in the literature also do not support cardiovascular, stroke, or mortality safety signals for tiotropium. In addition, the numerous methodological issues with the Singh analysis call the results into question.

5.13 Conclusions

With regards to potential safety signals under investigation for tiotropium, the UPLIFT trial did not show a clinically significant increase in mortality, stroke, or cardiovascular events in the tio HH18 group relative to placebo.

Overall, the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tiotropium group. Vital status information was known for 98% of tio HH18 treated patients and 97% of placebo treated patients including discontinued patients out to at least 45 months post-randomization. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued. The risk ratio for death from any cause (tiotropium/placebo) on treatment was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data.

The primary cause of each death in the UPLIFT trial was adjudicated by an independent committee. The most common causes (adjudicated) of death both on-treatment and including vital status were COPD exacerbation, lung cancer, and death of unknown cause. Combining the preferred terms of sudden death, sudden cardiac death, and death of unknown cause, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

Overall, these data are supportive of a beneficial effect on mortality, as UPLIFT is a major study that more than doubles the size of the safety database, prespecified mortality endpoints and vital status collection were appropriately collected and adjudicated, and the

salutary effect on mortality is robust across multiple different analyses. In addition, the mortality benefit was driven by a reduction in fatal COPD exacerbations, suggesting a plausible mechanism of action. However, outstanding issues with regards to mortality with Spiriva Respimat and literature references to cardiovascular mortality need to be considered. Also, the mortality benefit was observed in only a single, albeit very large, trial.

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs were generally balanced between treatment groups, although COPD exacerbations were significantly reduced in the tio HH18 group compared to placebo [RR 0.86, 95% CI (0.76, 0.94), $p=0.0014$]. While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Multiplicity is also an issue. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term “respiratory failure” is undefined and subject to investigator interpretation. There is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. A reduced number of patients in the tio HH18 group discontinued due to COPD exacerbations and dyspnea compared to the placebo group.

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. In addition, although the numbers were small, intestinal obstruction occurred significantly more frequently in the tio HH18 group and could represent an anticholinergic side effect related to constipation.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. Stroke-related adverse events (AEs, SAEs, or fatal events) were not increased in the tio HH18 group relative to placebo (Risk Ratio of 0.95, 0.97, and 0.85, respectively).

Cardiovascular events are also adverse events of interest based on a potential safety signal observed in a meta-analysis literature report. There was no increase in adverse events of myocardial infarction in the tiotropium group compared to placebo, with a Risk Ratio of 0.71, 95% CI (0.52, 0.99). Overall, there was a borderline significant decrease in AEs in the cardiac SOC [RR 0.84, 95% CI (0.73, 0.98)], driven by a decrease in congestive heart failure and MI. Likewise, there was no increase in deaths due to cardiac

disorders, sudden cardiac death, sudden death, or death due to unknown cause, although confidence intervals were wide.

6 APPENDICES

6.1 Review of Individual Study Reports: Spiriva HandiHaler

6.1.1 205.235 (UPLIFT trial)

6.1.1.1 Protocol 205.235 study design

Study title

UPLIFT: Understanding Potential Long-term Impacts on Function with Tiotropium

A randomized, double-blind, placebo-controlled, parallel group trial assessing the rate of decline of lung function with tiotropium 18 mcg inhalation capsule once daily in patients with chronic obstructive pulmonary disease (COPD)

Design

This was a 4-year, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel group study comparing the rate of decline in forced expiratory volume in one second (FEV1) in patients with COPD receiving tiotropium HandiHaler 18 mcg (tio HH18) to those receiving placebo in addition to their usual care for COPD. Usual care included short- and long-acting inhaled beta-agonists, steroids, and theophyllines but excluded inhaled anticholinergics. Following an initial screening period of 14-30 days, qualifying patients were randomized to tiotropium or placebo. Patients were seen after 1 month of treatment, at 3 months, and then every 3 months until study drug termination at 4 years. At study drug termination, patients received open-label ipratropium for 30 days. The final visit occurred approximately 30 days post-treatment.

Duration

The duration of active treatment was 4 years. Patients attended a screening visit 2-4 weeks prior to randomization. There was no run-in period. A post-treatment scheduled follow up period of 30 days was conducted for all patients completing 4-years of therapy. The study was performed during the period of January 9, 2003 to February 22, 2008. The final study report is dated October 28, 2008.

Investigators and centers

Patients were enrolled from 490 investigative centers and were randomized from 487 investigative centers in 37 countries: 95 in the United States; 36 in Spain; 31 in Italy; 30 in Denmark; 27 in Belgium; 26 in Czechia; 20 in Hungary; 17 in France; 14 each in Brazil, Germany, and the United Kingdom; 13 in The Netherlands; 12 each in Japan and Turkey; 11 in South Africa; 10 each in Argentina and Greece; 9 in Poland; 8 in Australia; 7 in Switzerland; 6 in Mexico; 5 each in Austria, Finland, Philippines, Portugal, Russia, Slovakia, Slovenia, and Thailand; 4 each in Hong Kong and Norway; 3 each in Ireland, Lithuania, Malaysia, Singapore, and Taiwan; and 2 in New Zealand

Materials

The study treatments were:

- tio HH18: tiotropium HandiHaler 18 mcg (1 capsule dry powder inhalation) once daily in the morning
- placebo: identical to HandiHaler capsule dry powder inhalation once daily in the morning

Patients received different batches of tiotropium and placebo over the 4 years of treatment. Open label ipratropium was supplied for use during the 30-days follow up period. Spacer (Aerochamber) devices were allowed to be used with the metered-dose inhaler (MDI) medication during the 30 day follow up period.

Objectives

The primary objective of this trial was to determine whether tio HH18 reduces the rate of decline of FEV₁ over time in patients with COPD.

Population

A total of 8,020 male and female patients with moderate to severe COPD (FEV₁ ≤ 70% predicted) were screened. Of these, 5993 were randomized; 2987 in the tio HH18 group, and 3006 in the placebo group. A total of 2457 (41%) of randomized patients prematurely discontinued study medication. Fewer patients in the tio HH18 group (1,099 patients, 36.8%) prematurely discontinued trial medication than in the placebo group (1,358 patients, 45.2%).

Inclusion criteria

Notable inclusion criteria included:

- Diagnosis of COPD and with the following spirometric criteria:
 - post-bronchodilator FEV₁ ≤ 70% of predicted normal and FEV₁ ≤ 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
- Maintained on stable respiratory medications for 6 weeks prior to Visit 2

Exclusion criteria

Notable exclusion criteria included:

- Significant diseases other than COPD which, in the opinion of the investigator, may either have put the patient at risk because of participation in the study or a disease which may have influenced the results of the study or the patient's ability to participate in the study
- Recent history (6 months or less) of myocardial infarction
- Unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia that required intervention or a change in drug therapy within the year prior to enrollment
- Hospitalization for heart failure (NYHA Class III or IV) within the year prior to enrollment
- Known active tuberculosis

- History of asthma, cystic fibrosis, bronchiectasis, interstitial lung disease, or pulmonary thromboembolic disease.
- History of thoracotomy with pulmonary resection.
- Patients who planned to undergo lung transplantation or lung volume reduction surgery.
- Malignancy for which the patient had undergone resection, radiation therapy, or chemotherapy within the last 5 years. Patients with treated basal cell carcinoma were allowed.
- Respiratory infection or exacerbation of COPD in the 4 weeks prior to the screening visit (Visit 1) or during the baseline period (between Visits 1 and 2).
- Known moderate to severe renal impairment.
- Known narrow angle glaucoma.
- Significant symptomatic prostatic hyperplasia or bladder-neck obstruction. Patients whose symptoms were controlled on treatment were allowed to be included.
- Oral corticosteroids in unstable daily dose or > 10 mg prednisone/day
- Significant alcohol or drug abuse within the year prior to enrollment.
- Use of supplemental oxygen therapy of >12 hours per day.

Reviewer comment:

Of note, bronchodilatory reversibility was not an inclusion criterion. The population was not enriched for patients with a history of COPD exacerbation. In comparison with Phase 3 tiotropium HandiHaler trials, exclusion criteria were liberalized to include a broader population of patients with COPD. These included shortened time periods from previous myocardial infarction and congestive heart failure episodes, inclusion of patients with stable arrhythmias, inclusion of patients with malignancy (not during active treatment), and liberalized use of oxygen (<12 hours per day). In addition, patients were permitted to be on all baseline medications except for anticholinergics.

Procedures

During the initial 14-30 day screening period, demographic data, baseline history and medications, a physical examination, and post-bronchodilator pulmonary function tests (PFTs) were collected. If a patient had a respiratory infection or COPD exacerbation during the screening period, Visit 2 could be postponed once in order for the patient to be stable for 6 weeks prior to randomization at Visit 2. Smoking patients were encouraged to stop. All patients were required to pass qualifying PFTs at both Visits 1 and 2 in order to be randomized into the study.

Following the initial screening period, patients were randomized into the 4-year, double-blind treatment period in which they received tio HH18 or placebo in a 1:1 ratio. The drugs were administered using the HandiHaler as one capsule taken once daily in the morning. All patients were instructed to take rescue medication (albuterol) as needed. Patients also received a patient record book to record any hospitalizations or exacerbations. Visit 3 was scheduled one month after randomization. All subsequent visits were at 3 month intervals.

At each visit, study personnel collected used and unused study drug capsules, reviewed washout compliance for PFTs, exacerbation information, concomitant therapies, smoking status, and adverse events since the previous visit. Pulmonary function testing and the St. George's Hospital Respiratory Questionnaire (SGRQ) were completed at baseline and every 6 months until the end of the trial (Visits 5, 7, 9, 11, 13, 15, 17, and 19). A new record book was provided at the end of each visit.

At the end of Visit 19, patients who completed the 4-year treatment period received open-label ipratropium with instructions to take 2 inhalations four times a day for 30 days. Pulmonary function testing pre- and post-bronchodilator and a complete physical examination was conducted 30 days later at the final study visit. In addition, patients who terminated study drug early were asked to follow up 30 days after their last dose of study drug.

The Applicant states that the study was conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki (1996 version), in accordance with the ICH Tripartite Guideline for Good Clinical Practice (GCP), and in accordance with applicable regulatory requirements and BI Standard Operating Procedures (SOPs). The sponsor held 4 investigator meetings worldwide (Miami, United States; Phuket, Thailand; Coolangub, Australia; and Helsinki, Finland) prior to the start of the study. The sponsor also held yearly world-wide investigator meetings, and annual international clinical monitor meetings throughout the course of the study.

The study flow chart as revised by protocol Amendment 1 is presented in Table 27.

Table 27: Protocol 205.235 study flow chart

Trial Periods	Screening (Baseline)	Treatment (4 years)					Follow up (30 days post treatment)
Visit Number	1	2	3	4	5-18 ²	19 ³	End of Trial
Months	N/A	0	1	3	Q3	48	49
Day	-30 to -14 ¹	1 ± 3 days	30 ± 3 days	90 ± 7 days	Q90 ± 7 days	1440 ± 7 days	1470 ± 7 days
Informed Consent	X						
Demographics	X						
Medical History	X						
Inclusion/Exclusion Criteria	X	X					
Physical Examination/ Vital Signs	X						X
Randomization		X					
Dispense Study Drug		X	X	X	X		
Train/Dispense HandiHaler®		X			X ⁴		
Patient Record		X	X	X	X	X	
Dispense Open-Label Ipratropium						X	
Collect Medication			X	X	X	X	X
Drug Accountability			X	X	X	X	X
Smoking Cessation Program and Patient Education Material ⁵	X	X	X	X	X	X	
Medication Washout Compliance		X	X		X	X	X
PFTs (SVC/FEV ₁ /FVC) ⁶	X ⁷	X ⁸	X ⁹		X ⁹	X ⁹	X ⁸
SGRQ ¹⁰		X			X	X	
EQ-5D ¹¹		X					
Smoking Status Assessment		X	X	X	X	X	X
Exacerbation Information	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X
Termination of Trial Medication						X	
Trial completion							X

¹ In the event of an exacerbation, the time between Visit 1 and 2 could be extended once.

² Visit 5-19 were separated by 3 months each and continued until the patient completed the protocol.

³ Visit 19 represents the final treatment visit occurring approximately 4 years from randomization.

⁴ New HandiHaler® dispensed each year after starting study medication.

⁵ A 4-week smoking cessation program was offered beginning at Visit 1 and completed at time of randomization. Additional materials were provided throughout the trial at the discretion of the investigator.

⁶ Pulmonary function testing (PFT) performed at the screening visit, Day 1, Day 30 and then every 6 months (Visits 5, 7, 9, 11, 13, 15, 17 and 19) until the end of treatment. A final PFT was done at the end of trial visit.

⁷ Post-bronchodilator spirometry (administer 4 inhalations ipratropium [80 mcg], wait 1 hour; then administer 4 inhalations salbutamol [400 mcg], wait 30 minutes; then perform PFT [no washout required prior to PFT]).

⁸ Spirometry pre- and post-bronchodilator (administer 4 inhalations ipratropium [80 mcg], wait 1 hour; then administer 4 inhalations salbutamol [400 mcg], wait 30 minute; then perform PFT [washout required prior to PFT]).

⁹ Two spirometry measurements were taken as follows (washout required prior to PFT): pre-study drug PFT; then administer study drug; then administer 4 inhalations of ipratropium (80 mcg), wait 1 hour; then administer 4 inhalations of salbutamol (400 mcg), wait 30 minutes; then conduct second PFT.

¹⁰ SGRQ is completed Day 1 and then every 6 months until end of treatment (Visits 5, 7, 9, 11, 13, 15, 17 and 19).

¹¹ EQ-5D was completed Day 1 (in a limited number of countries).

Protocol amendments

During the course of the trial, the protocol was amended on three occasions: Amendment 1 (dated 16 May 2003) to include a validated generic quality of life instrument, the EQ-5D questionnaire; Amendment 2 (dated 15 November 2005) to include the monitoring of long-term outcomes for patients prematurely discontinued from the study, and Amendment 3 (dated 25 April 07) to establish an external committee to independently assess the primary cause of deaths for all fatal cases.

Because Amendment 1 was initiated during the enrollment period, only the last 1235 patients from 13 countries with significant enrollment remaining (Australia, Belgium, Czechia, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, Russia, Spain, and the United States) completed the EQ-5D. The results of this questionnaire are not included in this supplement (S-029).

Reviewer comment:

Monitoring of long-term outcomes (vital status) of patients prematurely discontinued from the trial permits determination if an imbalance in premature discontinuations between treatment groups may lead to a “healthy survivor” effect. In addition, an independent committee to adjudicate cause of death is important to provide consistency in nomenclature across study sites in this multinational trial, thus providing improved safety reporting. All amendments were instituted prior to end of the trial.

Efficacy endpoints

Primary

- The yearly rate of decline in trough FEV₁ from day 30 (steady state) until completion of double blind treatment. Trough FEV₁ is the pre-dose value measured approximately 24 hours after the previous dose of study drug
- The yearly rate of decline in FEV₁ 90 minutes after study drug and ipratropium administration (including 30 minutes post albuterol) from day 30 (steady state) until completion of double blind treatment

Pulmonary function testing

Trough FEV₁ was defined as the FEV₁ measured at the -5 minute time point at the end of the dosing interval 24 hours post drug administration. Trough FEV₁ response was defined as the change from baseline in trough FEV₁. Baseline FEV₁ was the pre-treatment FEV₁ value measured at Visit 2 in the morning 5 minutes prior to administration of the first dose of study medication.

FEV₁, FVC, and SVC measurements were obtained through pulmonary function testing at screening (Visit 1), baseline (Visit 2), after 30 days (Visit 3) and every 6 months thereafter until the end of the double-blind treatment period (Visits 5, 7, 9, 11, 13, 15, 17, and 19). PFTs were also performed at the final visit after being off study drug (on open-label ipratropium) for 30 days. PFTs were performed using standardized spirometry equipment provided by the Applicant and calibrated by study staff on all test days. A calibration log was maintained for the spirometry equipment. Equipment and techniques conformed to American Thoracic Society (ATS) criteria.

Patients were instructed to arrive at the clinic approximately 1 hour prior to the time they were scheduled to take study drug having abstained from medications as specified in the protocol. Spirometric measurements commenced at approximately the same time at all visits. If a patient arrived for a visit without adequate washout, the visit was postponed (once).

The following medications were appropriately restricted prior to PFT testing:

- inhaled corticosteroids (withhold morning dose)
- short-acting theophylline (at least 24 hour washout)
- long-acting theophylline (at least 48 hour washout)
- short-acting beta-adrenergic bronchodilators (at least 8 hour washout)
- long-acting beta-adrenergics (LABA) or combination LABA/inhaled steroid products (at least 24 hour washout)
- study medications (not to be taken prior to test-day pre-dose PFTs)
- ipratropium (at least 8-hour washout prior to the final visit)

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.

If an oral corticosteroid burst occurred prior to PFT days, the visit was postponed for at least one, but no more than 2 weeks after the last increased or additional dose was given. The use of antibiotics was not restricted. Antibiotics were used as medically necessary for exacerbations and other infections. If antibiotics were prescribed for a respiratory illness prior to pulmonary function testing days, the visit was postponed for at least one, but no more than 2 weeks after the last dose was given. If an increase in or addition of theophylline dose occurred prior to PFT days, the visit was postponed for at least one, but no more than 2 weeks after the last increased dose was given.

PFTs were performed with the patient in a seated position. Slow vital capacity (SVC) by slow exhalation maneuver was the first spirometric maneuver performed. The forced maneuvers, FEV₁ and forced vital capacity (FVC) were done in triplicate after obtaining the SVC. The best of three efforts was recorded in the case report form (CRF). The best of three efforts was defined as the highest FEV₁ and the highest FVC each obtained on any of three blows (even if not from the same curve) meeting the ATS criteria (with a maximum of five attempts).

At screening (Visit 1), spirometry was performed at the 90-minute post-bronchodilator timepoint (after administration of 4 inhalations of ipratropium [80 mcg] and 4 inhalations of albuterol [400 mcg]). For this visit, washout of respiratory medications was not required. At the randomization visit (Visit 2) and the end of trial visit (30 days after completion of study medication), washout of restricted medications was required and spirometry was performed pre-bronchodilator and at the 90 minute post-bronchodilator timepoint (after administration of 4 inhalations of ipratropium [80 mcg] and 4 inhalations of salbutamol [400 mcg]). For visits at Day 30 (Visit 3) and then every 6 months until the end of treatment (Visits 5, 7, 9, 11, 13, 15, 17, and 19), washout of restricted medications

was required and spirometry was performed pre-bronchodilator and at the 90 minute post-bronchodilator timepoint (after administration of study drug, 4 inhalations of ipratropium [80 mcg], and 4 inhalations of salbutamol [400 mcg]).

nSpire Health Inc. centrally managed spirometry including providing spirometry equipment and training, and ensuring uniformity of the spirometry testing across all participating sites. All staff performing PFTs were required to have at least 6 months of experience performing spirometry and to have performed at least 120 PFTs over the last 6 months. All individuals performing spirometry tests were required to complete training including practice tests. Training on spirometry systems was provided at each investigator meeting. All spirometry technicians during the 4 years were required to demonstrate competency with the spirometer through completing a training checklist and submitting practice maneuvers for approval prior to study maneuvers being performed. The practice spirometry tests were reviewed for overall quality, protocol compliance, and integrity.

Standardized spirometry testing was completed via identical spirometers with secure access features (username and password). Custom software for use by the sites was designed and validated specifically for the study. This software incorporated both ATS criteria for acceptability, and criteria for calculating predicted values as specified by the Standardized Lung Function Testing of the European Community of Coal and Steel (ECCS).

Sites were expected to transmit spirometry data on each day of testing. Centralized quality review and data collection were performed by nSpire Health Inc. Spirograms were reviewed by nSpire Health Inc. technical staff for overall quality, morphology, and artifacts in accordance with the ATS criteria for acceptability, vendor quality assurance review standards, and protocol-specific quality review standard guidelines. Spirograms not meeting quality review standards were queried within 3 business days of receipt. The investigator signed copies of all spirometric reports to approve the data.

Secondary

- Time to first COPD exacerbation
- Time to first COPD exacerbation leading to hospitalization
- Yearly rate of decline in trough FVC and slow vital capacity (SVC)
- Yearly rate of decline in trough FVC and slow vital capacity (SVC) from day 30 until completion of double-blind treatment. Trough FVC and SVC are the pre dose values measured approximately 24 hours after the previous dose of study drug.
- Yearly rate of decline in FVC and SVC measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after albuterol) from day 30 until completion of double-blind treatment.
- Yearly rate of decline in FEV₁, FVC, and SVC prior to ipratropium and albuterol inhalation from day 1 until completion of the trial (30 days post study drug treatment).

- Yearly rate of decline in FEV₁, FVC, and SVC measured 90 minutes after inhalation of ipratropium (and 30 minutes after inhalation of salbutamol) from day 1 until completion of the trial (30 days post study drug treatment).
- Estimated mean pre- and post-bronchodilator FEV₁, FVC, and SVC from day 30 until completion of double-blind treatment.
- Yearly rate of decline in St. George's Respiratory Questionnaire (SGRQ) total, impact, symptom, and activity scores from 6 months until completion of double-blind treatment.
- Estimated mean SGRQ total, impact, symptom, and activity scores from 6 months until completion of double-blind treatment.
- Additional endpoints for COPD exacerbations and associated hospitalizations
 - Number of COPD exacerbations
 - Number of patients with at least one COPD exacerbation
 - Number of COPD exacerbation days
 - Time to first COPD exacerbation treated with steroids*
 - Number of COPD exacerbations treated with steroids*
 - Time to first COPD exacerbation treated with antibiotics*
 - Number of COPD exacerbations treated with antibiotics*
 - Number of COPD exacerbations leading to hospitalizations per patient year
 - Number of patients with at least one COPD exacerbation leading to hospitalization
 - Number of days hospitalized due to COPD exacerbations

Endpoints designated with a * were added by the Applicant in the Statistical Analysis Plan prior to unblinding.

Reviewer comment:

The time to first COPD exacerbation and the time to first COPD exacerbation leading to hospitalization were designated as key secondary endpoints and tested following the co-primary endpoints with a procedure used to address multiplicity. The Statistical Analysis Plan for this protocol was reviewed by FDA prior to unblinding the protocol.

The number of days between exacerbations was defined as a secondary endpoint in the protocol but was not included in the analyses due to potential bias. This is appropriate because for the first and last exacerbation it is impossible to accurately estimate the number of days from the previous exacerbation to the first event during the trial and from the last exacerbation in the trial to the next post-trial event.

Two other endpoints, estimated mean pre- and post-bronchodilator FEV₁, FVC, and SVC from day 30 until completion of double-blind treatment and estimated mean SGRQ total, impact, symptom, and activity scores from 6 months until completion of double-blind treatment, were not specified in the protocol. Both of these endpoints were specified in the Statistical Analysis Plan prior to unblinding. As these endpoints make clinical sense to

evaluate in the setting of looking at yearly rate of decline and do not add new measurements to the study, it is appropriate to evaluate them as secondary endpoints.

COPD exacerbations

COPD exacerbations were recorded on an ongoing basis throughout the study. As an aid to recall, patients were given a Patient Daily Record book that was reviewed at each visit.

For the purposes of this study, a COPD exacerbation was defined as “an increase or new onset of more than one respiratory symptom (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three days or more requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous steroids.” The onset of the COPD exacerbation was defined by the onset of the first recorded symptom. The end of the COPD exacerbation was recorded as defined by the investigator.

Exacerbation events were derived based on the adverse event (AE) records on the exacerbation AE CRF page. All events included by the investigator on the exacerbation AE CRF were included in the efficacy analysis whether or not BI determined that they met all components of the protocol exacerbation definition. In addition to standard AE reporting, total days on antibiotics, total days on systemic steroid bursts, and number of hospitalized days (broken into regular ward and intensive care unit) were also collected for all COPD exacerbation events. Overlapping exacerbations were collapsed into one exacerbation. Two exacerbations were considered distinct events if there were at least 7 exacerbation-free days between the end of one event and the start of the next one.

Exacerbations were categorized as mild, moderate, and severe according to the following definitions:

- mild: treated at home without seeing a health care provider
- moderate: visit with a health care provider (e.g., home visit, visit to an outpatient facility or an emergency department) but not requiring admission to hospital
- severe: hospitalization (emergency room visits >24 hours were considered hospitalizations)

Reviewer comment:

The definition of COPD exacerbation 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 definition is essentially the same as the one used for the Spiriva HandiHaler VA study (Protocol 205.266), with only a slight variation in wording. 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 exists, although in general the definition used in this study is acceptable.

The Applicant initially proposed to combine events with one day or fewer between events, and look at combination of 7 days between events as a sensitivity analysis. The Applicant changed the SAP based on feedback from FDA. From a clinical perspective, recurrence of an event a few days after stopping therapy likely represents recurrence of an incompletely treated exacerbation rather than a new event. In previous Spiriva trials

(including 205.266), sensitivity analysis evaluating combining events with one versus 7 days between events did not make a significant difference in overall outcome.

St. George's Respiratory Questionnaire

Disease-specific health related quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ) instrument. Each patient completed the SGRQ prior to PFTs on Day 1 and then every six months until completion of the double-blind treatment period.

The SGRQ⁸ 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 or 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.

Safety endpoints

- all adverse events (including serious adverse events)
- all-cause mortality
- lower respiratory mortality

Adverse events

All adverse events, serious and non-serious, were collected in an ongoing fashion throughout the study until the end of the double-blind treatment period. At each study visit, all AEs regardless of causality were recorded after review of the Patient Daily Record and discussion with the patient. In addition, all serious adverse events that occurred within 30 days of the last dose of study drug were reported. Adverse events were followed until resolution, until follow up was agreed adequate by the monitor and investigator, or until a patient was lost to follow up. Elective procedures planned prior to signing informed consent were not considered adverse events. Adverse events were monitored by an independent Data Safety Monitoring Board (DSMB). Stroke was defined as an adverse event of interest in the Statistical Analysis Plan (SAP) at the request of FDA.

Mortality

Protocol Amendment 2 allowed for long-term assessment of outcome for patients prematurely discontinued from UPLIFT. Vital status, including cause of death, if known, was collected every 6 months beginning November 15, 2005 for each discontinued patient until completion of the planned observation period (4 years). Vital status was recorded on a separate CRF that captured the following variables: 1) patient's vital status (alive, deceased, or unknown), 2) date of death, 3) cause of death, 4) source of information, 5) additional information regarding the circumstances, 6) if the patient's status was unknown, the date the patient was last known to be alive, and 7) the

investigator's signature and date. At the time the amendment was instituted, approximately 1,500 of the 6,000 patients enrolled in the UPLIFT trial had prematurely discontinued from participation. The UPLIFT Joint Advisory Committee and DSMB both recommended collection of vital status. Analyses for mortality were performed with a variety of cut-off dates including and not including those deaths collected in patients after discontinuation from the study.

Protocol Amendment 3 added an independent assessment of the primary cause of death for all reported fatal cases in the UPLIFT trial as determined by an external committee. Beginning April 2007 (52 months following randomization of the first patient), a Mortality Adjudication Committee (MAC) centrally adjudicated all reported deaths in the study between the screening of the first patient and database lock. The MAC consisted of three members who were external to the sponsor and were not involved in the conduct of the study. Two members were experts in pulmonary/critical care medicine and one had expertise in cardiology; members were from Ireland, Canada, and the United States. Members of the MAC were not involved in the DSMB.

The committee received a CIOMS (Council for International Organizations of Medical Sciences) form for each death that contained a summary of the information available concerning the case. The narrative in the CIOMS form was written based on the information and reported cause of death provided by the investigator at the study center. If available, information from the death certificate, autopsy report, or witness description of the death was also included in the narrative. In addition to the CIOMS form, the medical history, baseline pre- and post-bronchodilator FEV1 values obtained at Visit 2, and all events reported in the SAE reports for each patient were provided to the committee. The committee was permitted to request additional information, when needed, to determine the primary cause of death. The committee was blinded to treatment group assignments.

Adjudication was a two-step process. First, the deaths were adjudicated independently by each member of the committee. Secondly, the committee members met to discuss the cases to arrive at a consensus cause. At the central adjudication meeting, all cases with unanimous agreement were recorded by the committee. Cases with disagreement were adjudicated by the following method:

- 1) All three members of MAC discussed the case in an effort to achieve consensus on the primary cause of death.
- 2) If one or more members of the committee believed that additional supporting information was required to determine the primary cause of death, the chairperson requested the sponsor to obtain the additional data and adjudication of the case was deferred to a future meeting. The sponsor made all reasonable efforts to obtain the requested information and include it in the package sent for one of the future adjudication meetings.
- 3) In situations where agreement by all members was not possible, the primary cause of death was determined by a majority vote.

All mortality adjudications were completed before database lock. Analyses were conducted for cause of death as determined by both the investigator and by the committee.

Reviewer comment:

Adjudication of cause of death is very helpful in analysis of potential safety signals such as cardiovascular mortality and stroke.

Concomitant therapy

The following medications were permitted by the protocol:

- All pulmonary medications other than anticholinergic bronchodilators and combination drugs containing anticholinergic bronchodilators were permitted.
- The use of antibiotics was not restricted.
- The following medications were allowed to control acute exacerbations:
 - prn inhaled beta-agonists
 - increase or addition of theophylline
 - systemic steroids
 - antibiotics
- In the case of life-threatening exacerbations, any and all therapies (including ipratropium) and interventions deemed medically necessary by the treating physician were permitted.

The protocol included the following restrictions regarding concomitant therapy during the course of the study:

- All other investigational agents.
- Long-acting anticholinergics (tiotropium)
- Anticholinergic medications alone or in combination with other medications (e.g. Atrovent, oxitropium, Combivent, Berodual, Duovent).
- Intranasal anticholinergic formulations such as Atrovent nasal spray.
- Oxygen therapy of >12 hours per day

Medications were restricted on pulmonary function test days as described in the methods section on pulmonary function testing.

Reviewer comment:

There were very few medication restrictions in the UPLIFT study, consistent with evaluation of the effects of tiotropium in a “real world” setting. This is helpful to determine what the risks and benefits are of the drug as it is currently used in the community. In addition, it would be highly impractical to expect that a large number of treatment restrictions could be followed over the prolonged length (4 years) of the study.

Statistical plan

There were two co-primary endpoints for this study, yearly rate of decline in trough (pre-bronchodilator) FEV₁ and the yearly rate of decline in peak (post-bronchodilator) FEV₁ from Day 30 to the end of double-blind treatment. Time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization were key secondary endpoints.

Sample size

Based on data from previous long-term studies in patients with COPD, such as the Lung Health Studies, ISOLDE, and BRONCHUS, and data from the one-year and six-month studies of tiotropium, the standard deviation for the rate of decline in FEV₁ per year was assumed to be 90 mL. Therefore, to detect a difference of 15 mL in the rate of decline in FEV₁ between tiotropium and placebo at a 5% level of significance and 90% power, a sample of 758 patients per group was estimated to be needed. Assuming that 35% of patients would discontinue the study early, without adequate data, it was estimated that 1166 patients per treatment group would be required. To conduct subgroup analyses with adequate power (assuming 1166 patients were required per treatment group and 40% were current smokers as based on previous Phase 3 tiotropium studies), the sample size needed for the study was determined to be 2916 per treatment group or 5832 total. Thus, a total of 6000 patients were planned.

Statistical model and analysis

The random-effects model was used as the primary statistical model for the co-primary endpoints. The pre- and post-bronchodilator FEV₁ were assumed to follow linear trends over time. The primary analysis was conducted with center included as a random effect in the model. The primary endpoint was also analyzed for the subgroups (age, gender, smoking status, baseline concomitant medication use, COPD severity according to GOLD stages, race, region, reversibility, BMI) using a random-effects model. In addition, the primary analysis was carried out with adjusting for baseline covariates.

The two key secondary endpoints were compared between treatment groups using the log rank test. Additional analyses for the key secondary endpoints included an estimate of the hazard ratio between treatment groups using Cox regression with a single covariate of treatment and the Kaplan-Meier estimate of the probability of not having the event (first COPD exacerbation or first COPD exacerbation requiring hospitalization) for each treatment group.

Analyses for secondary efficacy endpoints included a repeated measures ANOVA model for PFT variables and SGRQ at each visit. The ANOVA model included treatment, visit, treatment by visit, and baseline by visit as covariates. Yearly rate of decline in SGRQ measures were analyzed using the regression slope from the random-effects model. Endpoints determining numbers of COPD exacerbations per patient year were estimated using Poisson regression adjusting for overdispersion with Pearson's method. Treatment exposure was adjusted as the offset of the model.

Descriptive statistics were used to report adverse events. Mortality events were analyzed for on treatment death (onset of the fatal AE was between first drug intake and last drug intake + 30 days) and all deaths including post-discontinuation visit vital status collection. Analyses were done for cause of death both as reported by the investigator and as adjudicated by the MAC. Analyses of time to death were performed using Kaplan-

Meier estimates and Cox regression censoring based on the cut-off of Day 1470. Mortality endpoints included all cause, lower respiratory, cardiac disorders, stroke, and any fatal AE that occurred in more than 1% (or 60 cases) of the patients. Subgroup analyses were also carried out for all-cause, lower respiratory, and cardiac death.

Reviewer comment:

The Statistical Analysis Plan (SAP) for this study was reviewed by FDA and comments were provided to BI. All of FDA's comments were incorporated into the SAP prior to unblinding.

Multiplicity adjustments

The Applicant took the following approaches to adjust for multiplicity in the UPLIFT trial:

- Hierarchical testing was performed for the co-primary endpoints. First, the rate of decline in pre-bronchodilator FEV₁ was compared between the tiotropium and the placebo groups at a significance level of 0.049. If significance was achieved in favor of tiotropium, the rate of decline in post-bronchodilator FEV₁ results was compared between groups at a significance level of 0.049.
- If statistical significance was achieved in favor of tiotropium for the co-primary endpoints, hierarchical testing of two key secondary endpoints, time to the first COPD exacerbation and time to the first COPD exacerbation leading to hospitalization, was performed using the log-rank test. First, the time to first exacerbation was tested at 0.049 level of significance. If significance was achieved, the time to the first COPD exacerbation leading to hospitalization was tested at 0.049 level of significance.
- In parallel with the testing of the co-primary endpoints, the number of COPD exacerbations leading to hospitalizations per patient year was compared between treatment groups at the significance level of 0.001.
- P-values for testing the co-primary endpoints, the number of COPD exacerbations leading to hospitalizations per patient year, and the two key secondary endpoints were adjusted for interim looks. For the other endpoints, p-values are reported at nominal p-values.
- As specified in the DSMB Charter, independent interim safety analyses were conducted and reviewed by the DSMB at approximately 12, 24, 36, 48, and 54 months after trial initiation. Also as specified in the DSMB Charter, independent interim efficacy analyses were conducted and reviewed by the DSMB at approximately 24 and 36 months after the trial initiation. For the final efficacy analyses, the p-values for the co-primary endpoint, number of exacerbations leading to hospitalization, and the two key secondary endpoints were adjusted for the DSMB efficacy data reviews.

Missing data

Missing data for PFTs and SGRQ were not imputed for the efficacy analysis. Missing data for exacerbation dates was first queried. Missing exacerbation dates that could not be resolved with data queries were imputed as follows:

- If the exacerbation was for a patient who died, the date of death was used for the exacerbation end date.
- The exacerbation end date for a patient who did not die was estimated using the exacerbation start date and the median length of an exacerbation based on all exacerbations with complete start and end dates starting during the treatment period.
- The exacerbation start date for a patient who did not die was estimated using the exacerbation start date and the median length of an exacerbation based on all exacerbations with complete start and end dates starting during the treatment period.
- No events occurred with that were missing both start and end dates.
- Missing values for antibiotic days, steroid days, and hospital days were not imputed.

Detailed rules regarding collapsing of exacerbation events with fewer than 7 days between events are provided in the statistical analysis plan for the study.

Data sets

For the primary efficacy analysis, patients with at least 3 acceptable FEV₁ measurements from Day 30 onward were included. As a sensitivity analysis, patients with at least 1 acceptable FEV₁ measurement from Day 30 onward were included in the analysis. Analysis of change in SGRQ included patients in the treated set who had at least 2 SGRQ measurements from month 6 onward. A sensitivity analysis was performed for SGRQ total score in patients with at least one SGRQ measurement from month 6 onward.

For all other endpoints (including AEs, mortality, and COPD exacerbations), the treated set was considered to be all randomized patients who received study medication and were documented to have taken at least one dose.

6.1.1.2 Protocol 205.235 results

Population characteristics

Disposition of patients

A total of 8,020 male and female patients with moderate to severe COPD (FEV₁ ≤ 70% predicted) were screened. Of these, 5,993 patients were randomized; 2987 in the tio HH18 group and 3006 in the placebo group. A total of 3535 (59.0%) patients completed the study per protocol on study medication, 1887 (63.2%) in the tio HH18 group and 1648 (54.8%) in the placebo group. The highest percentage of discontinuations occurred in the first year of treatment (14% tio HH18 and 20% placebo). Patient disposition in the trial is provided in Table 28.

Table 28: Protocol 205.235 patient disposition

	Placebo N (%)	Tio HH18 N (%)	Total N (%)
Enrolled			8016
Not entered			2023
Entered	3006	2987	5993
Not treated	0	1 [†]	1
Treated	3006 (100.0)	2986 (100.0)	5992 (100.0)
Not prematurely discontinued from trial medication	1648 (54.8)	1887 (63.2)	3535 (59.0)
Prematurely discontinued from trial medication	1358 (45.2)	1099 (36.8)	2457 (41.0)
Adverse events	746 (24.8)	627 (21.0)	1373 (22.9)
Worsening of disease under study	368 (12.2)	238 (8.0)	606 (10.1)
Worsening of other pre-existing disease	41 (1.4)	40 (1.3)	81 (1.4)
Other adverse event	337 (11.2)	349 (11.7)	686 (11.4)
Administrative	554 (18.4)	412 (13.8)	966 (16.1)
Non compliant with protocol	75 (2.5)	48 (1.6)	123 (2.1)
Lost to follow-up	76 (2.5)	64 (2.1)	140 (2.3)
Consent withdrawn	403 (13.4)	300 (10.0)	703 (11.7)
Other	58 (1.9)	60 (2.0)	118 (2.0)

[†]one patient was randomized twice in error

Reviewer comment:

A greater percentage of patients discontinued from the placebo group, primarily due to worsening of COPD and consent withdrawn. Because vital status was collected on all patients who discontinued from the trial, the mortality data is less likely to be biased by a “healthy survivor” effect.

The blind was broken for 22 patients in the trial, 9 in the tio HH18 group and 13 in the placebo group. In all cases, the unblinding occurred due to an adverse event. Of the 22 unblindings, 8 were related to COPD exacerbations, 2 in the tio HH18 group and 6 in the placebo group. Other events leading to unblinding in the tiotropium group were interstitial lung disease, pneumonia, ventricular fibrillation, acute myocardial infarction, atrial flutter, and hyperplasia of the prostate/bladder neck obstruction. Two cases were unblinded due to sudden death, 1 in the tio HH18 group and 1 in the placebo group. A summary of AEs leading to unblinding is presented in Table 29.

Table 29: Protocol 205.235 unblinded patients

Country	Site number	Patient number	Treatment	Adverse event
Argentina	0107	10181	tio HH18	interstitial lung disease
Brazil	0514	10591	placebo	fecal impaction
Denmark	0801	17543	placebo	acute laryngitis
Germany	1110	18852	tio HH18	COPD exacerbation
Greece	1201	19016	placebo	dysphonia, pharyngeal disorder
Hungary	1304	16123	placebo	COPD exacerbation
Italy	1629	19800	tio HH18	pneumonia
Mexico	2002	10680	tio HH18	prostate hyperplasia, bladder neck obstruction
Netherlands	2109	20602	tio HH18	shortness of breath, COPD exacerbation
New Zealand	0212	23831	placebo	increased shortness of breath on exertion, wheeze, sub-acute exacerbation of COPD with asthmatic component
Singapore	1906	27043	placebo	COPD exacerbation
Spain	3027	21600	placebo	COPD exacerbation
Switzerland	3203	24308	tio HH18	ventricular fibrillation
Thailand	3404	26645	placebo	chest tightness, sudden death
Thailand	3404	26639	tio HH18	acute myocardial infarction
Turkey	3512	22812	placebo	COPD exacerbation
Turkey	3512	22815	placebo	type 2 respiratory failure, COPD exacerbation
United States	3787	13557	placebo	atrial flutter
United States	3788	13581	tio HH18	atrial flutter
United States	3789	13606	placebo	prolonged ileus
United States	3789	13615	tio HH18	sudden death, presumably arrhythmic
United States	3789	13685	placebo	atrial fibrillation

Demographics and disease characteristics

The mean age of the patients was 64.5 years (range 40-88 years). The majority of the trial population (74.6%) was male and 89.9% were white. The mean duration of COPD was 9.8 years. All patients were current (29.6%) or ex-smokers (70.4%), with a mean

smoking history of 48.7 pack years. The mean pre-bronchodilator FEV₁ was 1.096L with a mean percent predicted of 39.4%. The mean pre-bronchodilator FEV₁/FVC was 42.3%. The overall demographic profile was generally balanced across the treatment groups. Pulmonary function data at baseline were generally comparable. Demographic and disease characteristics are provided in Table 30, and baseline PFT variables are provided in Table 31.

Table 30: Protocol 205.235 patient demographic and disease characteristics

	Placebo	Tio HH18	Total
Number of patients	3006	2986	5992
Gender [N (%)]			
Male	2222 (73.9)	2251 (75.4)	4473 (74.6)
Female	784 (26.1)	735 (24.6)	1519 (25.4)
Race [N (%)]			
White	2697 (89.7)	2691 (90.1)	5388 (89.9)
Black	53 (1.8)	38 (1.3)	91 (1.5)
Asian	185 (6.2)	192 (6.4)	377 (6.3)
Missing	71 (2.4)	64 (2.2)	136 (2.3)
Age [years]			
Mean	64.5	64.5	64.5
SD	8.5	8.4	8.5
Min	40.0	40.0	40.0
Max	88.0	88.0	88.0
Smoking history [N (%)]			
Ex smoker	2108 (70.1)	2112 (70.7)	4220 (70.4)
Smoker	898 (29.9)	874 (29.3)	1772 (29.6)
Smoking history [pack years]			
Mean	48.4	49	48.7
SD	27.9	28.0	27.9
Min	10.0	10.0	10.0
Max	285.0	225.0	285.0
Duration of COPD [years]³			
Mean	9.7	9.9	9.8
SD	7.4	7.6	7.5
Min	0.0	0.08	0.0
Max	53.0	55.0	55.0
Gold stage [N (%)]			
Stage I	1 (0.0)	2 (0.1)	3 (0.1)
Stage II	1355 (45.1)	1384 (46.3)	2739 (45.7)
Stage III	1331 (44.3)	1304 (43.7)	2635 (44.0)
Stage IV	271 (9.0)	250 (8.4)	521 (8.7)
missing	48 (1.6)	46 (1.5)	94 (1.6)

Table 31: Protocol 205.235 baseline PFT data

	Tio HH18	Placebo	Total
Number of patients	3006	2986	5992
Pre-bronchodilator FEV₁ [L]			
Mean	1.092	1.101	1.096
SD	0.40	0.40	0.40
Min	0.29	0.28	0.28
Max	2.71	2.64	2.71
Pre-bronchodilator % predicted normal FEV₁			
Mean	39.3	39.5	39.4
SD	11.9	12.0	12.0
Min	9.0	11.0	9.0
Max	76.0	73.0	76.0
Pre-bronchodilator FVC [L]			
Mean	2.63	2.63	2.63
SD	0.83	0.81	0.82
Min	0.64	0.67	0.64
Max	6.70	6.13	6.70
Pre-bronchodilator FEV₁ / FVC [%]			
Mean	42.1	42.4	42.3
SD	10.5	10.5	10.5
Min	15.0	14.0	14.0
Max	76.0	75.0	76.0

Obtained from Visit 2, Randomization Visit

Reviewer comment:

The demographics in this study are highly consistent with those across the Phase 3 program for Spiriva HandiHaler.

Protocol violations

There were a total of 440 patients with protocol violations in this study; 7.5% (223 patients) of the tioHH18 group and 7.2% (217 patients) of the placebo group. The most common protocol violations were due to use of anticholinergics on at least 2 consecutive visits (112 patients in the tiotropium group and 115 in the placebo group). Of the 60 patients with post-bronchodilator FEV₁ >70% of predicted or post-bronchodilator FEV₁>70% of FVC at either Visit 1 or 2, the majority had post-bronchodilator FEV₁% of predicted or post-bronchodilator FEV₁% of FVC values ranging from 71-75%. See Table 32.

Table 32: Protocol 205.235 protocol violations

Protocol violation	Tio HH18 N=3006 n (%)	Placebo N=2986 n (%)	Total N=5992 n (%)
Total with protocol violation	217 (7.2)	223 (7.5)	440 (7.3)
Entrance criteria not met			
Known active tuberculosis	0	1 (0.0)	1 (0.0)
History of excluded pulmonary disease	10 (0.3)	7 (0.2)	17 (0.3)
History of thoracotomy with resection	1 (0.0)	4 (0.1)	5 (0.1)
Respiratory infection/COPD exacerbation	26 (0.9)	29 (1.0)	55 (0.9)
Unstable respiratory medication use	7 (0.2)	10 (0.3)	17 (0.3)
Known narrow angle glaucoma	1 (0.0)	3 (0.1)	4 (0.1)
Symptomatic prostatic hyperplasia	0	1 (0.0)	1 (0.0)
Malignancy in last 5 years	5 (0.2)	2 (0.1)	7 (0.1)
Anticholinergic drug hypersensitivity	0	1 (0.0)	1 (0.0)
Involved in other trials	0	1 (0.0)	1 (0.0)
FEV1>70% or FEV1/FVC>70%	28 (0.9)	32 (1.1)	60 (1.0)
Informed consent signed late	2 (0.1)	2 (0.1)	4 (0.1)
Improper medication wash out	39 (1.3)	43 (1.4)	82 (1.4)
Incorrect trial medication taken	1 (0.0)	0	1 (0.0)
Anticholinergic use for ≥2 consecutive visits	115 (3.8)	112 (3.8)	227 (3.8)

Reviewer comment:

Protocol violations were generally balanced between the treatment groups. The persistent use of anticholinergics was noted in only a small percentage of patients, which was similar between treatment groups. This is unlikely to affect the results of the study.

Treatment compliance

Medication compliance was determined by counting returned capsules of study medication. Compliance was defined as the percentage of capsules taken over the planned total. As a patient should take one capsule per day, compliance of the patient was calculated as number of capsules used divided by the number of days that the patient was on treatment. More patients in the tio HH18 group than in the placebo group had compliance of >80%. See Table 33.

Table 33: Protocol 205.235 treatment compliance

Compliance	Placebo N=3006 N (%)	Tio HH18 N=2986 N (%)	Total N=5992 N (%)
0 - < 50%	212 (7.1)	138 (4.6)	350 (5.8)
50% - <80%	425 (14.1)	347 (11.6)	772 (12.9)
80% - <120%	2331 (77.5)	2467 (82.6)	4798 (80.1)
≥ 120%	8 (0.3)	7 (0.2)	15 (0.3)
incomplete	5 (0.2)	6 (0.2)	11 (0.2)
missing	25 (0.8)	21 (0.7)	46 (0.8)

Reviewer comment:

Compliance for this study overall was good, although lower than in the Phase 3 Spiriva HandiHaler program. This is to be expected, because the UPLIFT protocol had a duration of 4 years, during which compliance might be expected to decrease. It is also relevant that patients in the Spiriva group had improved compliance compared to the placebo group, suggesting that patients may have felt benefit from the drug.

Concomitant respiratory medications

As specified in the protocol, patients were allowed to take any pulmonary medication with the exception of anticholinergic bronchodilators. There was extensive use of maintenance medications, particularly LABAs and ICS in both treatment groups. Approximately 17% of patients used short-acting anticholinergics at least once during the trial, which likely reflects use during exacerbations. In contrast, only 3.8% of patients had protocol violations due to anticholinergic use. Anticholinergic use was counted as a protocol violation only if use persisted on 2 or more consecutive visits, which makes sense in light of the duration of the study. See Table 34.

Table 34: Protocol 205.235 concomitant pulmonary medications used at least once during the study

	Placebo N=3006 N (%)	Tio HH18 N=2986 N (%)	Total N=5992 N (%)
Taking any pulmonary medication	2819 (93.8)	2861 (95.8)	5680 (94.8)
Anticholinergic (long-acting)	66 (2.2)	71 (2.4)	137 (2.3)
Anticholinergic (short-acting)	520 (17.3)	501 (16.8)	1021 (17.0)
LABA	2166 (72.1)	2141 (71.7)	4309 (71.9)
Beta agonist (short acting or oral)	2371 (78.9)	2403 (80.5)	4775 (79.7)
LTRA	141 (4.7)	141 (4.7)	282 (4.7)
Mucolytics	804 (26.7)	817 (27.4)	1621 (27.1)
Oxygen	368 (12.2)	359 (12.0)	727 (12.1)
Steroids (inhaled)	2221 (73.9)	2210 (74.0)	4431 (73.9)
Steroids (other)	1654 (55.0)	1590 (53.2)	3244 (54.1)
Xanthines	1059 (35.2)	1035 (34.7)	2094 (34.9)
Xanthines/beta-agonist combination	7 (0.2)	5 (0.2)	12 (0.2)

Reviewer comment:

Almost all of the patients in this study were on concomitant medications. This study differs from most long-term COPD trials because long-acting beta-agonists (LABAs) were permitted as were inhaled corticosteroids. Note that these numbers differ from those used in subgroup analyses for the trial, which were based on baseline medication use. Presumably most of the anticholinergic use was in association with severe exacerbations, during which patients were permitted to use any medication, and use did not persist for more than one visit (a protocol violation).

Pharmacokinetic outcomes

No pharmacokinetic data were collected in this study.

Efficacy outcomes

Efficacy analyses for COPD exacerbations were performed on the treated set, which consisted of all randomized patients who took at least one capsule of the study drug.

For the analysis of rate of decline of FEV1, FVC, or SVC, treated patients with at least three corresponding acceptable PFT measurements after (including) Day 30 (Visit 2) until the completion of the double-blind treatment (Visit 19) were included. As a sensitivity analysis, the analysis of rate of decline was also conducted for patients with at least one acceptable PFT measurement between Day 30 and completion of double-blind treatment.

For the analysis of rate of decline of SGRQ scores, patients with at least 2 measurements between (including) months 6 (Visit 5) and the completion of double-blind treatment (Visit 19) were included. As a sensitivity analysis, rate of decline for the SGRQ endpoints was estimated for patients with at least one measurement between Visits 5 and 19. Turkish patients (N=128 or 2% of the treated set) were not included in the analysis of SGRQ endpoints due to a missing question in the Turkish version of the questionnaire.

See Table 35 for a summary of numbers of patients included in the analyses.

Table 35: Protocol 205.235 patients included in the analysis of rate of decline of PFT and SGRQ

	Placebo N = 3006 n (%)	Tio HH18 N = 2986 n (%)	Total N = 5992 n (%)
PFT endpoints			
Post-bronchodilator FEV1	2410 (80.2)	2554 (85.5)	4964 (82.8)
Post-bronchodilator FVC	2410 (80.2)	2554 (85.5)	4964 (82.8)
Post-bronchodilator SVC	2383 (79.3)	2527 (84.6)	4910 (81.9)
Pre-bronchodilator FEV1	2413 (80.3)	2557 (85.6)	4970 (82.9)
Pre-bronchodilator FVC	2413 (80.3)	2557 (85.6)	4970 (82.9)
Pre-bronchodilator SVC	2374 (79.0)	2531 (84.8)	4905 (81.9)
SGRQ endpoints			
Activity score	2362 (78.6)	2505 (83.9)	4867 (81.2)
Impact score	2362 (78.6)	2505 (83.9)	4867 (81.2)
Symptom score	2364 (78.6)	2512 (84.1)	4876 (81.4)
Total score	2362 (78.6)	2505 (83.9)	4867 (81.2)

Primary

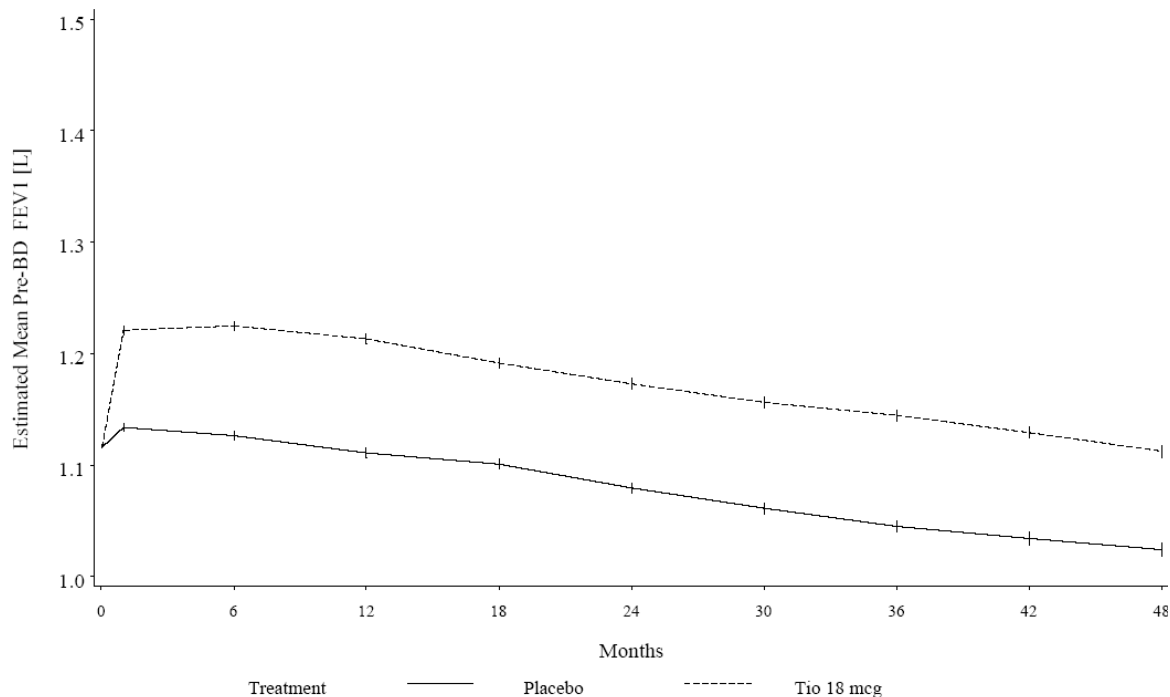
There were two co-primary endpoints for this study, rate of decline of pre- and post-bronchodilator FEV1 from Day 30 (steady state) until completion of double-blind treatment. The endpoints did not achieve statistical significance, thus the Applicant reported p-values as unadjusted for multiple comparisons.

There was no significant difference between treatment groups for rate of decline in either pre- or post-bronchodilator FEV1. The sponsor reports that sensitivity analyses including patients with at least one measurement and including center as a random effect also showed no significant treatment difference. Likewise, adjusting for baseline covariates of post-bronchodilator FEV1, age, sex, height and smoking status did not change significance. Pre-specified subgroups of age, gender, smoking status, baseline ICS use, baseline ICS/LABA combination use, baseline anticholinergic use, GOLD stage, race, region, reversibility, and BMI were evaluated. No significant treatment by subgroup interaction was detected. See Table 36 and Figure 10.

Table 36: Protocol 205.235 rate of decline in FEV1 (random effects model)

	Placebo		Tio HH18		Difference		
	N	Mean (SE) ml/yr	N	Mean (SE) ml/yr	Mean (SE) ml/yr	95%CI	p-value
Pre-BD	2413	30 (1)	2557	30 (1)	0 (2)	(-4, 4)	0.9524
Post-BD	2410	42 (1)	2554	40 (1)	2 (2)	(-6, 2)	0.2074

Figure 10: Protocol 205.235 mean pre-bronchodilator FEV1



Treated set with at least 3 measurements after and including Day 30. Estimated based on repeated measure ANOVA model. Model adjusted for baseline measurement. Day 1 (baseline) value is overall mean, not estimated from the mixed model.

An evaluation of the association between smoking status and rate of decline in FEV1 demonstrated that in both treatment groups, sustained smokers had the highest mean rate of decline in FEV1, sustained ex-smokers had the lowest rate, and intermittent smokers were in between. Smokers were distributed evenly between the groups, and rate of decline was comparable between treatment groups for all smoker subgroups. See Table 37.

Table 37: Protocol 205.235 rate of decline in FEV1 by smoking status

	Placebo		Tio HH18		Subgroup treatment interaction p-value	Difference	
	N	Mean (SE) ml/yr	N	Mean (SE) ml/yr		Mean (SE) ml/yr	p-value
Pre-BD					0.8889		
Sustained ex-smoker	1438	23 (2)	1486	23 (2)		0 (2)	0.8465
Sustained smoker	303	51 (4)	313	51 (4)		0 (5)	0.9865
Intermittent smoker	672	36 (2)	758	35 (2)		2 (3)	0.6493
Post-BD					0.8424		
Sustained ex-smoker	1432	36 (2)	1484	36 (2)		3 (2)	0.1909
Sustained smoker	305	59 (4)	312	59 (4)		0 (5)	0.9807
Intermittent smoker	673	48 (3)	754	46 (2)		2 (3)	0.5731

Reviewer comment:

This study failed on the primary endpoint, rate of decline of FEV1. However, it is important to note that the difference between treatment groups is maintained throughout the study, suggesting that tiotropium does not lose bronchodilator efficacy with prolonged use (see subsequent discussion of FEV1 at each timepoint). It is well-accepted in the COPD literature that sustained smoking causes a more rapid decline of lung function compared to patients who are able to quit smoking, in whom the rate of decline returns to similar slope as that of never smokers.^{2, 3} The UPLIFT trial demonstrates this fact nicely, providing internal validation for the FEV1 measurements in the study.

The Applicant conducted post-hoc analyses to evaluate the effect of LABA or ICS use as a potential confounder as well as the effect of differential discontinuation on rate of decline in FEV1. In the UPLIFT trial, 72% and 74% of patients used LABA and ICS, respectively, on at least one visit during the trial. The effect of these concomitant medications was evaluated in two ways: 1) modeling assuming two rates of decline in FEV1 for each patient (one during LABA or ICS use and one without LABA or ICS use), and 2) a subgroup analysis according to baseline LABA or ICS use. Results demonstrated that tio HH18 may reduce rate of decline in FEV1 for patients not on a LABA or ICS. See Table 38 and Table 39. Comparison of the rate of decline of FEV1 between patients who completed at least 45 months of the trial and non-completers demonstrated a higher rate of decline in non-completers (pre-bronchodilator loss of 29-30 ml/year in completers versus 37-40 ml/year in non-completers). Because 45% of placebo-treated patients discontinued prematurely compared to only 36% of tio HH18 treated patients, differential drop-outs may have biased against tio HH18.

Table 38: Protocol 205.235 rate of decline in FEV1 modeled for different slopes during ICS/LABA use and non-use

	Placebo Mean (SE) ml/yr	Tio HH18 Mean (SE) ml/yr	Mean (SE) ml/yr	Difference 95%CI	p-value
Pre-BD					
On LABA/ICS	28 (2)	29 (1)	-1 (2)	(-6, 3)	0.5244
Off LABA/ICS	39 (3)	33 (3)	6 (4)	(-2, 13)	0.1258
Post-BD					
On LABA/ICS	40 (2)	40 (2)	0 (2)	(-4, 5)	0.9285
Off LABA/ICS	49 (3)	39 (3)	10 (4)	(3, 18)	0.0082

Table 39: Protocol 205.235 rate of decline in FEV1 by baseline LABA or ICS use

	Placebo		Tio HH18		Subgroup treatment interaction p-value	Difference	
	N	Mean (SE) ml/yr	N	Mean (SE) ml/yr		Mean (SE) ml/yr	p-value
Pre-BD					0.0409		
No LABA/ICS	767	39 (3)	789	33 (2)		6 (3)	0.0846
LABA/ICS use	2096	26 (2)	2117	28 (1)		-2 (2)	0.2715
Post-BD					0.1070		
No LABA/ICS	764	47 (3)	787	40 (3)		7 (4)	0.0464
LABA/ICS use	2087	39 (2)	2117	39 (2)		0 (2)	0.8719

Reviewer comment:

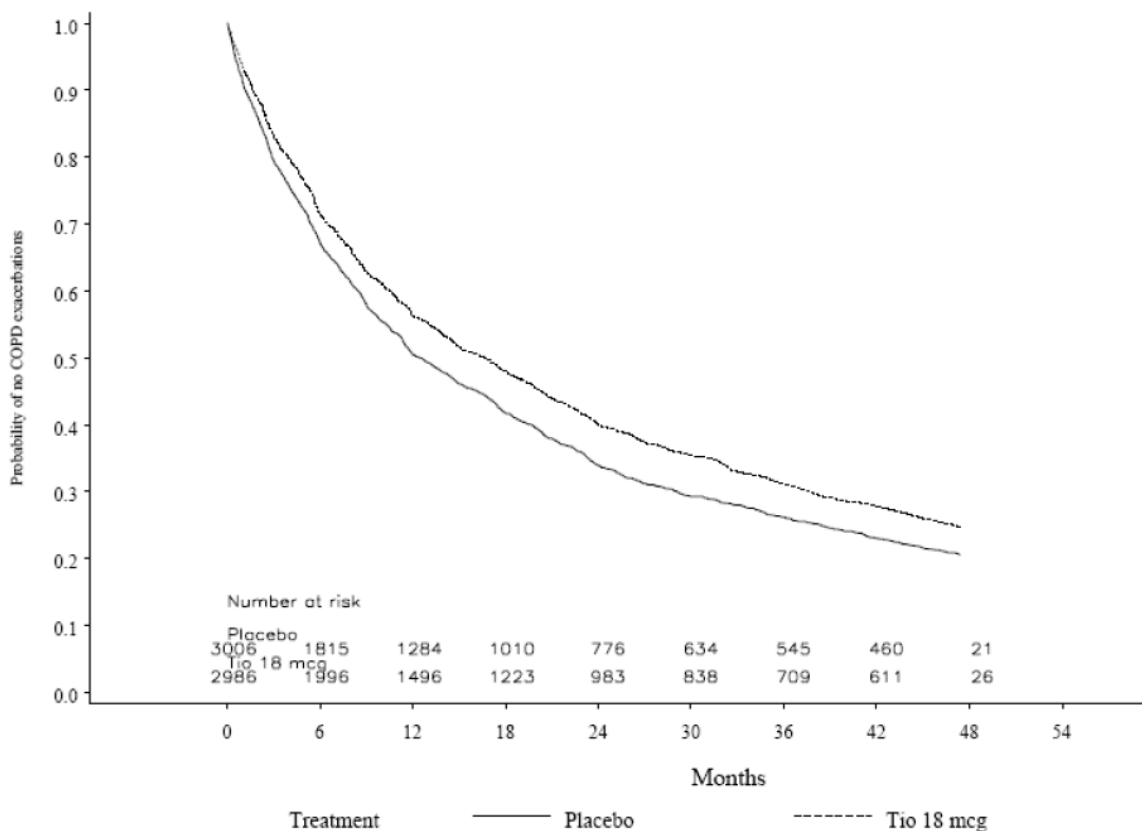
The Applicant offers two plausible explanations for the failure of the UPLIFT trial to demonstrate a difference in long-term rate of decline in FEV1, confounding by concomitant disease-modifying therapy and differential discontinuation biasing against tiotropium. While these effects may be real, the UPLIFT design overall was significantly strengthened by its “real world” approach to inclusion of multiple concomitant medications, similar to the situation encountered in the COPD population in the United States. Thus, one can conclude that in the setting of high-quality COPD care, the addition of tiotropium is unlikely to significantly impact the natural history of disease.

Key secondary

There were two key secondary endpoints: time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization.

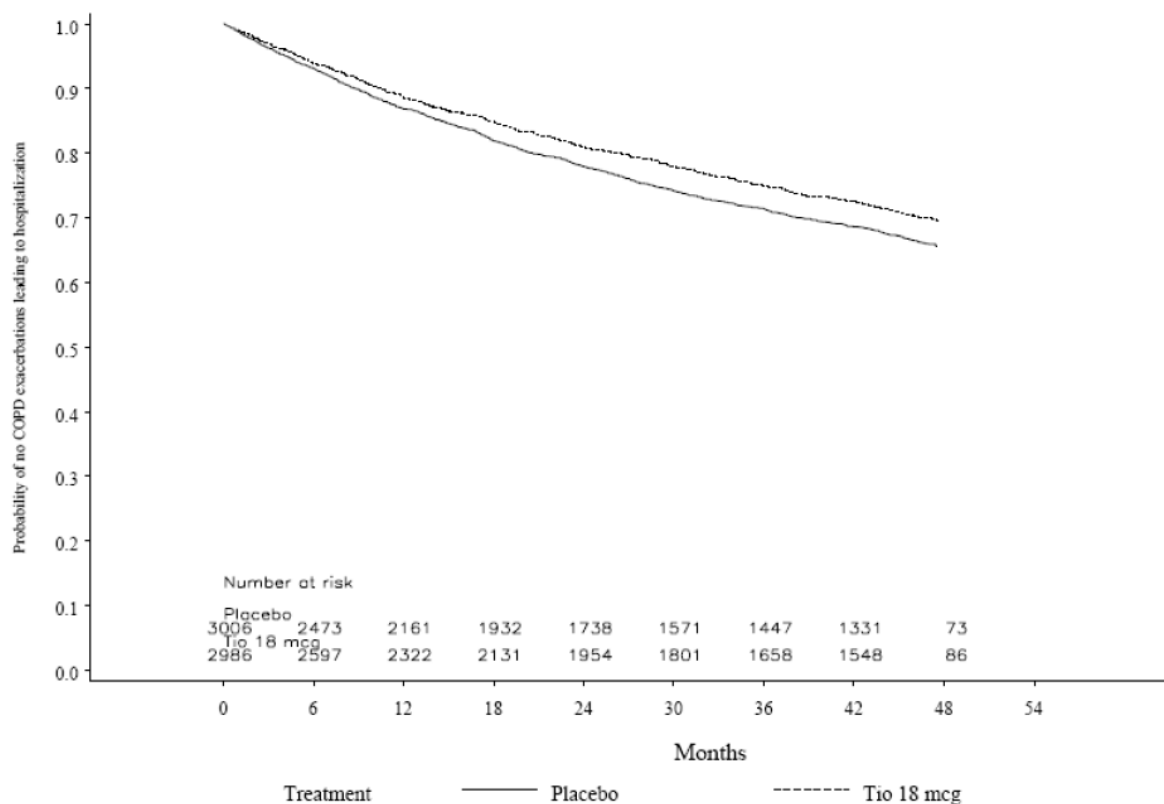
For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p < 0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. A Kaplan-Meier estimate of the probability of no exacerbation as provided by the Applicant is presented in Figure 11.

Figure 11: Study 205.235 Kaplan-Meier estimates of the probability of no exacerbation



The Applicant also reports that patients in the tio HH18 group had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p = 0.0024$, RR 0.86, 95% CI 0.78, 0.95). The median time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group. Since only 27% of the placebo group and 25% of the tio HH18 group experienced exacerbations leading to hospitalizations, the median time to first exacerbation was calculated based on the first 25% of patients with exacerbations. A Kaplan-Meier estimate of the probability of no exacerbation resulting in hospitalization as provided by the Applicant is presented in Figure 12.

Figure 12: Protocol 205.235 Kaplan-Meier estimates of the probability of no exacerbation leading to hospitalization



Reviewer comment:

Significance was not achieved for the co-primary endpoints; however, the key secondary endpoints showed a significant difference from placebo with an unadjusted p-value of <0.0001 . Strictly speaking, because the trial adjusted for multiplicity using a step-wise approach, i.e. allowing testing of secondary endpoints only if the primary endpoints were met, the trial could be considered “failed” for the secondary endpoints as well. Adjusting for multiplicity in a more-conventional way, a $p < 0.01$ would be considered to show statistical significance. [See Statistical Review by Dr. Joan Buenconsejo, NDA 21-395, S029]

Clinically, the exacerbation endpoints are clinically important, and the failure of the study to show an improvement in disease progression does not detract from the finding of improvement in exacerbations, which was also replicated in a second, independent study (Protocol 205.235). If the exacerbation finding had been less robust, adjustments for multiplicity would pose a greater concern.

This same argument also applies to labeling claims regarding lung function, which from a statistical standpoint also represent secondary endpoints with a failed primary. In addition, it would be difficult to provide a description of the study in the label without discussing lung function. Regardless of efficacy, it is important to describe the UPLIFT in the product label due to the safety implications of such a large, long-term trial.

Other secondary

PFT endpoints

Mean pre- and post-bronchodilator FEV1 at each visit was estimated using a repeated measure ANOVA model with visit as a discrete variable and baseline value as a covariate. The tio HH18 group had a significantly higher pre- and post-bronchodilator FEV1 compared to placebo at all timepoints. Pre-bronchodilator FEV1 was a trough level performed after wash-out of appropriate pulmonary medications (see section on PFT measurements). For mean pre-bronchodilator FEV1, the estimated mean difference between tio HH18 and placebo groups ranged from 87 to 103 ml ($p < 0.0001$), with an overall mean difference of 94 ml. See Table 40. Post bronchodilator FEV1 was measured after four puffs of albuterol, four puffs of ipratropium and administration of study drug. For post-bronchodilator FEV1, the treatment difference ranged from 47 to 65 ml ($p < 0.0001$), with an overall mean difference of 57 ml.

Table 40: Protocol 205.235 FEV1

Test Day	Broncho-dilator	Placebo [L]	Tio HH18 [L]	Treatment difference [L]	p-value	95% CI
Day 1	Pre	1.116	1.116			
	Post	1.347	1.347			
Month 1	Pre	1.134	1.221	0.087	<0.0001	0.077, 0.098
	Post	1.372	1.418	0.047	<0.0001	0.037, 0.057
Month 6	Pre	1.126	1.225	0.099	<0.0001	0.087, 0.110
	Post	1.365	1.423	0.058	<0.0001	0.047, 0.069
Month 12	Pre	1.111	1.213	0.103	<0.0001	0.091, 0.115
	Post	1.345	1.398	0.054	<0.0001	0.042, 0.065
Month 18	Pre	1.101	1.192	0.091	<0.0001	0.078, 0.104
	Post	1.326	1.379	0.053	<0.0001	0.040, 0.066
Month 24	Pre	1.079	1.173	0.094	<0.0001	0.081, 0.107
	Post	1.294	1.356	0.062	<0.0001	0.049, 0.075
Month 30	Pre	1.061	1.156	0.095	<0.0001	0.081, 0.109
	Post	1.274	1.335	0.061	<0.0001	0.047, 0.075
Month 36	Pre	1.045	1.144	0.099	<0.0001	0.085, 0.114
	Post	1.250	1.315	0.065	<0.0001	0.051, 0.080
Month 42	Pre	1.034	1.129	0.095	<0.0001	0.080, 0.110
	Post	1.236	1.297	0.061	<0.0001	0.045, 0.076
Month 48	Pre	1.024	1.112	0.088	<0.0001	0.073, 0.103
	Post	1.219	1.268	0.049	<0.0001	0.033, 0.065
Overall mean	Pre	1.080	1.174	0.094	<0.0001	0.084, 0.105
	Post	1.298	1.354	0.057	<0.0001	0.046, 0.067

Pre-BD N=2363 placebo, N=2494 tio HH18; Post-BD N=2374 placebo, N=2516 tio HH18

Mean and 95% CI estimated using repeated measured ANOVA adjusted for D1 baseline overall mean value.

Reviewer comment:

Bronchodilatory effect of tio HH18 is slightly lower than that observed in the Spiriva HandiHaler Phase 3 program. For Spiriva HandiHaler Phase 3 pivotal trials the FEV₁ trough response was 0.110-0.130L. Overall, however, the results are comparable. The spirometry results from this study demonstrate bronchodilator efficacy in a more “real world” patient population in which there was high use of concomitant respiratory medications. In addition, the results (trough FEV₁ treatment difference of 0.09-0.10L) are similar to that observed in Spiriva HandiHaler Protocol 205.266, a Phase 3 trial conducted in a Veteran’s Affairs setting (NDA 21-395, S024), with similar “real world” inclusion criteria.

Rate of decline in PFT measurements

A number of additional rate of decline endpoints were examined in this trial. These included:

- rate of decline in pre-bronchodilator FEV₁ from Day 1 until end of trial (30 days post-treatment)
- rate of decline in post-bronchodilator FEV₁ from Day 1 until end of trial (30 days post-treatment)
- rate of decline in pre-bronchodilator FVC from Day 1 until end of trial (30 days post-treatment)
- rate of decline in pre-bronchodilator FVC from Day 1 until end of trial (30 days post-treatment)
- rate of decline in pre-bronchodilator SVC from Day 1 until end of trial (30 days post-treatment)
- rate of decline in post-bronchodilator SVC from Day 1 until end of trial (30 days post-treatment)
- rate of decline in pre-bronchodilator FEV₁ from Day 1 until end of trial (30 days post-treatment)—nonparametric approach
- change in FEV₁ from Day 1 to Day 30 and from Day 30 until completion of treatment
- rate of decline in pre-bronchodilator FVC from Day 30 until completion of treatment
- rate of decline in post-bronchodilator FVC from Day 30 until completion of treatment
- rate of decline in pre-bronchodilator SVC from Day 30 until completion of treatment
- rate of decline in post-bronchodilator SVC from Day 30 until completion of treatment

The rate of decline in FEV₁ from Day 1 (randomization) until the end of trial after the 30 day washout was estimated using the following equation: (FEV₁ at end of trial – FEV₁

on Day 1)/(duration between Day 1 and end of trial). The limitation of this endpoint was that many patients did not have the end of trial visit, and therefore were excluded from the analysis (approximately 44% of patients).

All of the rate of decline variables showed no significant difference between treatment groups with the exception of post-bronchodilator FEV1 from Day 1 until end of trial. For this parameter, there was a median decline of 32 ml/year in the placebo group compared to 27 ml/year in the tio HH18 group ($p=0.0145$).

FVC measurements

Mean pre- and post-bronchodilator FVC values were significantly increased in the tio HH18 group compared to placebo at all time points from Day 30 to Month 48, with treatment differences for pre-bronchodilator (trough) values ranging from 0.17-0.20 ($p<0.0001$). The overall mean pre-bronchodilator difference was 0.19L ($p<0.0001$). The differences for post-bronchodilator (peak) values ranged from 0.03-0.07L ($p=0.04$, $p<0.0001$), with an overall mean difference of 0.05L ($p<0.0001$).

SVC measurements

Mean pre-bronchodilator (trough) SVC values were significantly increased in the tio HH18 group compared to placebo at all time points from Day 30 to Month 48, with treatment differences ranging from 0.15 to 0.19L ($p<0.0001$). The overall mean pre-bronchodilator difference was 0.17L ($p<0.0001$). The mean post-bronchodilator (peak) SVC values were significantly increased in the tio HH18 group compared to placebo out to Month 36, becoming non significant at months 42 and 28. The differences ranged from 0.03-0.05L. The overall mean post-bronchodilator SVC difference was 0.035L ($p=0.0006$).

Reviewer comment:

The increases in FVC and SVC are consistent with the known bronchodilator properties of tiotropium.

St. George's Respiratory Questionnaire (SGRQ) endpoints

For SGRQ scores, an increase indicates a worsening of quality of life, while a decrease indicates an improved quality of life. Both rate of decline in SGRQ and mean SGRQ scores during the trial were evaluated.

There were no differences in rate of decline in SGRQ scores from month 6 until completion of treatment for the activity component, impact component, or total scores. The SGRQ symptom component was significantly increased (worsened quality of life) in the tio HH18 group compared to placebo (treatment difference 0.45, $p=0.02$). The Applicant notes that this effect was seen only in the last year of the study, and attributes it to differential drop out rates.

The mean SGRQ scores showed a statistically significant decrease across all domains and timepoints for the tio HH18 group compared to placebo, with a treatment difference ranging from -2.30 to -3.35 ($p<0.0001$) for the total SGRQ score. Overall mean SGRQ scores are provided in Table 41.

Table 41: Protocol 205.235 overall mean SGRQ scores

Score	Placebo Mean (SE)	Tio HH18 Mean (SE)	Difference Mean (95% CI)	p-value
Activity	61.08 (0.282)	58.07 (0.272)	-3.01 (-3.78, -2.43)	<0.0001
Impact	33.85 (0.263)	31.42 (0.253)	-2.43 (-3.14 -1.71)	<0.0001
Symptom	45.83 (0.322)	42.79 (0.309)	-3.04 (-3.91, -2.16)	<0.0001
Total	44.09 (0.240)	41.40 (0.231)	-2.69 (-3.34, -2.04)	<0.0001

Activity: placebo N=2337, tio HH18 N=2478
Symptom: placebo N=2363, tio HH18 N=2510

Impact: placebo N=2337, tio HH18 N=2478
Total: placebo N=2337, tio HH18 N=2478

In a responder analysis, a significantly higher proportion of patients in the tio HH18 group compared to placebo had a ≥ 4 unit decrease (improvement) in SGRQ scores from baseline at 1, 2, 3, and 4 years (tio HH18 45-49% versus placebo 36-41%, $p < 0.0001$). In addition, significantly fewer patients in the tio HH18 group compared to placebo experienced a deterioration in scores from baseline.

Reviewer comment:

A clinically meaningful difference in SGRQ total score is reported to be 4 points. This is the difference used in the responder 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 FEV1.

The Applicant is not making labeling claims regarding SGRQ, nor would the data support such a claim.

COPD exacerbation related endpoints

A number of additional endpoints related to COPD exacerbations were examined, including:

- number of COPD exacerbations
- time to first exacerbation treated with steroids
- time to first exacerbation treated with antibiotics
- number of patients with at least one COPD exacerbation
- number of exacerbations treated with steroids
- number of exacerbation days
- number of COPD exacerbations leading to hospitalization
- number of patients with at least one exacerbation leading to hospitalization
- number of days hospitalized due to exacerbation per patient year

The endpoints involving number of exacerbation events are calculated per person year, with a correction for overdispersion. Results as calculated by the Applicant are presented

in Table 42. All recorded COPD events were included in the analysis. The Applicant reports that 98.8% of the recorded exacerbation events agreed with the protocol definition.

Table 42: Protocol 205.235 COPD related events endpoints

Endpoint	Placebo	Tio HH18	Risk Ratio	p-value
Exacerbations/pt year	0.85	0.73	0.86	<0.0001
Time to first exacerbation with steroids [median, month]	26.4	36.5	0.84	<0.0001
Time to first exacerbation with antibiotics [median, month]	16.2	19.8	0.87	<0.0001
Pts with exacerbations [%]	68	67	NC	0.3481
Exacerbations with steroids	0.52	0.44	0.84	<0.0001
Exacerbations with antibiotics	0.71	0.62	0.87	<0.0001
Exacerbation days [mean]	13.6	12.1	0.89	0.0011
Exacerbations with hospitalization	0.16	0.15	0.94	0.3413
Pts hospitalized due to exacerbation [%]	27	25	NC	0.1766
Days in hospital due to exacerbations [mean]	3.13	3.17	1.01	0.8624

All endpoints other than time to first event and percent of patients are reported as number of events per patient-year. Poisson regression analysis adjusted for overdispersion was used.

NC=not calculated

Reviewer comment:

These exacerbation endpoints are generally in favor of tiotropium. The number of exacerbations per patient year is consistent with that found in Study 205.266 (VA study, NDA 21-395, S-024), in which the number of exacerbations per patient year was 0.876 in the placebo group and 0.711 in the tio HH18 group, giving a risk ratio of 0.812. The percent of patients with exacerbations and hospitalized with exacerbations may be biased against tiotropium due to differential drop out from the placebo group.

This analysis correctly adjusts for overdispersion. The default Poisson regression technique assumes that all patients are homogenous with respect to their rate of exacerbation. The correction for overdispersion takes into account that for COPD, the majority of exacerbations occur in a small portion of patients while the rest of the population has no exacerbations.⁴ The method of calculation of exacerbation rate and correction for overdispersion is critical as different statistical methodologies may give very different results.

Safety outcomes

Safety outcomes for Study 205.235 included collection of non-serious and serious adverse events, as well as assessment of mortality on all patients including those who discontinued prematurely. All patients who were randomized and received at least one dose of study drug were included in the safety analyses. Adverse events with an onset of up to 30 days after discontinuation of study drug were assigned to the treatment period.

Extent of exposure

A total of 5992 COPD patients were randomized and received at least one dose of study drug. The planned exposure for each patient was 1440 days (approximately 48 months). One eligible patient withdrew at the randomization visit, prior to receiving study drug. One additional patient was randomized twice in error (once to each treatment group).

Mean exposure to study drug for all patients was 1080 days. Significantly fewer ($p < 0.0001$) patients in the tio HH18 group prematurely discontinued than in the placebo group [1080 (36.2%) versus 1341(44.6%)]. The highest percentage of discontinuations occurred in the first year of treatment. A summary of patient exposure is provided in Table 43.

Table 43: Protocol 205.235 summary of treatment exposure

	Placebo N=3006 n (%)	Tio HH18 N=2986 n (%)	Total N=5992 n (%)
Total treated			
Exposure (months)			
≥ 1	2867 (95.4)	2915 (97.6)	5782 (96.5)
≥ 3	2740 (91.2)	2816 (94.3)	5556 (92.7)
≥ 6	2618 (87.1)	2726 (91.3)	5344 (89.2)
≥ 9	2513 (83.6)	2634 (88.2)	5147 (85.9)
≥ 12	2418 (80.4)	2565 (85.9)	4983 (83.2)
≥ 15	2344 (78.0)	2496 (83.6)	4840 (80.8)
≥ 18	2249 (74.8)	2432 (81.4)	4681 (78.1)
≥ 21	2161 (71.9)	2363 (79.1)	4524 (75.5)
≥ 24	2090 (69.5)	2293 (76.8)	4383 (73.1)
≥ 27	2013 (67.0)	2236 (74.9)	4249 (70.9)
≥ 30	1947 (64.8)	2177 (72.9)	4124 (68.8)
≥ 33	1891 (62.9)	2117 (70.9)	4008 (66.9)
≥ 36	1831 (60.9)	2060 (69.0)	3891 (64.9)
≥ 39	1779 (59.2)	2001 (67.0)	3780 (63.1)
≥ 42	1723 (57.3)	1970 (66.0)	3693 (61.6)
≥ 45	1665 (55.4)	1904 (63.8)	3569 (59.6)
Treatment exposure (days)			
Mean	1032.7	1128.1	1080.3
Min	1	1	1
Max	1550	1655	1655

Adverse events

Overall, 92% of patients in the UPLIFT trial experienced an adverse event (AE), and 51% experience a serious adverse event (SAE). The incidence of various categories of AEs was generally balanced between the groups, except for drug-related adverse events (as determined by the investigator), which were more frequent in the tio HH18 group (7.8% placebo versus 10.2% tio HH18). This was largely driven by the increased incidence of dry mouth in the tio HH18 group. See Table 44.

Table 44: Protocol 205.235 overall adverse event summary

	Placebo N=3006 N (%)	Tio HH18 N=2986 N (%)	Total N=5992 N (%)
Any AE	2774 (92.3)	2764 (92.6)	5538 (92.4)
Drug-related AEs	233 (7.8)	306 (10.2)	539 (9.0)
AEs leading to discontinuation	735 (24.5)	618 (20.7)	1353 (22.6)
Serious AEs	1509 (50.2)	1540 (51.6)	3049 (50.9)
Fatal	411 (13.7)	381 (12.8)	792 (13.2)
Life threatening	112 (3.7)	103 (3.4)	215 (3.6)
Disabling	75 (2.5)	73 (2.4)	148 (2.5)
Hospitalization	1357 (45.1)	1369 (45.8)	2726 (45.5)
Other	135 (4.5)	158 (5.3)	293 (4.9)

Deaths

Vital status was collected on all patients who prematurely discontinued from the trial extending to 4 years post-randomization. The primary cause of each death was adjudicated by an independent committee. Time to death was defined as time to the end date of the fatal AE (date of death). The primary analysis evaluated deaths with a cut off date of 1440 days (4 years); however, evaluations with a cut off date of 1470 days (4 years plus 30 days) and no cut off date were also conducted. The Applicant also presents fatal events in two ways: 1) deaths on treatment and 2) deaths including post-discontinuation vital status. The adjudicated cause of death is presented as the primary analysis, but investigator-reported cause of death is also presented.

Overall, the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tio HH18 group. The risk ratio for death from any cause (tiotropium/placebo) was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data. See Table 45.

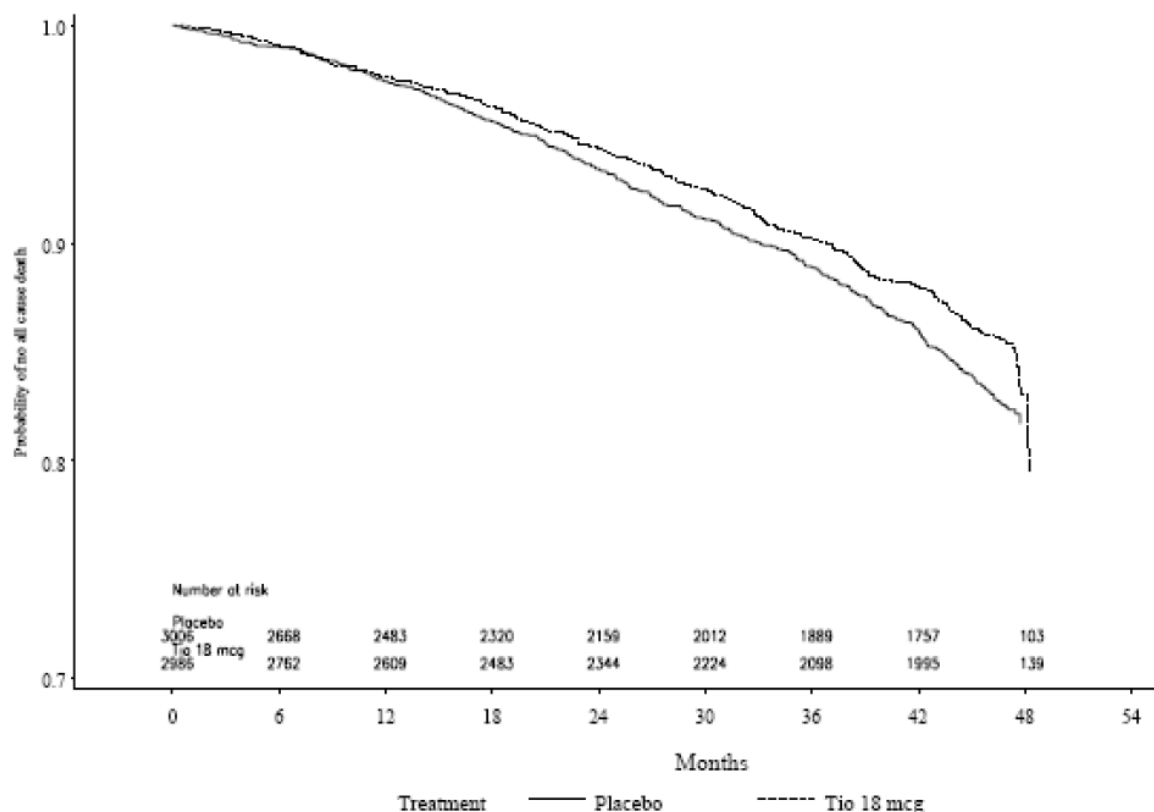
Table 45: Protocol 205.235 fatal event summary

	Placebo N (%)	Tio HH18 N (%)	Rate difference	Risk Ratio	Risk Ratio Tio HH18 vs. Placebo 95% CI p-value	
On treatment (Day 1440)	400 (13.3)	361 (12.1)	1.2%	0.83	0.72, 0.95	0.010
On treatment (Day 1470)	402 (13.4)	374 (12.5)	0.9%	0.85	0.74, 0.98	0.024
On treatment (all)	411 (13.7)	381 (12.8)	0.9%	0.84	0.73, 0.97	0.016
Vital status (Day 1440)	491 (16.3)	430 (14.4)	1.9%	0.87	0.76, 0.99	0.034
Vital status (Day 1470)	495 (16.5)	446 (14.9)	1.6%	0.89	0.79, 1.02	0.086
Vital status (all)	514 (17.1)	467 (15.6)	1.5%	0.89	0.78, 1.00	0.058

On-treatment mortality

A Kaplan-Meier estimate of the probability of no death on treatment as presented by the Applicant is given in Figure 13. The curves show separation after 12 months out to 48 months.

Figure 13: Protocol 205.235 Kaplan-Meier estimates of probability of no all cause mortality [adjudicated on treatment deaths censored at Day 1470]



The most common causes (adjudicated) of death on-treatment were COPD exacerbation, lung cancer, and death of unknown cause. See Table 46. There were 271 patients who died of lower respiratory causes by Day 1470, 140 (4.7%) in the placebo group and 131 (4.4%) in the tio HH18 group [RR=0.85, 95% CI (0.67, 1.08)]. Forty-nine patients died of cardiac causes, 25 (0.8%) in the placebo group and 24 (0.8%) in the tio HH18 group [RR=0.88, 95% CI (0.50, 1.55)]. The preferred terms of sudden death, sudden cardiac death, and death of unknown cause are coded by MedDRA under the General Disorders System Organ Class; however, these terms are often considered cardiac events. Combining these three preferred terms, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

Table 46: Protocol 205.235 on-treatment adjudicated cause of death occurring in ≥ 10 patients in either treatment group

Cause of death	Placebo N (%)	Tio HH18 N (%)	Risk Ratio	p-value (95% CI)
	[n=3006]	[n=2986]		
COPD exacerbation	121 (4.0)	103 (3.4)	0.79	0.07 (0.60, 1.02)
Lung cancer	66 (2.2)	73 (2.4)	1.02	0.89 (0.73, 1.43)
Death (unknown cause)	36 (1.2)	29 (1.0)	0.74	0.23 (0.46, 1.21)
Sudden cardiac death	23 (0.8)	15 (0.5)	0.60	0.13 (0.31, 1.15)
Pneumonia	18 (0.6)	27 (0.9)	1.39	0.28 (0.76, 2.52)
Congestive heart failure	14 (0.5)	15 (0.5)	0.99	0.98 (0.48, 2.05)
Sudden death	12 (0.4)	14 (0.5)	1.08	0.85 (0.50, 2.33)
Cerebrovascular accident	13 (0.4)	12 (0.4)	0.85	0.69 (0.39, 1.87)

Vital status mortality

Vital status information was known for 98% of tiotropium treated patients and 97% of placebo treated patients out to at least 45 months post-randomization. There were a total of 921 deaths, including vital status, for the full 4 year protocol defined study period (1440 days). There were 941 deaths for the period of 4 years plus 30 days (1470 days). See Table 45. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued.

Similar to on-treatment causes of death, the most frequent causes of death in the group including vital status were COPD exacerbation, lung cancer, and death of unknown cause.

Reviewer comment:

Since UPLIFT is a major study that more than doubles the size of the safety database for tio HH18, it is reasonable to describe major findings such as reduction in mortality in the product label. The persistence of the effect across many different analyses strengthens the evidence for a mortality benefit. However, a number of factors come into consideration for this claim:

- *Mortality is a major claim which requires a substantive body of evidence for approval. To support a labeling claim, the Agency typically requires replication of findings in two or more clinical trials. However, according to the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products, reliance on a single study is possible in situations in which a*

trial has demonstrated a clinically meaningful effect on mortality or irreversible morbidity. In addition, the single study would typically be large multicenter center, such as UPLIFT, with consistency across study subsets and statistically very persuasive findings.

- A small numerical imbalance in mortality in favor of the placebo group was observed in 3 one-year Phase 3 studies of Spiriva Respimat. Although Spiriva Respimat is a different drug product, it contains the same drug substance as Spiriva HandiHaler, thus the safety issue regarding mortality warrants discussion. A summary of the Spiriva Respimat data is included in the Appendix. These data complicate interpretation of the mortality data from UPLIFT.*
- A recent meta-analysis by Singh, et al.¹ concludes that anticholinergic medications including tiotropium increase long-term cardiovascular mortality. Dr. Simone Pinheiro of the Office of Surveillance and Epidemiology reviewed the relevant literature, including this meta-analysis. Dr. Pinheiro concluded that the currently available data implicating tiotropium and ipratropium in increasing risk of cardiovascular death, myocardial infarction, and stroke is not compelling. Refer to the Office of Surveillance and Epidemiology briefing document for details.*

Serious adverse events

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs occurring in more than 1% in either treatment group are given in Table 47. SAEs were generally balanced between treatment groups.

For some of the most common adverse events, the Applicant appropriately grouped MedDRA terms in order to create a single category which incorporates a variety of different terms for the same or very similar conditions. These grouped terms included angina, atrial fibrillation, myocardial infarction, bronchitis, COPD exacerbation, dyspnea, and pneumonia. As part of the review process, the clinical reviewer also grouped terms for some of the more common SAEs as follows:

- Cardiac failure: cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, acute right ventricular failure, left ventricular dysfunction, left ventricular failure, right ventricular failure
- Coronary artery disease: coronary artery disease, coronary artery embolism, coronary artery insufficiency, coronary artery occlusion, coronary artery restenosis, coronary artery stenosis, coronary artery thrombosis
- Gall bladder disease: bile duct obstruction, bile duct stone, biliary colic, biliary dyskinesia, cholangitis, cholangitis acute, cholecystitis, cholecystitis acute, cholecystitis chronic, cholelithiasis, cholelithiasis obstructive, cholestasis, gallbladder disorder

- Sepsis: enterococcal sepsis, escherichia sepsis, klebsiella sepsis, neutropenic sepsis, pneumococcal sepsis, sepsis, sepsis syndrome, septic shock, staphylococcal sepsis, wound sepsis
- Bladder cancer: bladder adenocarcinoma stage unspecified, bladder cancer, bladder cancer recurrent, bladder cancer stage II, bladder cancer stage IV, bladder neoplasm, bladder transitional cell carcinoma
- Prostate cancer: prostate cancer, prostate cancer metastatic, prostate cancer stage I, prostate cancer stage III
- Stroke: this combined term is handled separately under adverse events of interest
- Respiratory failure: acute respiratory failure, chronic respiratory failure, respiratory failure

While a combination of terms resulted in an increase in the percentage of patients with the event over the 1% threshold for each event other than bladder cancer which remained at 0.7% overall, the combination did not result in identification of new safety signals. Combination of the respiratory failure term did not result in diminution of the treatment difference between groups in favor of tiotropium.

Table 47: Protocol 205.235 serious adverse events occurring in $\geq 1\%$ of patients in either treatment group (as reported by Applicant)

MedDRA System Organ Class MedDRA Preferred Term	Placebo N (%)	Tio HH18 N (%)	Total N (%)
Total Treated N (%)	3006 (100)	2986 (100)	5992 (100)
Total with serious adverse events	1509 (50.2)	1540 (51.6)	3049 (50.9)
Cardiac disorders	350 (11.6)	322 (10.8)	672 (11.2)
Angina#	31 (1.0)	48 (1.6)	79 (1.3)
Atrial fibrillation#	67 (2.2)	69 (2.3)	136 (2.3)
Cardiac failure	42 (1.4)	57 (1.9)	99 (1.7)
Cardiac failure congestive	42 (1.4)	27 (0.9)	69 (1.2)
Coronary artery disease	32 (1.1)	20 (0.7)	52 (0.9)
Myocardial infarction#	84 (2.8)	65 (2.2)	149 (2.5)
Neoplasms	170 (5.7)	197 (6.6)	367 (6.1)
Prostate cancer	22 (0.7)	31 (1.0)	53 (0.9)
Respiratory system disorders* (Lower)	985 (32.8)	911 (30.5)	1896 (31.6)
Acute respiratory failure	31 (1.0)	29 (1.0)	60 (1.0)
Bronchitis#	27 (0.9)	35 (1.2)	62 (1.0)
COPD exacerbation#	742 (24.7)	688 (23.0)	1430 (23.9)
Dyspnea#	54 (1.8)	36 (1.2)	90 (1.5)
Pneumonia#	290 (9.6)	296 (9.9)	586 (9.8)
Respiratory failure	113 (3.8)	85 (2.8)	198 (3.3)
Respiratory system disorders* (Other)	156 (5.2)	170 (5.7)	326 (5.4)
Lung neoplasm malignant	34 (1.1)	40 (1.3)	74 (1.2)
Pulmonary embolism	29 (1.0)	25 (0.8)	54 (0.9)

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.

Reviewer comment:

Based on the SAE data, the Applicant is requesting a claim for reduction in respiratory failure. While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term “respiratory failure” is undefined and subject to investigator interpretation. In addition, multiplicity is a concern since many adverse event variables were evaluated in the safety analysis and the effect is only marginally significant. Inclusion of the term respiratory failure may be appropriate as part of adverse event reporting for the study; however, there is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

Serious adverse events of interest

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. Stroke-related adverse events were not significantly increased in the tiotropium groups in Protocol 205.235. See Table 48.

Table 48: Protocol 205.235 stroke adverse events

	Tio HH18 N=2986		Placebo N=3006		Risk Ratio (95% CI)
	N	Rate/100 pt yrs	N	Rate/100 pt yrs	
AE	82	0.88	80	0.93	0.95 (0.70, 1.29)
SAE	66	0.70	63	0.73	0.97 (0.69, 1.37)
Fatal (on treatment)	12	0.13	13	0.15	0.85 (0.39, 1.87)
Fatal (vital status, D1470)	14	0.13	17	0.15	0.82 (0.40, 1.66)

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 25 trials from the Spiriva HandiHaler program and 4 trials from the Spiriva Respimat program (205.251, 205.252, 205.254, and 205.255). The analysis also investigated a large number of other adverse events without correction for multiplicity.

The UPLIFT trial does not show a specific signal for stroke events. The Risk Ratio for adverse events of stroke is less than one, and the upper bound of the confidence interval is less than 1.3, suggesting that if there is any adverse drug effect, it is minimal. Because

stroke was a pre-specified term for the adjudication of cause of death, readers can have confidence that fatal strokes were appropriately classified and are not “hiding” under some other preferred term. Serious adverse events and fatal adverse events of stroke are subgroups and as expected, have slightly wider confidence intervals, although the conclusions are the same.

Adverse events leading to discontinuation

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. Fewer patients in the tio HH18 group discontinued due to a lower respiratory AE compared to patients in the placebo group [291 (9.7%) versus 412 (13.7%), respectively]. This was driven by a reduced number of patients in the tio HH18 group with COPD exacerbations and dyspnea. See Table 49.

Table 49: Protocol 205.235 adverse events leading to discontinuation occurring in ≥ 10 patients overall

MedDRA System Organ Class MedDRA Preferred Term	Placebo N (%)	Tio HH18 N (%)	Total N (%)
Total Treated N (%)	3006 (100)	2986 (100)	5992 (100)
Total with AEs leading to discontinuation	735 (24.5)	618 (20.7)	1353 (22.6)
Cardiac disorders	81 (2.7)	70 (2.3)	151 (2.5)
Atrial fibrillation#	7 (0.2)	7 (0.2)	14 (0.2)
Cardiac failure	7 (0.2)	13 (0.4)	20 (0.3)
Cardiac failure congestive	6 (0.2)	5 (0.2)	11 (0.2)
Myocardial infarction#	21 (0.7)	15 (0.5)	36 (0.6)
Gastrointestinal disorders	32 (1.1)	29 (1.0)	61 (1.0)
Dry mouth#	4 (0.1)	9 (0.3)	13 (0.2)
General disorders	38 (1.3)	47 (1.6)	85 (1.4)
Death	12 (0.4)	19 (0.6)	31 (0.5)
Sudden death	11 (0.4)	9 (0.3)	20 (0.3)
Nervous system disorders	38 (1.3)	39 (1.3)	77 (1.3)
Cerebrovascular accident	8 (0.3)	11 (0.4)	19 (0.3)
Respiratory system disorders* (Lower)	412 (13.7)	291 (9.7)	703 (11.7)
Acute respiratory failure	10 (0.3)	8 (0.3)	18 (0.3)
COPD exacerbation#	209 (7.0)	152 (5.1)	361 (6.0)
Dyspnea#	118 (3.9)	54 (1.8)	172 (2.9)
Pneumonia#	51 (1.7)	48 (1.6)	99 (1.7)
Respiratory failure	31 (1.0)	21 (0.7)	52 (0.9)
Respiratory system disorders* (Other)	82 (2.7)	89 (3.0)	171 (2.9)
Bronchial carcinoma	5 (0.2)	11 (0.4)	16 (0.3)
Lung neoplasm	5 (0.2)	8 (0.3)	13 (0.2)
Lung neoplasm malignant	19 (0.6)	21 (0.7)	40 (0.7)
Non-small cell lung cancer	7 (0.2)	5 (0.2)	12 (0.2)
Non-small cell lung cancer, malignant	4 (0.1)	6 (0.2)	10 (0.2)
Pulmonary embolism	9 (0.3)	5 (0.2)	14 (0.2)
Small cell lung cancer, stage unspecified	3 (0.1)	7 (0.2)	10 (0.2)

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.

Overall adverse events

Non serious adverse events were reported in almost all patients in both groups (92.3% of placebo patients and 92.6% of tio HH18 patients), an expected finding given the length of the study and the severity of disease in this patient population. In order to account for differential drop out, the Applicant also reported AEs as exposure adjusted rates (number of patients experiencing an event divided by the person-years at risk).

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. Other known anticholinergic side effects also occurred with greater frequency in the tiotropium group although not significantly so. These included constipation, benign prostatic hypertrophy, dizziness, sinusitis, nasopharyngitis, cough, and urinary tract infection. See Table 50.

All AEs with a risk ratio ≥ 3 in the tio HH18 group compared to placebo are presented in Table 51. Analysis of these events reveals that while the risk ratio may be high, the number of patients with each event is very low and in most cases there is no biologic plausibility for a causal relationship. The risk ratio reached statistical significance for only one event, intestinal obstruction. Events that could be secondary to anticholinergic effects include atrial tachycardia, tachyarrhythmia, intestinal obstruction, and prostate infection. Supraventricular tachyarrhythmic events in general did not appear to be increased overall in the tio HH18 group, with atrial fibrillation occurring in 113 (3.8%) patients in the placebo group and 119 (4.0%) patients in the tio HH18 group [RR 0.97, 95% CI (0.75, 1.26)] and tachycardia occurring in 43 (1.4%) patients in the placebo group and 40 (1.3%) patients in the tio HH18 group [RR 0.86, 95%CI (0.56, 1.32)].

Table 50: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs occurring in >3% of either treatment group

	Placebo N=3006		Tio HH18 N=2986		Tio HH18/ placebo Rate Ratio (95% CI)
	N (%)	Incidence Rate	N (%)	Incidence Rate	
Total with AE	2774 (92.3)		2764 (92.6)		
COPD exacerbation#	1986 (66.1)	45.5	1934 (64.8)	38.1	0.84 (0.79, 0.89)
Pneumonia#	418 (13.9)	5.14	433 (14.5)	4.94	0.96 (0.84, 1.10)
Dyspnea#	443 (14.7)	5.49	364 (12.2)	4.09	0.75 (0.65, 0.86)
Nasopharyngitis	324 (10.8)	4.06	373 (12.5)	4.33	1.07 (0.92, 1.24)
Upper respiratory tract infection#	290 (9.6)	3.57	298 (10.0)	3.38	0.95 (0.81, 1.11)
Hypertension	284 (9.4)	3.45	275 (9.2)	3.08	0.89 (0.75, 1.05)
Bronchitis#	233 (7.8)	2.82	232 (7.8)	2.57	0.91 (0.76, 1.10)
Cough	213 (7.1)	2.57	238 (8.0)	2.64	1.03 (0.86, 1.24)
Back pain	188 (6.3)	2.25	198 (6.6)	2.18	0.97 (0.79, 1.18)
Urinary tract infection#	169 (5.6)	2.00	190 (6.4)	2.08	1.04 (0.85, 1.28)
Sinusitis#	160 (5.3)	1.90	194 (6.5)	2.14	1.12 (0.91, 1.39)
Influenza	158 (5.3)	1.87	158 (5.3)	1.73	0.92 (0.74, 1.15)
Headache	136 (4.5)	1.61	171 (5.7)	1.88	1.17 (0.94, 1.47)
Edema#	130 (4.3)	1.52	145 (4.9)	1.57	1.03 (0.82, 1.31)
Constipation	111 (3.7)	1.29	151 (5.1)	1.63	1.26 (0.99, 1.61)
Diarrhea	122 (4.1)	1.43	138 (4.6)	1.5	1.04 (0.82, 1.33)
Cataract	123 (4.1)	1.45	120 (4.0)	1.3	0.90 (0.70, 1.15)
Atrial fibrillation#	113 (3.8)	1.32	119 (4.0)	1.28	0.97 (0.75, 1.26)
Dry mouth#	80 (2.7)	0.93	152 (5.1)	1.68	1.80 (1.37, 2.36)
Depression	98 (3.3)	1.14	131 (4.4)	1.42	1.25 (0.96, 1.62)
Insomnia	91 (3.0)	1.06	131 (4.4)	1.42	1.34 (1.02, 1.75)
Arthralgia	94 (3.1)	1.10	125 (4.2)	1.36	1.24 (0.95, 1.62)
Benign prostatic hyperplasia	96 (3.2)	1.12	122 (4.1)	1.32	1.18 (0.90, 1.54)
Rhinitis	112 (3.7)	1.32	101 (3.4)	1.09	0.83 (0.63, 1.08)
Abdominal pain#	96 (3.2)	1.12	113 (3.8)	1.22	1.09 (0.83, 1.43)
Respiratory failure	120 (4.0)	1.39	88 (2.9)	0.94	0.67 (0.51, 0.89)
Hypercholesterolemia	97 (3.2)	1.13	104 (3.5)	1.12	0.99 (0.75, 1.31)
Nausea	94 (3.1)	1.09	93 (3.1)	1.00	0.91 (0.69, 1.22)
Dizziness	81 (2.7)	0.94	103 (3.4)	1.11	1.18 (0.88, 1.58)

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.

Table 51: Protocol 205.235 frequency and incidence rates (per 100 patient years) of patients with AEs with a risk ratio of ≥ 3

	Placebo N=3006		Tio HH18 N=2986		Tio HH18/ placebo Rate Ratio (95% CI)
	N (%)	Incidence Rate	N (%)	Incidence Rate	
Total with AE	2774 (92.3)		2764 (92.6)		
Atrial tachycardia	1 (0.0)	0.01	8 (0.3)	0.08	7.39 (0.92, 59.1)
Tachyarrhythmia	2 (0.1)	0.02	8 (0.3)	0.08	3.70 (0.79, 17.4)
Tricuspid valve incompetence	1 (0.0)	0.01	6 (0.2)	0.06	5.54 (0.67, 46.1)
Epigastric discomfort	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Intestinal obstruction*	2 (0.1)	0.02	12 (0.4)	0.13	5.55 (1.24, 24.8)
Large intestinal perforation	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Peritonitis	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Tongue disorder	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Ulcer	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Bile duct stone	2 (0.1)	0.02	8 (0.3)	0.08	3.70 (0.79, 17.4)
Abscess	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Appendicitis	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Osteomyelitis	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Prostate infection	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Foreign body trauma	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Tendon rupture	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Ulna fracture	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
INR increased	1 (0.0)	0.01	5 (0.2)	0.05	4.62 (0.54, 39.6)
Vitamin B12 deficiency	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Costochondritis	2 (0.1)	0.02	9 (0.3)	0.10	4.16 (0.90, 19.3)
Lumbar spinal stenosis	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Musculoskeletal discomfort	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Intercostal myalgia	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Non-Hodgkin's lymphoma	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Esophageal carcinoma	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Neurosis	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Restlessness	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Urethral stenosis	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Metastases to lung	2 (0.1)	0.02	7 (0.2)	0.07	3.24 (0.67, 15.6)
Small cell lung cancer, metastatic	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)
Rash generalized	1 (0.0)	0.01	6 (0.2)	0.06	5.55 (0.67, 46.1)
Skin disorder	1 (0.0)	0.01	4 (0.1)	0.04	3.70 (0.41, 33.1)

*p=0.02

Reviewer comment:

The adverse events observed in the UPLIFT trial are consistent with the known adverse event profile of Spiriva HandiHaler. The findings of significant reductions in COPD exacerbation, dyspnea, and respiratory failure are supportive of the efficacy findings in the trial. Intestinal obstruction is in the post-marketing section of the Spiriva HandiHaler label, but could be consistent with the known anticholinergic side effect of constipation. No particular cardiac signals or stroke signals were identified.

Laboratory findings

There were no laboratory evaluations performed in this trial aside from pregnancy testing conducted at screening for women of childbearing potential.

ECG findings

There were no ECGs performed in this trial.

Physical examination

Vital signs were performed as part of the complete physical examination at the start and end of each patient's participation in the trial. Any new or clinically relevant worsening of baseline conditions detected at the follow up physical examination were reported as adverse events. The Applicant did not conduct additional analyses of vital sign or physical examination data.

6.1.1.3 Protocol 205.235 conclusions

The UPLIFT study showed no significant difference between treatment groups in the primary endpoints of rate of decline in pre- and post-bronchodilator FEV1. In a subgroup analysis, patients who were sustained quitters from smoking did experience a significant decrease in rate of decline in FEV1 compared to sustained smokers. This effect was observed across both treatment groups.

The Applicant offers two plausible explanations for the failure of the UPLIFT trial to demonstrate a difference in long-term rate of decline in FEV1, confounding by concomitant disease-modifying therapy and differential discontinuation biasing against tiotropium. While these effects may be real, the UPLIFT design overall was significantly strengthened by its "real world" approach to inclusion of multiple concomitant medications, similar to the situation encountered in the COPD population in the United States. Thus, one can conclude that in the setting of high-quality COPD care, the addition of tiotropium is unlikely to impact the natural history of disease.

For the key secondary endpoints of time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization, tiotropium showed significant decrease compared to placebo. For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p < 0.0001$, RR 0.86, 95% CI 0.81-0.91). The median time to first exacerbation was 12.5 months in the placebo group and 16.7 months in the tio HH18 group. Patients in the tio HH18 group also had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p = 0.0024$, RR 0.86, 95% CI 0.78, 0.95). The median time to first exacerbation requiring hospitalization was 28.6 months in the placebo group and 35.9 months in the tio HH group.

A significant improvement in most of the additional COPD exacerbation-related endpoints was also observed. These included the number of COPD exacerbations, time to first exacerbation treated with steroids, time to first exacerbation treated with antibiotics, number of exacerbations treated with steroids, number of exacerbation days, number of COPD exacerbations leading to hospitalization, and number of days hospitalized due to exacerbation per patient year. In conjunction with supportive evidence from Protocol 205.266 (VA study, submitted under NDA 21-395, S-024), these data are generally supportive of an exacerbation claim.

SGRQ endpoints included rate of SGRQ deterioration, as well as total and component SGRQ scores. There were no differences in rate of decline in SGRQ scores from month 6 until completion of treatment for the activity component, impact component, or total scores. The mean SGRQ scores showed a statistically significant but not clinically important decrease across all domains and timepoints for the tio HH18 group compared to placebo, with a treatment difference ranging from -2.30 to -3.35 ($p < 0.0001$) for the total SGRQ score.

Spirometry endpoints included trough FEV₁, FVC, and SVC response and 90 minute FEV₁ FVC, and SVC response. Endpoints were measured every six months throughout the four year treatment period. Consistent with the known bronchodilator properties of the drug, the tio HH18 group generally demonstrated a significant improvement ($p < 0.0001$) over placebo for all endpoints and time points tested.

Overall, the total number of deaths during treatment (including the last day of study drug plus 30 days) was 792; 411 (13.7%) in the placebo group and 381 (12.8%) in the tiotropium group. Vital status information was known for 98% of tio HH18 treated patients and 97% of placebo treated patients including discontinued patients out to at least 45 months post-randomization. Compared to the on-treatment mortality, an additional 149 deaths were collected for patients who discontinued. The risk ratio for death from any cause (tiotropium/placebo) on treatment was 0.84 [95% CI (0.73, 0.97)]. The risk ratio for death remains significantly or nearly significantly different from placebo regardless of the cut off used or inclusion of vital status data.

The primary cause of each death in the UPLIFT trial was adjudicated by an independent committee. The most common causes (adjudicated) of death both on-treatment and including vital status were COPD exacerbation, lung cancer, and death of unknown cause. Combining the preferred terms of sudden death, sudden cardiac death, and death of unknown cause, 127 patients died with sudden or unknown causes of death. Of these, 70 (2.3%) were in the placebo group and 57 (1.9%) were in the tio HH18 group [RR=0.75, 95% CI (0.53, 1.06)].

Serious adverse events (SAEs) occurred in 50.9% of the overall study population, including 51.6% of the tio HH18 group and 50.2% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and respiratory failure. SAEs were generally balanced between treatment groups. While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term

“respiratory failure” is undefined and subject to investigator interpretation. There is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

There were 618 (20.7%) patients in the tio HH18 group and 735 (24.5%) patients in the placebo group who discontinued prematurely due to an adverse event. The most frequent AEs leading to discontinuation were all lower respiratory events—COPD exacerbation, dyspnea, pneumonia, and respiratory failure. A reduced number of patients in the tio HH18 group discontinued due to COPD exacerbations and dyspnea compared to the placebo group.

The most frequently reported AEs were COPD exacerbation, pneumonia, dyspnea, nasopharyngitis, and upper respiratory tract infection. If evaluated by exposure adjusted rates, COPD exacerbation, dyspnea, and respiratory failure occurred significantly less frequently in the tio HH18 group compared to placebo. In contrast, dry mouth and insomnia occurred significantly more frequently in the tio HH18 group. Dry mouth is a known anticholinergic side effect of tiotropium. In addition, although the numbers were small, intestinal obstruction occurred significantly more frequently in the tio HH18 group and could represent an anticholinergic side effect related to constipation.

Stroke is an adverse event of interest based on a potential safety signal observed in an analysis of combined tiotropium HandiHaler and Respimat trials. Stroke-related adverse events (AEs, SAEs, or fatal events) were not significantly increased in the tio HH18 group relative to placebo.

6.1.2 205.266 (VA Trial)

6.1.2.1 Protocol 205.266 study design

Study title

A randomized, double-blind, placebo-controlled, parallel group trial assessing the proportion of patients experiencing an exacerbation and proportion of patients hospitalized for an exacerbation over 6 months during treatment with tiotropium 18 mcg capsule once daily in patients with COPD in a Veterans Affairs setting.

Design

The study was a multicenter, randomized, double-blind, parallel group study to compare the effect of tiotropium 18 mcg capsule dry powder inhaler (tio HH18) on COPD exacerbations in patients with moderate to severe COPD in a US Veterans Affairs setting. The placebo group received a HandiHaler placebo product. All patients also received albuterol MDI inhalers for rescue use.

Duration

The duration of active treatment was 6 months. Patients attended a screening visit 1-4 weeks prior to randomization. There were no run-in periods or post-treatment scheduled follow up. The study was performed during the period of September 6, 2001 to February 20, 2003. The final study report is dated February 4, 2004.

Investigators and centers

The study was conducted at 26 investigative sites within the Veterans Affairs Medical System in the United States.

Duke Clinical Research Institute (DCRI) (Durham, NC) performed data entry and data clarification functions for this trial.

Materials

The study treatments were:

- tio HH18: tiotropium HandiHaler 18 mcg (1 capsule dry powder inhalation) once daily in the morning
- placebo: identical to HandiHaler capsule dry powder inhalation once daily in the morning

Table 52: Protocol 205.266 identity of investigational product

Investigational Product	Expiration Date	Ingelheim Batch No.
Tiotropium Bromide lactose powder capsule	11/2002 10/2003	009585 – Lot#PD-2102 106840 – Lot#PD-2161
Placebo lactose powder capsule	06/2004 04/2005	009586 – Lot#PD-2103 106321 – Lot#PD-2162

Objectives

The primary objectives of this trial were to determine whether tio HH18 reduces the proportion of patients experiencing exacerbation and the proportion of patients hospitalized due to exacerbation.

Population

A total of 1829 male and female patients with moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were enrolled; 914 in the tio HH18 group, and 915 in the placebo group. Of these, 1435 (78.5%) completed the study.

Inclusion criteria

Notable inclusion criteria included:

- 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:

- Any unstable medical condition which would preclude effective participation in the study or would reduce life expectancy to <6 months
- Clinical diagnosis of asthma
- Oral corticosteroids in unstable daily dose or > 20 mg prednisone/day
- Upper respiratory tract infection or COPD exacerbation within 30 days of Visit 1
- History (6 months or less) of myocardial infarction
- Unstable/life-threatening arrhythmia or hospitalized for heart failure within the past year
- Current treatment of any malignancy with radiation or chemotherapy
- Moderate to severe renal impairment
- Narrow-angle glaucoma, moderate to severe symptomatic prostatic hypertrophy or bladder-neck obstruction

Reviewer comment:

Of note, bronchodilatory reversibility was not an inclusion criterion. The population was not enriched for patients with a history of COPD exacerbation. In comparison with previous tiotropium HandiHaler trials, exclusion criteria were liberalized to include a broader population of patients with COPD. These included shortened time periods from previous myocardial infarction and congestive heart failure episodes, inclusion of patients with stable arrhythmias, inclusion of patients with malignancy (not during active treatment), a higher permitted dose of oral corticosteroids, and unrestricted use of oxygen.

Procedures

Following an initial screening period, patients were randomized into the 6-month, double-blind treatment period in which they received tio HH18 or placebo in a 1:1 ratio. The drugs were administered using the HandiHaler as one capsule taken once daily in the morning. Open label albuterol MDI was also provided as a rescue medication.

Two study visits were conducted during the treatment period, at three months (Visit 3) and at the conclusion of the trial (Visit 4). Patients were contacted by the site staff by telephone every 30 days for interim safety and efficacy evaluations.

One amendment was made to the protocol prior to initiation of the study. This amendment liberalized the criteria for exclusion due to renal impairment and prostatic hypertrophy.

The protocol and protocol amendment, patient informed consent, and patient information sheet were approved by the appropriate IRBs 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 1.17, Study report 205.266, page 21]

The study flow chart as revised by protocol Amendment 1 is presented in Table 53.

Table 53: Protocol 205.266 study flow chart

Trial period	Treatment							
Visit	1	2			3			4⁶
Month	-1	0	1	2	3	4	5	6
Day	-28 to -7	1	30	60	90	120	150	180
Informed consent	X ¹							
Demographics	X							
Medical history	X							
12-lead ECG	X							
Pregnancy test	X ²							
Prescribe rescue albuterol	X							
Physical exam		X						X
Inclusion/exclusion criteria		X						
Randomization		X						
Dispense study medication		X			X			
Dispense HandiHaler		X						
HandiHaler training		X						
Health care utilization		X	X	X	X	X	X	X
Collect medication					X			X
Drug accountability					X			X
Medication washout compliance		X			X			X
Pulmonary function testing		X ³			X ³			X ³
Telephone contact			X ⁴	X ⁴		X ⁴	X ⁴	
Serious adverse events		X	X	X	X	X	X	X ⁵
Termination of trial medication								X
Trial completion								X

1 Prior to any medication washout or restrictions

2 Pregnancy testing required of all women of childbearing potential.

3 Spirometric evaluations at visits were performed both prior to (-5 min) and 90 minutes post-inhalation of study medication. The initial spirometry maneuver at Visit 2 was the qualifying spirometry.

4 Telephone contacts were performed at Months 1, 2, 4, and 5 to collect information on serious adverse events, exacerbations, and hospitalizations from exacerbations.

5 Sites reported all serious adverse events (SAEs) for 30 days after patients have completed the trial.

6 Evaluations were performed for all completed and early termination patients.

Efficacy endpoints

Primary

- Proportion of patients experiencing an exacerbation over 6 months
- Percentage of patients hospitalized with COPD exacerbations

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 or more requiring treatment with antibiotics and/or systemic steroids and/or hospitalization admission.” A complex of respiratory events/symptoms means ≥ 2 of the following (increase of symptom or new onset):

- cough
- sputum
- wheezing
- dyspnea
- chest tightness

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.

Exacerbations were categorized as mild, moderate, and severe according to the following definitions:

- mild: treatment with antibiotics but not requiring a visit to a health care facility
- moderate: visit to an outpatient facility including an emergency room or treatment with systemic steroids (but not requiring admission to hospital)
- severe: traditional admissions as well as ER visits >24 hours will be characterized as hospitalizations

Patients completed a daily patient record which asked for detailed information regarding their study medication usage, daily COPD symptoms, whether or not they had experienced an exacerbation, antibiotic and steroid usage for an exacerbation, hospitalizations, and scheduled and unscheduled visits to a health care provider. The daily patient records were reviewed by the study coordination and patient at each clinic visit and interim telephone call. In addition, at each telephone contact, a standard questionnaire was administered. Patient daily records were retained by the study center as source documentation. Relevant information was transcribed by the study coordinator onto specific exacerbation and hospitalization pages of the CRF. Only events meeting the protocol defined criteria for an exacerbation were counted in the analysis.

Reviewer comment:

The definition of COPD exacerbation 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 exists, although in general the definition is acceptable.

The definition used for this trial is consistent with the definition of COPD exacerbation used in the UPLIFT trial (Protocol 205.235).

Secondary

- time to first COPD exacerbation
- time to first hospitalization associated with a COPD exacerbation
- total number of days on corticosteroids for exacerbations
- total number of days on antibiotics for exacerbation
- number of unscheduled out-patient visits for exacerbation
- total number of days spent in hospital
- total number of days spent in hospital for exacerbation
- total number of days spent in skilled nursing facilities (deleted in statistical analysis plan)
- numbers of hospitalizations
- number of hospitalizations due to COPD exacerbation (added in statistical analysis plan)
- number of exacerbations
- number of exacerbation days
- trough FEV₁ and FVC
- 90 minute FEV₁ and FVC

FEV₁

Trough FEV₁ was defined as the FEV₁ measured at the -5 minute time point at the end of the dosing interval 24 hours post drug administration. Trough FEV₁ response was defined as the change from baseline in trough FEV₁. Baseline FEV₁ was the pre-treatment FEV₁ value measured at Visit 2 in the morning 5 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 (baseline), 3 (3 months), and 4 (6 months). Testing was performed both prior to (-5minutes) and 90 minutes post-inhalation of study medication. To ensure consistency in spirometric evaluations across all centers, the MicroLab ML3500 (Micro Medical Ltd, United Kingdom) spirometer was utilized in this study. All sites were supplied with identical spirometry systems, and standardized training was provided during the investigator meeting. The spirometry equipment conformed to American Thoracic Society (ATS) technical specifications.

Measurements of FEV₁ and FVC were performed in a seated position according to ATS guidelines. A uniform set of nomograms was used at all sites to calculate percent predicted value. The best of three efforts was recorded on the CRF and was defined as the highest FEV₁ and the highest FVC each obtained on any of three efforts, even if not obtained from the same curve.

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 beta-adrenergic bronchodilators (at least 8 hour washout)
- long-acting beta-adrenergics (at least 24 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. If a steroid burst for a COPD exacerbation occurred prior to pulmonary function testing days, the testing was postponed for at least one, but no more than two weeks after the last increased or additional dose of steroid was given.

Hospitalizations

When patients were hospitalized, the investigator collected additional relevant sources of information in order to determine the primary cause for admission. Relevant sources included hospital records, telephone or written correspondence with primary physicians, discharge summaries, and death certificates. Heavy reliance was placed on the first diagnosis listed on the discharge summary in determining the primary cause for the hospitalization.

Safety endpoints

No significant SAEs were prespecified for this study. All SAEs were recorded at each visit after review of the patient's diary card and discussion with the patient. Non-serious AEs were not reported. COPD exacerbations meeting the definition of serious were also reported as SAEs. Particular attention was paid to respiratory events indicative of bronchoconstriction related to administration of the study drug, specifically drop in FEV₁ $\geq 15\%$ from study day baseline, need for rescue medication, cough, wheeze and dyspnea within 30 minutes after inhaling randomized treatment on each test day.

A standard 12-lead ECG was to be performed on all patients at the screening visit in order to determine baseline condition and eligibility for the trial. All ECGs were interpreted by the investigator or other qualified site personnel. ECG equipment and reading were not standardized across sites, and ECGs were not repeated at any other time during the trial.

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.

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.
- All pulmonary medications other than anticholinergics were permitted.

- The use of antibiotics was not restricted.
- All patients were advised to obtain influenza and pneumococcal vaccinations.

The protocol included the following restrictions regarding concomitant therapy during the course of the study:

- All other investigational agents.
- Anticholinergic medications alone or in combination with other medications (e.g. Atrovent, Combivent, Berodual, Duovent).
- Intranasal anticholinergic formulations such as Atrovent nasal spray.

Statistical plan

There were two co-primary endpoints for this study, proportion of patients experiencing a COPD exacerbation and the proportion of patients with a hospitalization associated with a COPD exacerbation during the 6-month period. Treatment response was defined to be the odds-ratio for tiotropium compared to placebo. The two co-primary efficacy endpoints were tested in order, only going to the second co-primary endpoint when the first showed significant efficacy compared to placebo. Because of the pre-specified closed hierarchical testing of hypotheses, no penalty for multiple endpoints testing was included.

Sample size

From previous tiotropium studies, the proportion of patients not experiencing an exacerbation at six months was 0.7165 for tio HH18, and 0.6542 for placebo giving an odds ratio of 1.336. Therefore, a sample size of 900 patients per group was determined to have 80% power to detect whether this ratio is significantly different than 1 using the Cochran-Mantel-Haenzel test with a 0.05 two-sided alpha level.

Statistical model and analysis

The following methods were used for analysis:

- Primary endpoints: Cochran-Mantel-Haenzel test with center as a variable
- Time-to-event endpoints: a Cox proportional hazards model
- Counts of events: Poisson regression with terms for treatment and center
- FEV₁ and FVC: general linear model with terms for treatment, center, and baseline value as a continuous variable.

The analysis was conducted as intent-to-treat including all patients who took at least one dose of study medication. For the survival analyses, each patient's event history up to the time of the first event or to termination from the study was used in the analysis. The event history of those terminated from the study was to be censored at the time of termination. Although a per protocol analysis was specified, it was not conducted.

In the final statistical analysis plan (prior to unblinding), one additional endpoint was added, "number of hospitalizations due to COPD exacerbation." In addition, the endpoint "number of days in a skilled nursing facility" was deleted since over 98% of patients had

a value of zero for this endpoint. All health economic endpoints were not included in the CSR.

Reviewer comment:

The planned per protocol analysis was to include randomized patients with at least one follow up contact who administered at least 80% of the assigned medication according to protocol directions prior to the end of the study, their death or their termination from the study. The Applicant states that the per protocol analysis was not conducted due to lack of reliability of the data for determining medication compliance.

Missing data

Per protocol, missing data were not to be imputed except for FEV₁ and FVC. These data were imputed using the last observation carried forward. In patients discontinuing the study early due to worsening COPD, the missing data were imputed by the least favorable data prior to discontinuation. Prior to unblinding, the Applicant decided to impute additional data which are documented in the final statistical analysis plan. These data included missing exacerbation end dates, missing drug-stopped dates, missing antibiotic days and steroid days when it could be determined that therapy was given.

Data sets

The analysis was conducted as intent-to-treat including all patients who took at least one dose of study medication. For the survival analyses, each patient's event history up to the time of the first event or to termination from the study was used in the analysis. The event history of those terminated from the study was to be censored at the time of termination. Although a per protocol analysis was specified, it was not conducted.

Likewise, the safety data set consisted of all randomized patients receiving at least one dose of study medication.

6.1.2.1 Protocol 206.266 results

Population characteristics

Disposition of patients

A total of 1829 male and female patients with moderate to severe COPD (FEV₁ ≤ 60% predicted) were randomized; 914 in the tio HH18 group and 915 in the placebo group. Of these, 1435 (78.5%) completed the study per protocol on study medication, and 1640 (89.7%) completed the study follow up (whether or not on study medication). The blind was broken for three patients in the trial. In two of these cases, the blind was broken by the Applicant's drug safety group for serious, unexpected adverse events. One case (Patient 5223, tio HH18) was due to hyponatremia and one (Patient 5452, placebo) due to hypoxia. The hypoxia event was later determined to be secondary to a transient ischemic attack, which is the final adverse event listed for this patient. The third case was unblinded on autopsy at the request of the medical examiner (Patient 8463, placebo). In this case, the patient suffered a cervical spine fracture approximately one week after the last dose of study medication, which resulted in a lengthy, complicated hospital course and death one day after transfer to a skilled nursing facility. A summary of patient disposition for the trial is presented in Table 54.

Table 54: Protocol 205.266 patient disposition

	Tio HH18 N (%)	Placebo N (%)	Total N (%)
Enrolled			2498
Not entered			669
Entered	914	915	1829
Not treated	0	0	0
Treated	914 (100.0)	915 (100.0)	1829 (100.0)
Not prematurely discontinued from trial medication	765 (83.7)	670 (73.2)	1435 (78.5)
Prematurely discontinued from trial medication	149 (16.3)	245 (26.8)	394 (21.5)
Adverse events	100 (10.9)	158 (17.3)	258 (14.1)
Worsening of disease under study	49 (5.4)	114 (12.5)	163 (8.9)
Worsening of other pre-existing disease	17 (1.9)	11 (1.2)	28 (1.5)
Other adverse event	34 (3.7)	33 (3.6)	67 (3.7)
Administrative	41 (4.5)	71 (7.8)	112 (6.1)
Non compliant with protocol	14 (1.5)	25 (2.7)	39 (2.1)
Lost to follow-up	4 (0.4)	7 (0.8)	11 (0.6)
Consent withdrawn	23 (2.5)	39 (4.3)	62 (3.4)
Other	8 (0.9)	16 (1.7)	24 (1.3)
Prematurely discontinued from trial	78 (8.5)	111 (12.1)	189 (10.3)

Reviewer comment:

A greater percentage of patients discontinued from the placebo group, primarily due to adverse events and worsening of COPD. The majority of adverse events leading to discontinuation were not tabulated because the data for nonserious adverse events were not collected.

In order to follow the intent to treat principle, patients who prematurely discontinued from study medication were encouraged to stay in the trial for follow up for the full 180 day observation period. While there is a large differential in discontinuation from study medication between the treatment arms, the difference is much smaller for those who actually discontinued from the trial. This is a positive design feature of this trial.

Demographics and disease characteristics

The mean age of the patients was 67.9 years (range 40-90 years), with a large percentage of elderly patients (41.3% \geq 71 years of age). The vast majority of the trial population (98.5%) was male and 91.3% were white. The mean duration of COPD was 12.1 years. All patients were current (29.3%) or ex-smokers (70.7%), with a mean smoking history of 68.4 pack years. The mean pre-bronchodilator FEV₁ was 1.04L with a mean percent predicted of 35.6%. The mean pre-bronchodilator FEV₁/FVC was 47.8%. 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 for spirometry endpoints. Demographic and disease characteristics are provided in Table 55, and baseline PFT variables are provided in Table 56.

Table 55: Protocol 205.266 patient demographic and disease characteristics

	Tio HH18	Placebo	Total
Number of patients¹	914	915	1829
Gender [N (%)]			
Male	898 (98.2)	904 (98.8)	1802 (98.5)
Female	16 (1.8)	11 (1.2)	27 (1.5)
Race [N (%)]			
White	847 (92.7)	823 (89.9)	1670 (91.3)
Black	65 (7.1)	85 (9.3)	150 (8.2)
Asian	2 (0.2)	7 (0.8)	9 (0.5)
Age [years]²			
Mean	67.6	68.1	67.9
SD	8.7	8.5	8.6
Min	44.0	40.0	40.0
Max	90.0	89.0	90.0
Smoking history [N (%)]			
Ex smoker	651 (71.2)	643 (70.3)	1294 (70.7)
Smoker	263 (28.8)	272 (29.7)	535 (29.3)
Smoking history [pack years]			
Mean	67.4	69.4	68.4
SD	35.4	36.6	36.0
Min	10.0	10.0	10.0
Max	300.0	260.0	300.0
Duration of COPD [years]³			
Mean	12.2	11.9	12.1
SD	10.4	10.5	10.4
Min	0.2	0.1	0.1
Max	58.5	65.0	65.0

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 56: Protocol 205.266 baseline PFT data

	Tio HH18	Placebo	Total
Number of patients	914	915	1829
Pre-bronchodilator FEV₁ [L]			
Mean	1.04	1.04	1.04
SD	0.40	0.40	0.40
Min	0.23	0.24	0.23
Max	2.88	2.44	2.88
Pre-bronchodilator % predicted normal FEV₁			
Mean	35.60	35.58	35.59
SD	12.58	12.59	12.58
Min	7.52	7.72	7.52
Max	93.20	67.47	93.20
Pre-bronchodilator FVC [L]			
Mean	2.17	2.18	2.17
SD	0.66	0.66	0.66
Min	0.59	0.58	0.58
Max	4.68	4.99	4.99
Pre-bronchodilator FEV₁ / FVC [%]			
Mean	47.94	47.65	47.79
SD	11.47	11.13	11.30
Min	22.54	19.52	19.52
Max	81.03	100.00	100.00

Obtained from Visit 2, Randomization Visit

Reviewer comment:

The distribution of baseline FEV₁ is a bit skewed to the left (towards lower values). Median values are not given in the CSR, but the reviewer calculated them as 0.98L in the tio HH group and 0.99 in the placebo group.

Protocol violations

There was no per-protocol analysis for this study; therefore, protocol violations were not used to exclude patients from any analysis.

Protocol violations were divided into 6 types: entrance criteria not met, examination (visit window or PFT timing violations), improper medication wash out, missing data examination (entire endpoint is missing), missing data value (one data point for an examination is missing), and prohibited medication use. Overall, there were a very large number of protocol violations in this trial. See Table 57. The majority of violations were for “examination,” which were evenly distributed between the treatment groups. A larger number of improper medication wash-outs, missing data, and prohibited medication use occurred in the placebo group compared to the tio HH18 group. The Applicant attributes this observation to the greater number of patients who discontinued in the placebo group.

Table 57: Protocol 205.266 protocol violations

Protocol violation	Tio HH18 N=914 n (%)	Placebo N=915 n (%)	Total N=1829 n (%)
Entrance criteria not met	51 (5.6)	30 (3.3)	81 (4.4)
Examination	766 (83.8)	740 (80.9)	1506 (82.3)
Improper medication wash out	87 (9.5)	138 (15.1)	225 (12.3)
Missing data (examination)	177 (19.4)	243 (26.6)	420 (23.0)
Missing data (value)	43 (3.7)	44 (4.8)	78 (4.3)
Prohibited medication use	262 (28.7)	301 (32.9)	563 (30.8)

Reviewer comment:

The large number of protocol violations in this study is concerning, but may reflect the population studied (Veterans Affairs Administration). From a review of the data listing for protocol violations, prohibited medication use was nearly exclusively due to ipratropium. Protocol violations appeared to be distributed evenly across the sites.

Protocol violations of prohibited medication use and improper medication wash out, which were more common in the placebo group, would tend to bias against the drug. Entrance criteria not met occurred less frequently, although still more often than in most other Spiriva Phase 3 studies.

The protocol violations of greatest concern are missing data for an entire examination, which occurred in 23% of patients. This does not include data which are missing due to discontinuations. However, this potentially large amount of missing data represents a “worst case scenario” that did not actually occur. The data listings reveal that many of these missing examinations are for COPD exacerbation data. For spirometry data, protocol-specified guidelines are in place for handling missing data in an appropriate fashion. Likewise, for COPD exacerbations, data handling guidelines permitted collection of missing exacerbation data at the next visit by review of the diary data, which resulted in a minimal amount of actual missing data. Because the data regarding COPD exacerbations was recorded in a daily diary, recall bias from late collection is not a major issue.

Treatment compliance

Medication compliance was determined from a checkbox on the CRF indicating whether the patient’s compliance since the last visit was greater than or equal to 80%. Based on these criteria, an estimated 84-86% of patients were compliant in the tiotropium group compared to 78% in the placebo group. However, the Applicant notes that the reliability of the data is questionable since actual compliance percentages were not calculated.

Reviewer comment:

Although the Applicant correctly notes that the data reliability is questionable due to the method of collection, the percentages given likely represent an upper bound of

compliance (i.e. overestimate) rather than an underestimate. This suggests that compliance was quite poor in this study.

Concomitant respiratory medications

A total of 96.3% of patients in the study took baseline concomitant respiratory medications. At baseline, 75.8% of patients were taking inhaled short-acting anticholinergics, 16.1% were taking nebulized anticholinergics, 38.1% were taking inhaled long-acting β -agonists, 89.9% were taking short-acting β -agonists, 25.8% were taking nebulized short-acting β -agonists, and 14.2% were taking theophylline preparations. In addition, 60.6% of patients overall were taking inhaled steroids, and 10.4% were taking oral corticosteroids. Finally, 26.7% were on chronic oxygen therapy. During the study, the percentage of patients taking short acting anticholinergics, a protocol prohibited medication decreased to 6.2% nebulized and 14.3% inhaled, while oral steroid use (17.1%) and oxygen use (32.1%) increased. The respiratory medications were generally balanced between groups.

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 β -agonists, 53.0% were taking short-acting β -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.

Reviewer comment:

Almost all of the patients in this study were on concomitant medications. The percentage of patients on oxygen is much higher than in other Spiriva Phase 3 trials, in which chronic oxygen use was prohibited. This suggests that although the mean baseline FEV₁ is comparable, either the population in this study actually had more severe disease (gas transfer defect was not measured). Long-acting anticholinergic medications are not mentioned in this study because the study was conducted prior to the approval of Spiriva HandiHaler in the US.

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 any follow up contact who took at least one capsule of the study drug. Since the baseline value was used as a covariate for the analysis of PFT data, patients without baseline data were excluded from analysis of PFT variables. In the case of exacerbations all data for the exacerbation was used as long as the exacerbation started by the patient's last visit. Hospitalizations were likewise included if either the hospitalization or the adverse event leading to hospitalization started by the patient's last visit. For the survival analyses, each patient's event history up to the time of the first event or to completion of or early discontinuation from the study was used in the analysis.

Primary

There were two co-primary endpoints for this study, proportion of patients experiencing a COPD exacerbation and the proportion of patients with a hospitalization associated with a COPD exacerbation during the 6-month period. Treatment response was defined to be the odds-ratio for tiotropium compared to placebo.

The percentage of patients with a COPD exacerbation meeting the protocol definition was significantly lower for tio HH18 compared to placebo ($p=0.04$), with an odds ratio of 0.806. A sensitivity analysis evaluating all events reported by the investigator as exacerbations whether or not meeting protocol definitions demonstrated similar results. The percentage of patients with a hospitalization due to COPD exacerbation was numerically lower in the tio HH18 group compared to placebo, but did not reach statistical significance ($p=0.06$), with an odds ratio of 0.718. See Table 58.

Table 58: Protocol 205.266 percentage of patients with COPD exacerbations

Endpoint (percent of patients)	Tio HH18 (N=914)	Placebo (N=915)	Odds ratio	p-value
Exacerbations meeting protocol definition	27.9	32.3	0.806	0.0368
Hospitalizations due to exacerbation	7	9.5	0.718	0.0557
All reported exacerbations	27.9	32.6	0.798	0.0287

Reviewer comment:

This study corrects for multiplicity in the co-primary endpoints by serial testing, i.e. the second endpoint can only be tested if the first is positive. The study demonstrates efficacy on only the first two primary endpoints; however, the Applicant has requested a labeling claim for the first primary endpoint and a secondary endpoint. Because COPD exacerbation endpoints are not independent, an argument can be made that the risk of a Type I error due to inadequate multiplicity correction is low.

The primary analysis does not adjust for differential treatment exposure. Thus, in the primary analysis, a patient is counted only once regardless of the number of exacerbations he reported. Patients were followed to six months even if they discontinued study medication. A greater percentage of patients discontinued the study in the placebo group compared to the tio HH18 group (12.1% versus 8.5%). In addition, a greater percentage of patients in the placebo group discontinued study medication (26.8% versus 16.3%). Without adjustment for treatment exposure, this differential discontinuation would tend to bias towards the placebo group.

In the Advair program 70% of patients experienced an exacerbation while on study medication (Protocol SCO3003). The Advair program enriched the patient population for exacerbations by including only those patients with a history of frequent exacerbations.

Percentage of patients with exacerbations and hospitalizations due to COPD exacerbation were also compared across subgroups. The following subgroup parameters were investigated:

- Race (white/non-white)
- Age (<61/ 61-<71/ ≥71)
- Smoking history (active smoker/ex-smoker)
- Inhaled corticosteroid use at Visit 2 (yes/no)
- Theophylline use at Visit 2 (yes/no)
- Hospitalizations for COPD in the last year (none/≥1)
- COPD severity (FEV₁ percent predicted <35%/ 35-<50%/ ≥50%)
- Prednisone burst in the last year (none/≥1)
- Antibiotics course for respiratory use in the last year (none/≥1)
- Chronic home oxygen use at Visit 2 (yes/no)
- Long-acting β-agonist use at Visit 2 (yes/no)

The percentage of patients with COPD exacerbations was lower in every subgroup for the tio HH18 group compared to placebo. Overall, patients with more severe disease or with a history of hospitalization, steroid burst, home oxygen use, antibiotic use, or theophylline use were more likely to have an exacerbation. Inhaled corticosteroid use and long-acting β-agonist use resulted in a lesser extent of increase in percentage of patients with a COPD exacerbation.

With regards to hospitalization due to COPD exacerbation, a similar pattern was observed. However, there were an increased percentage of patients in the tio HH18 group compared to placebo with hospitalization due to exacerbation in three subgroups: mild COPD, moderate COPD, and history of hospitalization in the last year. The test for non-homogeneity of odds ratios was significant in patients with a history of hospitalization in the last year, with 23.5% in tio HH18 and 18.0% in placebo experiencing a hospitalization due to COPD exacerbation in this group.

Reviewer comment:

Overall, these results do not demonstrate a clinically important subgroup interaction, given that no trend was observed in the percentage of patients with an exacerbation. The percentages of patients with hospitalizations due to COPD were small and dividing further by subgroups is likely to result in higher variability. The subgroup analysis is generally supportive of the conclusion that tio HH18 reduces the percentage of patients with COPD exacerbations.

Evaluating COPD exacerbations by severity demonstrates that the majority of exacerbations were classified as moderate (requiring an outpatient visit or systemic steroids). The proportions of patients with moderate and severe exacerbations were lower in the tio HH18 group compared to placebo, whereas mild exacerbations were similar between the two groups. The Applicant does not provide statistical analysis of these data. See Table 59.

Table 59: Study 205.266 percentage of patients with COPD exacerbations by severity

Exacerbation severity	Tio HH18 N=914	Placebo N=915
Mild	8.1	8.2
Moderate	24.6	29.2
Severe	8.5	12.1

Secondary

Secondary endpoints are grouped into three categories, time to event endpoints, number of event endpoints, and spirometric endpoints.

- time to first COPD exacerbation
- time to first hospitalization associated with a COPD exacerbation
- total number of days on corticosteroids for exacerbations
- total number of days on antibiotics for exacerbation
- number of unscheduled out-patient visits for exacerbation
- total number of days spent in hospital
- total number of days spent in hospital for exacerbation

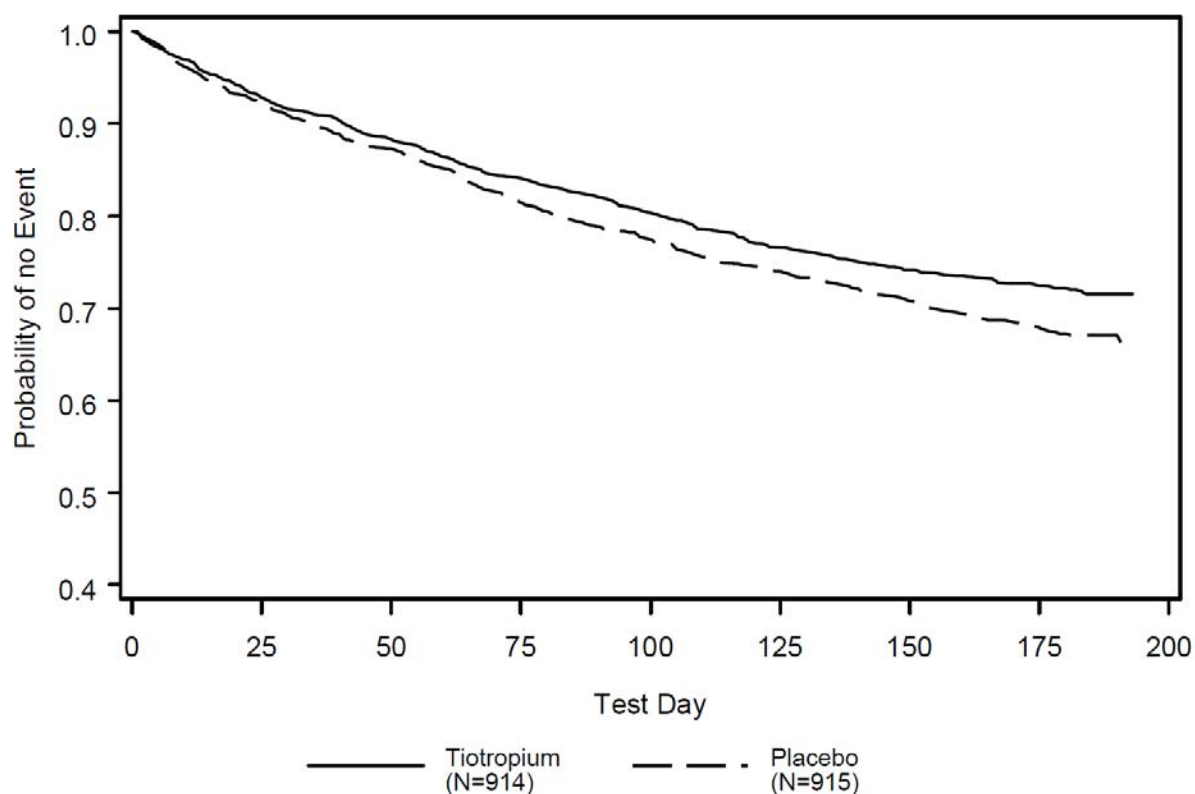
- total number of days spent in skilled nursing facilities (deleted in statistical analysis plan)
- numbers of hospitalizations
- number of hospitalizations due to COPD exacerbation (added in statistical analysis plan)
- number of exacerbations
- number of exacerbation days
- trough FEV₁ and FVC
- 90 minute FEV₁ and FVC

Time to event

Time to event endpoints included time to first COPD exacerbation and time to first hospitalization associated with a COPD exacerbation.

For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p=0.04$, RR 0.834). Time to first exacerbation is not given for either group. A Kaplan-Meier estimate of the probability of no exacerbation as provided by the Applicant is presented in Figure 14.

Figure 14: Study 205.266 Kaplan-Meier estimates of the probability of no exacerbation



The Applicant also reports that patients in the tio HH18 group had a statistically significantly longer time to first hospitalization due to COPD exacerbation compared to placebo ($p=0.05$, RR 0.723).

The same subgroups were investigated for the time to event analyses as for the primary endpoints. Tio HH18 had a numerically longer time to exacerbation in all of the subgroups. Overall, the time to first exacerbation was shorter for the following groups:

- oldest patients (≥ 71 years of age)
- patients with antibiotic therapy in the past year
- patients with severe disease ($FEV_1 < 35\%$ predicted)
- patients with at least one hospitalization for COPD in the past year
- patients with one or more steroid bursts in the past year
- patients using theophylline at Visit 2

With the exception mild and moderate COPD patients and patients with at least one hospitalization due to exacerbation, the tio HH18 had a numerically longer time to hospitalization for exacerbation. Overall, the time to first hospitalization for exacerbation was shorter for the following groups:

- oldest patients (≥ 71 years of age)
- patients with severe disease ($FEV_1 < 35\%$ predicted)
- patients with at least one hospitalization for COPD in the past year
- patients with one or more steroid bursts in the past year

Number of COPD related events

Secondary endpoints evaluated by number of events include total number of days on corticosteroids for exacerbations, total number of days on antibiotics for exacerbations, number of unscheduled out-patient visits for exacerbations, total number of days spent in hospital, total number of days spent in hospital for exacerbations, numbers of hospitalizations, number of hospitalizations due to COPD exacerbations, number of exacerbations, and number of exacerbation days. Events were expressed per patient year (exacerbation rate), so a correction for time of therapy is built into this endpoint. See Table 60 for the analysis as presented in the clinical study report.

Table 60: Study 205.266 COPD related events endpoints (as reported in the Clinical Study Report)

Endpoint	Tio HH18 N=914	Placebo N=915	Risk Ratio	p-value
Exacerbations	0.853	1.051	0.812	0.0028
Exacerbation days	12.61	15.96	0.790	<0.0001
Antibiotic days	8.045	9.759	0.824	<0.0001
Corticosteroid days	6.251	7.396	0.845	<0.0001
Unscheduled outpatient visits for exacerbations	0.387	0.494	0.783	0.0169
Hospitalizations due to exacerbations	0.177	0.253	0.697	0.0131
Days in hospital due to exacerbations	1.433	1.702	0.842	0.0013
Hospitalizations (all cause)	0.453	0.505	0.897	0.2417
Days in hospital (all)	3.666	3.524	1.040	0.3230

All endpoints are reported as number of events per patient-year.

Poisson regression analysis adjusted for treatment. No correction for center or overdispersion is included.

Reviewer comment:

In response to an Information Request from FDA, the Applicant provided revised exacerbation rate tables which correct the analysis for center and for overdispersion. This analysis is critical as it changes the outcome for several secondary endpoints from significant to not significant. See Table 61. Based on this corrected analysis, only exacerbation rate shows a statistically significant difference from placebo. This difference remains significant ($p=0.0233$) when corrected for overdispersion using a negative binomial approach as well. While not statistically significant, the other COPD exacerbation related secondary endpoints are numerically supportive of the exacerbation claim.

The default Poisson regression technique assumes that all patients are homogenous with respect to their rate of exacerbation. The correction for overdispersion takes into account that for COPD, the majority of exacerbations occur in a small portion of patients while the rest of the population has no exacerbations.⁴ The method of calculation of exacerbation rate and correction for overdispersion is critical as different statistical methodologies may give very different results.

Table 61: Study 205.266 COPD related events endpoints, corrected for overdispersion

Endpoint	Tio HH18 N=914	Placebo N=915	Risk Ratio	p-value
Exacerbations	0.711	0.876	0.812	0.0370
Exacerbation days	9.961	12.62	0.790	0.0564
Antibiotic days	6.507	7.856	0.828	0.1050
Corticosteroid days	4.447	5.256	0.846	0.3746
Unscheduled outpatient visits for exacerbations	0.300	0.384	0.783	0.0550
Hospitalizations due to exacerbations	0.148	0.212	0.698	0.0544
Days in hospital due to exacerbations	1.071	1.271	0.842	0.4713
Hospitalizations (all cause)	0.389	0.436	0.893	0.3781
Days in hospital (all cause)	2.798	2.702	1.035	0.8419

All endpoints are reported as number of events per patient-year.

Poisson regression analysis adjusted for treatment, center and corrected for overdispersion.

Spirometry

Spirometry endpoints included trough FEV₁ and FVC response and 90 minute FEV₁ and FVC response. Endpoints were measured both after 3 months and after 6 months of treatment. The tio HH18 group demonstrated a significant improvement ($p<0.0001$) over placebo for all endpoints and time points tested. For trough FEV₁ the treatment difference was 0.09 - 0.10L, while for 90 minute FEV₁ the treatment difference was 0.13L on the first test day and 0.016 - 0.17L for subsequent test days. For trough FVC, the treatment

difference was 0.21L, while for 90 minute FVC the treatment difference was 0.30L on the first test day and 0.35 - 0.36L on subsequent test days. See Table 62.

There were 10 patients in the tio HH18 group and 7 patients in the placebo group with missing baseline data (or set to missing due to failed washout). These patients were not included in the spirometry analyses.

Table 62: Protocol 205.266 spirometry

Test Day	Time point	Tio HH18 N=904 [L]	Placebo N=908 [L]	Treatment difference [L]	p-value	95% CI
FEV₁						
1	90 min	1.18	1.05	0.13	<0.0001	(0.12, 0.14)
90	-5 min	1.14	1.05	0.10	<0.0001	(0.08, 0.11)
	90 min	1.23	1.07	0.16	<0.0001	(0.14, 0.18)
150	-5 min	1.15	1.06	0.09	<0.0001	(0.07, 0.11)
	90 min	1.24	1.07	0.17	<0.0001	(0.15, 0.19)
FVC						
1	90 min	2.48	2.19	0.30	<0.0001	(0.27, 0.32)
90	-5 min	2.36	2.15	0.21	<0.0001	(0.18, 0.24)
	90 min	2.55	2.20	0.35	<0.0001	(0.32, 0.39)
150	-5 min	2.39	2.18	0.21	<0.0001	(0.18, 0.25)
	90 min	2.55	2.19	0.36	<0.0001	(0.32, 0.39)

Common baseline mean FEV₁ = 1.04L; Common baseline mean FVC = 2.17L

-5 min time point = trough

Reviewer comment:

Bronchodilatory effect of tio HH18 is slightly lower than that observed in the Spiriva HandiHaler Phase 3 program. For Spiriva HandiHaler Phase 3 pivotal trials, the FEV₁ trough response was 0.110-0.130L. Overall, however, the results are comparable. The spirometry results from this study demonstrate bronchodilator efficacy in a more “real world” patient population in which there were likely compliance issues as well as a myriad of concomitant respiratory medications and medical conditions.

Safety outcomes

Safety outcomes for Study 205.266 included only serious adverse events and physical examinations (screening and at the end of treatment). The Applicant states that non-serious adverse events were not systematically collected as the safety profile of tiotropium has been well described in several previously conducted large scale trials. Non-serious adverse events which occurred concomitantly with SAEs and were deemed clinically relevant by the investigators were sporadically reported. Because non-serious adverse events were not systematically collected, no conclusions can be drawn regarding the overall frequency of non-serious events. 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 1829 COPD patients were randomized and received at least one dose of study medication. The planned exposure for each patient was 180 days. The planned exposure for each patient was 180 days. More patients in the tio HH18 group had at least 170 days of exposure to study medication than did placebo patients (83.7% versus 73.9%, respectively). The maximum extent of exposure exceeded planned exposure because study visits were postponed for some patients due to COPD exacerbations or other intercurrent illnesses. See Table 63.

Table 63: Protocol 205.266 summary of treatment exposure

	Tio HH18	Placebo	Total
Total Treated N	914	915	1829
Maximum Exposure n (%)			
1 – 7 days	11 (1.2)	30 (3.3)	41 (2.2)
8 – 60 days	56 (6.1)	98 (10.7)	154 (8.4)
61 – 120 days	48 (5.3)	78 (8.5)	126 (6.9)
121 – 170 days	43 (3.7)	33 (3.6)	67 (3.7)
>170 days	765 (83.7)	676 (73.9)	1441 (78.8)
Treatment Exposure (days)			
Median	182	101	182
Min	1	1	1
Max	232	231	232

Adverse events

Deaths

Overall, there were 41 deaths occurring during the study, with 22 (2.4%) in the tio HH18 group and 19 (2.1%) in the placebo group. There were an additional 21 deaths which were reported post-treatment, more than 30 days after discontinuing trial medication. Deaths that were reported post-treatment were not necessarily due to adverse events that began while the patient was taking study medication, and were not divided by treatment group for analysis. The most frequent causes of death were cardiac disorders, neoplasms (primarily lung cancer), unknown, COPD exacerbations, and pneumonia. Cause of death for those patients who died during the study is provided in Table 46.

There were 5 deaths during the study of unknown cause, four in the tio HH18 group and one in the placebo group. All four patients with deaths of unknown cause in the tio HH18 group died at home (Patients #6207, #7063, #8071, and #8313). Three of the four had a history of coronary artery disease. The fourth patient was noted by his girlfriend to be complaining of increased dyspnea for two days prior to death. The patient in the placebo group with death of unknown cause (Patient #5439) died in the hospital during an admission for Candida esophagitis secondary to steroid use for his COPD. Just prior to nursing home transfer, he became hypotensive and was treated with IV fluids. No additional therapy was instituted because of the patient's Do Not Resuscitate status.

Table 64: Protocol 205.266 fatal events by treatment group and primary cause of death

Events leading to death	Tio HH18	Placebo	Post treatment	Total
	[n=914]	[n=915]	[n=1829]	[n=1829]
Total deaths	22	19	21	62
Cardiac disorders	3	6	7	16
Gastrointestinal disorders	3	0	0	3
Death	4	1	5	10
Infection	3	1	1	5
Injury	0	1	1	2
Neoplasms (other than lung)	3	2	0	5
Neoplasms (lung) [†]	5	3	1	9
Renal failure acute	1	0	0	1
Choking	0	0	1	1
COPD exacerbation [†]	1	3	3	7
Pneumonia [†]	1	3	2	6
Respiratory failure	0	1	2	3
Pulmonary embolism	1	0	0	1
Cerebral infarction	1	0	0	1

† Terms collapsed by reviewer: neoplasms (lung) = lung adenocarcinoma NOS, lung carcinoma cell type unspecified stage IV, lung squamous cell carcinoma stage IV, lung squamous cell carcinoma stage unspecified, non small cell lung cancer NOS, and small cell lung cancer stage unspecified; COPD exacerbation = COPD exacerbation and emphysema; Pneumonia = pneumonia aspergilla, pneumonia staphylococcal, and pneumonia

Reviewer comment:

Deaths were generally balanced between the treatment groups. Causes of death are not unexpected in this severely ill patient population with an extensive smoking history. No particular cause of death is disproportionately represented in the tio HH18 group with the exception of deaths of unknown cause. If all of these deaths are attributed to cardiac causes, balance is still maintained between the treatment groups.

Serious adverse events

Serious adverse events (SAEs) occurred in 17.4% of the overall study population, including 17.7% of the tio HH18 group and 17.0% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and congestive heart failure. SAEs occurring in more than two patients in either treatment group are given in Table 65. SAEs were generally balanced between treatment groups. A subgroup analysis was not performed for SAEs.

Table 65: Protocol 205.266 serious adverse events occurring in >2 patients in either treatment group

MedDRA System Organ Class MedDRA Preferred Term	Tio HH18 N (%)	Placebo N (%)	Total N (%)
Total Treated N (%)	914	915	1829
Total with serious adverse events	162 (17.7)	156 (17.0)	318 (17.4)
Cardiac disorders			
Angina#	6 (0.7)	7 (0.8)	13 (0.7)
Atrial fibrillation#	2 (0.2)	9 (1.0)	11 (0.6)
Cardiac arrest	2 (0.2)	3 (0.3)	5 (0.3)
Cardiac failure congestive#	10 (1.1)	10 (1.1)	20 (1.1)
Coronary artery disease#	4 (0.4)	6 (0.7)	10 (0.5)
Myocardial infarction#	9 (1.0)	7 (0.8)	16 (0.9)
Myocardial ischemia	0 (0.0)	3 (0.3)	3 (0.2)
Ventricular tachycardia	5 (0.5)	4 (0.4)	9 (0.5)
Gastrointestinal disorders			
Gastritis	0 (0.0)	3 (0.3)	3 (0.2)
General disorders and administration site conditions			
Chest pain	6 (0.7)	3 (0.3)	9 (0.5)
Death#	4 (0.4)	1 (0.1)	5 (0.3)
Infections and infestations			
Cellulitis	3 (0.3)	2 (0.2)	5 (0.3)
Sepsis	4 (0.4)	1 (0.1)	5 (0.3)
Injury, poisoning and procedural complications			
Road traffic accident	1 (0.1)	3 (0.3)	4 (0.2)
Nervous system disorders			
Dizziness (excl. vertigo)	3 (0.3)	5 (0.5)	8 (0.4)
Syncope	3 (0.3)	1 (0.1)	4 (0.2)
Transient ischemic attack	3 (0.3)	3 (0.3)	6 (0.3)
Psychiatric disorders			
Depression#	1 (0.1)	3 (0.3)	4 (0.2)
Renal and urinary disorders			
Renal failure acute	4 (0.4)	1 (0.1)	5 (0.3)
Respiratory system disorders* (Lower)			
Bronchitis#	10 (1.1)	5 (0.5)	15 (0.8)
COPD exacerbation#	38 (4.2)	61 (6.7)	99 (5.4)
Dyspnea#	3 (0.3)	2 (0.2)	5 (0.3)
Pneumonia#	25 (2.7)	39 (4.3)	64 (3.5)
Pulmonary edema aggravated#	3 (0.3)	0 (0.0)	3 (0.2)
Respiratory failure#	4 (0.4)	7 (0.8)	11 (0.6)
Vascular disorders			
Hypotension	3 (0.3)	2 (0.2)	5 (0.3)

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.

Serious adverse events of interest

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 Protocol 205.266. Combining SAE terms of cerebral infarction, CVA, transient ischemic attack, and cerebrovascular insufficiency gives 6 events in the tio HH18 and 4 in the placebo group.

Adverse events leading to discontinuation

There were 100 (10.9%) patients in the tio HH18 group and 158 (17.3%) patients in the placebo group who discontinued prematurely due to an adverse event. Of these, 46 (5.0%) in the tio HH18 group and 45 (4.9%) in the placebo group discontinued due to SAEs. The most frequent SAEs leading to discontinuation were COPD exacerbation, pneumonia, and cardiac disorders. A total of 54 (5.9%) patients in the tio HH18 group and 113 (12.3%) of patients in the placebo group discontinued due to non-serious adverse events. Because non-serious adverse events were not collected during the conduct of the trial, the Applicant did not tabulate non-serious adverse events leading to discontinuation.

Overall adverse events

Non serious adverse events were reported sporadically and only in association with an SAE. A total of 17 patients (1.9%) in the tio HH18 group and 21 patients (2.3%) in the placebo group reported non-serious adverse events.

Reviewer comment:

Analysis of non-serious adverse events is not useful due to the limited reporting. Although an extensive safety database exists for Spiriva HandiHaler, design of a large-scale trial with no adverse event reporting is suboptimal, particularly as the VA population enrolled in this study with liberalized enrollment criteria differs from that found in Phase 3 Spiriva HandiHaler trials.

Laboratory findings

There were no laboratory evaluations performed in this trial.

ECG findings

Twelve-lead ECGs were recorded at Visit 1 to determine patient eligibility. Two patients were noted to have clinically significant findings at baseline. One patient was randomized to tio HH18 (#6560) and one to placebo (#7059). No SAEs were recorded for either patient.

ECGs were not collected during or after administration of study drug.

Reviewer comment:

The clinically significant findings on baseline ECG noted in two patients were not reported under concomitant diagnoses in the data listing. A data listing of baseline ECG findings was not provided. Further information on what these diagnoses are was not provided in the CSR. Since these two patients did not have SAEs, case report forms were not provided. According to the protocol, enrollment of these patients with clinically significant findings on ECG was a protocol violation.

Physical examination

Vital signs were performed as part of the complete physical examination at the start and end of each patient's participation in the trial. However, no analyses were conducted on vital signs. At baseline, two patients in the placebo group and no patients in the tio HH18 group were noted to have clinically relevant findings on baseline physical examination. Changes in physical examination in comparison to baseline were not assessed.

Reviewer comment:

No data listings are provided for the physical examination and further information regarding findings is not provided in the CSR. Review of the case report form shows that only height, weight, blood pressure, pulse rate, and date of the examination were collected. In addition, the investigator was asked whether or not there were any clinically relevant findings which would exclude the patient from participating in the trial. Further information regarding the two patients with clinically relevant findings on baseline physical examination, including the patient number, was not provided. According to the protocol, enrollment of these patients was a protocol violation.

6.1.2.2 Protocol 205.266 conclusions

One of the two co-primary endpoints was met in this study. The percentage of patients with a COPD exacerbation meeting the protocol definition was significantly lower for tio HH18 compared to placebo ($p=0.04$), with an odds ratio of 0.806. The percentage of patients with a hospitalization due to COPD exacerbation was numerically lower in the tio HH18 group compared to placebo, but did not reach statistical significance ($p=0.06$), with an odds ratio of 0.718.

For COPD exacerbations, the Applicant reports that patients in the tio HH18 group had a significantly longer time to event than patients in the placebo group ($p=0.04$, RR 0.834). In addition, patients in the tio HH18 group had a significantly shorter time to first hospitalization due to COPD exacerbation compared to placebo ($p=0.05$, RR 0.723).

A significant reduction in number of exacerbations, exacerbation days, antibiotic days, corticosteroid days, and unscheduled visits for exacerbations was observed in the tio HH18 group compared to placebo. Events were expressed per patient year (exacerbation rate), so a correction for time of therapy is built into this endpoint. With regards to hospitalizations, tio HH18 significantly reduced the number of hospitalizations and hospitalizations due to COPD, but not all cause hospitalizations.

Spirometry endpoints included trough FEV₁ and FVC response and 90 minute FEV₁ and FVC response. Endpoints were measured both after 3 months and after 6 months of treatment. The tio HH18 group demonstrated a significant improvement ($p<0.0001$) over placebo for all endpoints and time points tested.

Overall, there were 41 deaths occurring during the study, with 22 (2.4%) in the tio HH18 group and 19 (2.1%) in the placebo group. There were an additional 21 deaths which were reported post-treatment, more than 30 days after discontinuing trial medication. The most frequent causes of death were cardiac disorders, neoplasms (primarily lung cancer), unknown, COPD exacerbations, and pneumonia.

Serious adverse events (SAEs) occurred in 17.4% of the overall study population, including 17.7% of the tio HH18 group and 17.0% of the placebo group. The most common SAEs were COPD exacerbation, pneumonia, and congestive heart failure. SAEs were generally balanced between treatment groups.

Non-serious adverse events were not collected as part of this trial. Likewise, laboratory studies and ECGs were not performed. Physical examinations were conducted at the screening visit and at the end of study treatment, but results were not collected.

Protocol 205.266 had a very large number of protocol violations and relatively poor compliance with study medication. The enrollment criteria were “real world.” Despite these factors which would tend to bias against the drug, the spirometry findings suggest that the study population achieved a level of bronchodilator effectiveness that is not out of line with anticipated results based on other Phase 3 pivotal trials for tiotropium.

6.2 Review of Individual Study Reports: Spiriva Respimat

6.2.1 Protocols 205.254 and 205.255, including Protocol 205.392 (vital status)

6.2.1.1 Protocols 205.254, 205.255, and 205.392 study design

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_{0-3h} , 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.

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.

Study 205.392 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 (ICON) that undertook the conduct of the study on behalf of the applicant. 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.

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 was considered to be alive.
- If a patient refused consent but the last contact date is after the predicted exit date, the patient was considered to be alive.
- If a patient is lost to follow up and the last contact date a patient was known to be alive was after the predicted exit date, the patient was considered to be alive.

6.2.1.2 Protocols 205.254, 205.255, and 205.392 results

Efficacy

Treatment of bronchospasm

In each of the pivotal studies (205.254 and 205.255), both tiotropium groups were superior to placebo for the primary endpoint, trough FEV₁ at the end of treatment. Trough FEV₁ showed an improvement of 0.11L for tio R5 and 0.14L for tio R10 over placebo ($p < 0.0001$ for both differences). While tio R10 was generally numerically superior to tio R5, the differences were generally small and not statistically significant. The differences between the tiotropium groups and placebo were also highly statistically significant ($p < 0.0001$) for mean FEV₁ AUC_(0-3h) response and mean FEV₁ peak_(0-3h) response throughout the treatment period. The effects of tiotropium on FEV₁ appeared to reach steady state after 15 days of dosing.

In each of the 1-year studies (205.254 and 205.255), the FVC results generally paralleled the FEV₁ 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.

COPD exacerbations

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.

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.

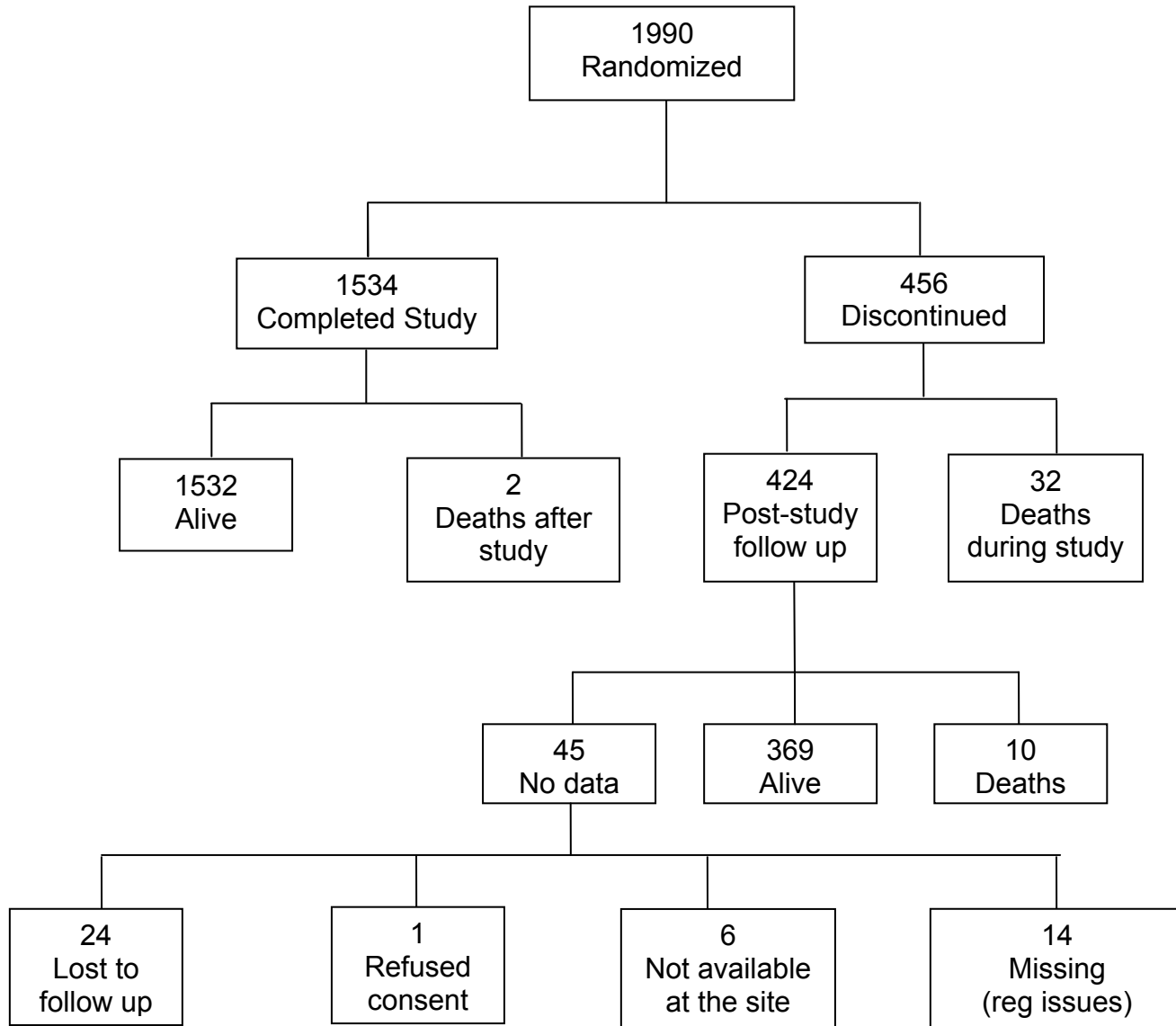
Mortality

Number of deaths

An imbalance in deaths in Studies 205.254 and 205.255 was noted upon unblinding. In order to ascertain if differential discontinuation rates accounted for the mortality imbalance the Applicant obtained additional follow up on the discontinued patients as part of Study 205.392.

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 15 for a graphical representation of patient disposition.

Figure 15: Disposition and vital status for patients originally enrolled in Studies 205.254 and 205.255, as determined in Study 205.394



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). 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.

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 66 for a summary of numbers of deaths in the trials.

Table 66: Protocol 205.392 number of deaths by study treatment

	205.254			205.255			Combined			total
	tio R5	tio R10	plac	tio R5	tio R10	plac	tio R5	tio R10	plac	
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.

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 67 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 16 and Figure 17.

Table 67: 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)

¹Kaplan-meier estimates at 366 days

²As estimated by Cox proportional hazards regression with treatment as independent variable, stratified by study for pooled analysis.

³As estimated by the difference in Kaplan-Meier estimates at 366 days, expressed per 1000 person years

* p<0.05

Figure 16: Studies 205.254, 205.255, and 205.392 Kaplan-Meier time to death for tiotropium RespiMat 5 mcg versus placebo

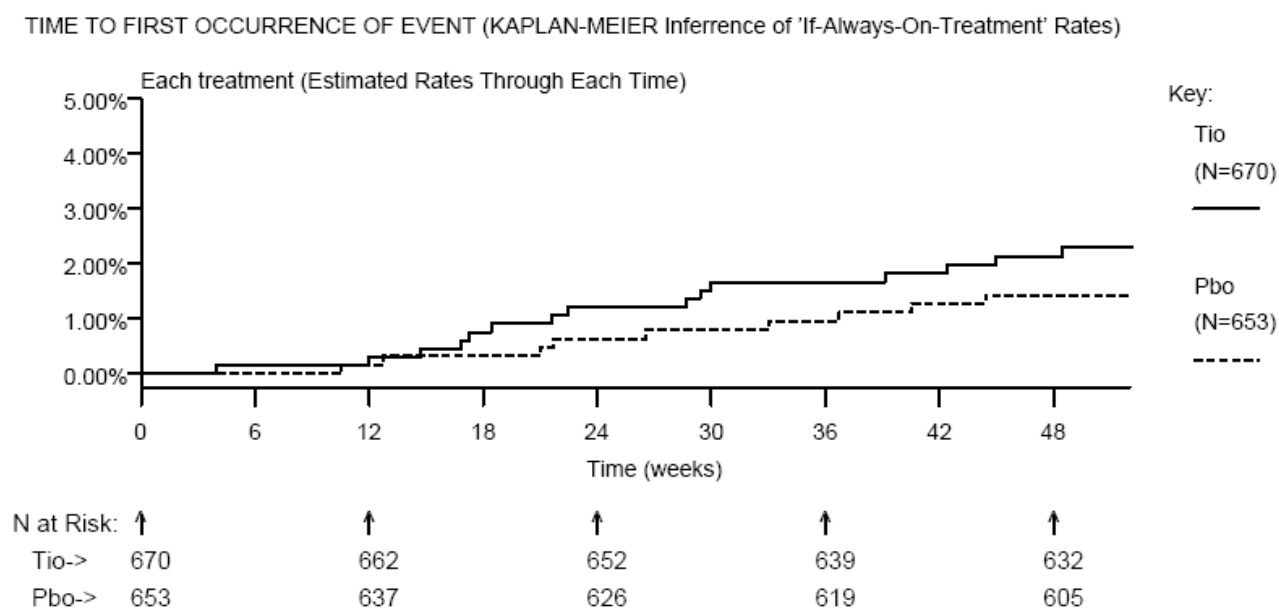
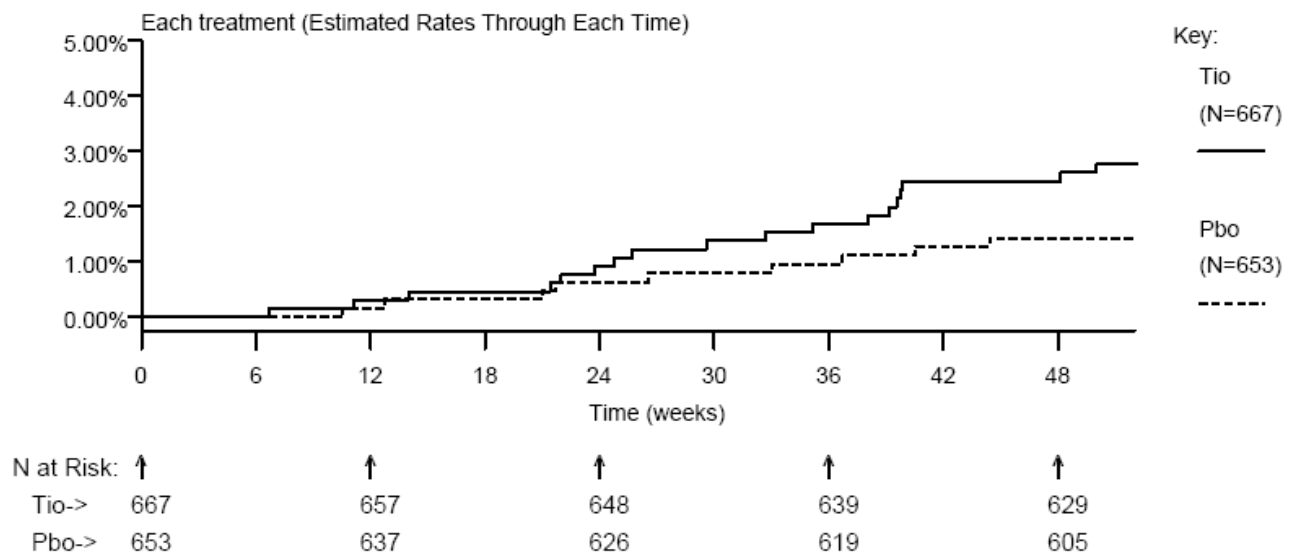


Figure 17: Studies 205.254, 205.255, and 205.392 Kaplan-Meier time to death for tiotropium Respimat 5 mcg versus placebo

TIME TO FIRST OCCURRENCE OF EVENT (KAPLAN-MEIER Inference of 'If-Always-On-Treatment' Rates)



Cause of death

Cause of death was not adjudicated for Studies 205.254, 205.255, and 205.392, 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. 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.

Reviewer comment:

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 68.

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 68: Protocol 205.255, 205.255 and 205.392 fatal events by treatment group (reviewer adjudication)

Events leading to death	Tio R5 [n=670]	Tio R10 [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

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 69. 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 analysis presented is per reviewer 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 69: 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)

6.2.1.3 Protocols 205.254, 205.255, and 205.392 conclusions

With regards to efficacy, both Study 205.254 and 205.255 met their two relevant primary endpoints, trough FEV1 at the end of treatment and the mean COPD exacerbation rate

per patient year. Trough FEV1 showed an improvement of 0.11L for tio R5 and 0.14L for tio R10 over placebo ($p < 0.0001$ for both differences). The mean COPD exacerbation rate per patient year for all patients in the combined studies was 0.93 for tio R5 ($p = 0.002$), 1.02 for tio R10 ($p = 0.0008$), and 1.91 for placebo.

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 discontinuation. 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.

6.2.2 Protocol 205.372 (exacerbation study)

6.2.2.1 Protocol 205.372 study design

The trial was a multicenter, multinational, randomized, double-blind, parallel group Phase 3b study to compare the long-term efficacy and safety of 5 mcg [2 actuations of 2.5 mcg] of tiotropium inhalation solution administered by the Respimat inhaler compared with placebo in patients with moderate-severe COPD. The placebo group received a Respimat placebo product. All patients also received albuterol MDI inhalers for rescue use and were permitted to use stable baseline respiratory medications other than anticholinergics (usual care). The duration of active treatment was 48 weeks. There was also a 4-week follow up period after completion of randomized treatment. The primary efficacy endpoints were trough FEV1 response at the end of the 48-week treatment period (Day 337) and time to first COPD exacerbation. There were also a number of other COPD exacerbation secondary endpoints. All discontinued patients were followed up for vital status, and cause of death was adjudicated by an independent mortality committee.

The study was conducted at 336 centers from 31 different countries. Countries were included from Africa, Asia (including India and China), Australia, Eastern Europe, North America, South America, and Western Europe. A total of 3991 male and female patients with stable moderate to severe COPD ($FEV_1 \leq 60\%$ predicted) were randomized; 1989 in the tio R5 group and 2002 in the placebo group. Of these, 3300 (82.7%) completed the study.

6.2.2.2 Protocol 205.372 results

Efficacy

The tiotropium group met both primary endpoints for the study, increase in trough FEV_1 response, and time to first COPD exacerbation. At the end of 48 weeks of treatment, the adjusted mean change from baseline FEV_1 trough value was 0.119L for the tio R5 group as compared to 0.018L in the placebo group. The difference of 0.102L was statistically significant at $p < 0.0001$. A subgroup analysis showed that the treatment difference from placebo was statistically significant regardless of LABA use (0.104L in LABA users and 0.101L in non-LABA users at Day 337). Tio R5 showed a significant benefit on time to first COPD exacerbation, regardless of LABA use. The lower quartile of time to first exacerbation was 169 days in the tio R5 group compared to 119 days in the placebo group ($p < 0.0001$). There were 685/1939 (35.3%) patients overall in the tio R5 group and 842/1953 (43.1%) in the placebo group with at least one exacerbation, giving a Hazard ratio (tio R5/placebo) of 0.693 (95% CI 0.625, 0.769; $p < 0.0001$).

Secondary endpoints included FEV_1 trough and FVC on Day 29, 169, and 337 as well as St. George's Respiratory Questionnaire and a variety of other COPD exacerbation endpoints. The pairwise differences for FEV_1 and FVC between the active group and placebo were statistically significant ($p < 0.0001$) at all time points post-dose on all test days. In general, all secondary COPD exacerbation endpoints were significantly improved in the tio R5 group compared to placebo. For SGRQ, the improvement in total score and in the individual domains were statistically significant ($p < 0.0001$) for the tio R5 group compared to the placebo group on both Day 169 and 337. While the differences between the tiotropium groups and placebo in SGRQ reached a high level of statistical significance, differences of less than 4 as shown in this trial may not be clinically meaningful. The responder analysis, however, did show a significant difference in number of patients with an SGRQ improvement of 4 or greater.

Mortality

Deaths

There were 49 deaths during treatment, 30 (1.5%) in the tio R5 group and 19 (1.0%) in the placebo group. Deaths were also evaluated for a variety of other time periods and cut offs. See Table 70. Including vital status out to Day 337, there were 52 deaths (2.7%) in the tio R5 group and 38 deaths (1.9%) in the placebo group.

Table 70: Protocol 205.372 summary of deaths by treatment interval

	Tio R5 N=1952		Placebo N=1965		Tio R5 vs Placebo	
	n (%)	Incidence density	n (%)	Incidence density	Rate Ratio	(95% CI) p-value
Deaths during actual treatment + 1 day washout						
With death cut off ¹	30 (1.5)	1.81	19 (1.0)	1.18	1.54	(0.87, 2.74) 0.14
Without death cut off ²	41 (2.1)		26 (1.3)			
Deaths during actual treatment + 30 day washout						
With death cut off ¹	44 (2.3)	2.44	31 (1.6)	1.75	1.39	(0.88, 2.21) 0.16
Without death cut off ²	50 (2.6)		34 (1.7)			
Deaths during planned treatment (Day 337)						
With death cut off ¹	52 (2.7)	2.94	38 (1.9)	2.13	1.38	(0.91, 2.10) 0.13
Without death cut off ²	54 (2.8)		42 (2.1)			
Deaths during planned treatment + 30 day washout (Day 367)						
With death cut off ¹	55 (2.8)	2.87	43 (2.2)	2.22	1.29	(0.87, 1.92) 0.21
Without death cut off ²	57 (2.9)		44 (2.2)			

¹Deaths were counted if the onset of the fatal event and the date of death occurred within the interval.

²Deaths were counted if the onset of the fatal event occurred within the interval.

'Actual' refers to the data on treatment; 'planned' includes the vital status follow up of all prematurely discontinued patients.

Reviewer comment:

The Applicant included a variety of analyses of mortality for each of the groupings delineated in Table 70. However, for the purposes of this review, only deaths including vital status at Day 337 with a death cut off are presented. This analysis was prespecified in the statistical analysis plan for the trial and takes into account any potential bias introduced by differential discontinuation. Where appropriate, on treatment deaths (actual treatment plus one day washout with death cut off) are mentioned. Although the numbers differ slightly depending on what data set is used, the conclusions are generally the same.

Cause of death

Adverse events with an outcome of death were most frequent in the general disorders, lower respiratory disorders, and cardiac disorders system organ class (SOC). Adverse events in the general disorders (19 tio R5 vs. 12 placebo, RR=1.60) and cardiac disorders SOCs (9 tio R5 vs. 4 placebo, RR=2.27) were most frequent in the tio R5 group. Adverse events in the lower respiratory disorders were most frequent in the placebo group (tio R5 9 vs. 16 placebo, RR=0.57).

The most frequent causes of death were death of unknown cause, sudden death, COPD exacerbation, and pneumonia. Of the most frequent causes of death, death of unknown cause, sudden death, lung cancer, other cancer, and myocardial infarction occurred more frequently in the tio R5 group. COPD exacerbation, pneumonia, and sepsis occurred more frequently in the placebo group. See Table 71.

Table 71: Protocol 205.372 fatal events by treatment group and most frequent cause of death (planned treatment Day 337) occurring in at least 0.2% of either treatment group

Cause of death[†]	Tio R5 N=1952 n (%)	Placebo N=1965 n (%)	Rate Ratio	p-value (95% CI)
Death (unknown cause)	10 (0.5)	7 (0.4)	1.44	0.46 (0.55, 3.79)
Sudden death	9 (0.5)	5 (0.3)	1.82	0.28 (0.61, 5.42)
COPD exacerbation	4 (0.2)	6 (0.3)	0.67	0.54 (0.19, 2.38)
Pneumonia	1 (0.1)	8 (0.4)	0.13	0.05 (0.02, 1.01)
Sepsis [†]	3 (0.2)	5 (0.3)	0.61	0.49 (0.14, 2.53)
Lung cancer [†]	5 (0.3)	1 (0.1)	5.05	0.14 (0.59, 43.2)
Other cancer	4 (0.2)	2 (0.1)	2.02	0.42 (0.37, 11.02)
Myocardial infarction	3 (0.2)	2 (0.1)	1.51	0.65 (0.25, 9.06)

[†]The groupings of sepsis and lung cancer are per reviewer.

For the purposes of this review, cause of death is reported as adjudicated. The expert panel disagreed with the cause of death as reported by the investigator in 37% of deaths. The majority of these deaths were reclassified from the cardiac or lower respiratory SOC into the general site disorders SOC (death of unknown cause or sudden death).

Reviewer comment:

Of the most frequent causes of death, death of unknown cause, sudden death, and cancer occurred more frequently in the tio R5 group. Under the preferred term of “death” there were 8 cases that were labeled by the investigators as respiratory in origin but were felt by the expert panel to have insufficient information to determine a cause. Under the preferred term sudden death, 8 patients (5 tio R5 and 3 placebo) were initially labeled by the investigators as cardiac. Overall, deaths in the category “sudden death” are more concerning than other categories as they could potentially be caused by an arrhythmic event precipitated by an anticholinergic mechanism.

There were more cancer deaths in the tio R5 group than the placebo group (9 versus 3). Other than lung cancer, the neoplasms were diverse. The apparent differential is less pronounced at D367, with 9 cancer deaths in the tio R5 group and 5 placebo. Of the 9 patients in the tio R5 group, 5 were exposed to drug for less than 100 days, suggesting that the cancers were pre-existing conditions. There was also a differential in serious adverse events in the SOC of neoplasms [29 (1.5%) tio R5 versus 18 (0.9%) placebo, RR=1.58]] as well as an increase in SAEs of lung cancer in the tio R5 group. This differential in cancer deaths has not been observed in other tiotropium studies; thus, may have been due to random chance.

Death by country

Of the 31 countries participating in Protocol 205.372, deaths occurred in 21 of them, with 10 countries reporting no deaths at any investigative site. In general, the countries with no deaths tended to be low enrollers. For the most part, deaths were balanced between treatment groups by country. The country with the highest incidence of death was Mexico, followed by Brazil, Taiwan, and Portugal. The number of deaths by frequency per country is presented in Table 72.

Table 72: Protocol 205.372 mortality by country by frequency and treatment group, including incidence $\geq 2\%$ overall

Country	Tio R5 n/N (%)	Placebo n/N (%)	Total n/N (%)
Mexico	1/40 (2.5)	5/39 (12.8)	6/79 (7.6)
Brazil	0/26	4/30 (13.3)	4/56 (7.1)
Taiwan	3/63 (4.8)	4/66 (6.1)	7/129 (5.4)
Portugal	1/30 (3.3)	2/28 (7.1)	3/58 (5.2)
Hong Kong	1/23 (4.3)	1/23 (4.3)	2/46 (4.3)
Hungary	4/70 (5.7)	2/74 (2.7)	6/144 (4.2)
Malaysia	2/50 (4.0)	2/49 (4.1)	4/99 (4.0)
India	8/165 (4.8)	3/164 (1.8)	11/329 (3.3)
Canada	3/96 (3.1)	3/95 (3.2)	6/191 (3.1)
Korea	3/103 (2.9)	2/99 (2.0)	5/202 (2.5)
China	4/167 (2.4)	4/171 (2.3)	8/388 (2.4)
France	4/121 (3.3)	1/120 (0.8)	5/241 (2.1)

Mortality subgroup analyses by LABA use

The Applicant evaluated all mortality analyses by LABA use, as defined as use at randomization. This subgroup analysis was pre-specified in the SAP. Fifty-three percent of patients were considered to be LABA users. There was a notable interaction between LABA use and mortality. In the overall group, the D337 rate ratio for death was 1.38 (95% CI 0.91, 2.10). For LABA users the RR=1.59 (95% CI 0.85, 2.97), whereas for non-LABA users the RR=1.23 (95% CI 0.70, 2.18). This change was primarily driven by differences in the preferred terms of “death” and “sudden death”, with 12 fatal events in

the tio R5 group versus 3 in placebo for LABA users compared to 7 fatal events (tio R5) versus 9 (placebo) for non-LABA users. See Table 73 for mortality and most frequent cause of death by subgroup.

Table 73: Protocol 205.372 fatal events by treatment group and LABA use for most frequent causes of death (planned treatment D337)

Cause of death [†]	LABA Users			Non-LABA Users		
	Tio R5 N=1058 n (%)	Placebo N=1033 n (%)	Rate Ratio	Tio R5 N=894 n (%)	Placebo N=932 n (%)	Rate Ratio
All causes	26 (2.5)	16 (1.5)	1.59	26 (2.9)	22 (2.4)	1.23
Death (unknown cause)	6 (0.6)	1 (0.1)	5.88	4 (0.4)	6 (0.6)	0.70
Sudden death	6 (0.6)	2 (0.2)	2.94	3 (0.3)	3 (0.3)	1.04
COPD exacerbation	3 (0.3)	3 (0.3)	0.98	1 (0.1)	3 (0.3)	0.35
Pneumonia	0 (0.0)	4 (0.4)	n/a	1 (0.1)	4 (0.4)	0.26
Sepsis	2 (0.2)	4 (0.4)	0.49	1 (0.1)	1 (0.1)	1.04
Lung cancer	0 (0.0)	1 (0.1)	n/a	5 (0.6)	0 (0.0)	n/a
Other cancer	1 (0.1)	1 (0.1)	0.98	3 (0.3)	1 (0.1)	3.13
Myocardial infarction	1 (0.1)	0 (0.0)	n/a	2 (0.2)	2 (0.2)	1.04

[†]The groupings of sepsis and lung cancer are per reviewer.

Reviewer comment:

While some interaction for mortality with LABA use appears to be occurring in this trial, the nature of the interaction is complex. The evaluation is confounded by inhaled corticosteroids, which were used with LABAs in the majority, but not all, patients. There were 8.6% of patients overall who were receiving ICS without a LABA and 5.0% of patients receiving LABAs without ICS. For the ICS alone group, the total number of deaths was 3 (tio R5) versus 8 (placebo), RR=0.42. For the LABA alone group there were 4 deaths (tio R5) versus 0 (placebo). In addition, while patients generally stayed on their baseline medications for the duration of the study, there could have been crossover in concomitant therapies.

Other mortality subgroup analyses

The Applicant also completed a number of post-hoc mortality subgroup analyses. These included age, smoking status, COPD severity at baseline, history of cardiac disease, history of coronary artery disease, history of cardiac arrhythmias, and use of cardiovascular medication at baseline. There was no interaction with tiotropium and age, smoking status, or COPD severity on mortality. As expected, mortality rates did increase in both treatment groups with age and in patients with more severe COPD. The overall rate of fatal adverse events was also higher for ex-smokers as compared to current smokers, probably due to the higher age and greater COPD severity in this group. Subgroup analyses related to cardiac history are discussed separately.

Cardiac disorders

Overall, there were 9 patients (0.5%) in the tio R5 group and 4 (0.2%) in the placebo group with deaths due to cardiac disorders. The overall rate ratio for cardiac events leading to death was 2.27 (95% CI 0.70, 7.37; p=0.17). The cardiac disorders leading to death included acute coronary syndrome (1 tio R5), cardiac arrest (2 tio R5), myocardial infarction (3 tio R5, 2 placebo) and heart failure diagnoses of cardiac failure, cardiac failure congestive, cardiopulmonary failure, and left ventricular failure. Grouping the heart failure diagnoses together gives 3 fatal events in each group.

The Applicant notes that there were four patients (3 tio R5, 1 placebo) who were admitted to the hospital with a COPD exacerbation and developed the cardiac fatal event on the basis of the underlying COPD exacerbation. In addition, there was one patient (tio R5) who developed cardiac failure from an exacerbation of his underlying nephrotic syndrome.

Subgroup analyses of mortality by baseline cardiac history showed an increase in both treatment groups in overall fatal adverse events for patients with a known baseline history of cardiac disease (RR=4.03 tio R5 vs. placebo), and cardiac rhythm disorder (RR=8.61), but not for patients with baseline use of cardiovascular medications, or history of coronary artery disease. Fatal cardiac events were increased in the tiotropium group but not in the placebo group for patients with a baseline history of cardiac disease or cardiac rhythm disorder. See Table 74.

Table 74: Protocol 205.372 mortality subgroup analysis by cardiac history

	Baseline history—No				Baseline history—Yes			
	Tio IR	Pbo IR	RR	95% CI	Tio IR	Pbo IR	RR	95% CI
Cardiac disease¹								
All deaths	2.22	1.78	1.25	0.73-2.14	4.40	2.37	1.86	0.87-3.97
Cardiac deaths	0.44	0.52	0.86	0.29-2.55	2.86	0.71	4.03	1.15-14.13
Coronary artery disease²								
All deaths	2.91	1.79	1.63	1.02-2.60	1.59	2.94	0.54	0.13-2.16
Cardiac deaths	1.05	0.51	2.06	0.89-4.77	1.06	0.98	1.08	0.15-7.67
Rhythm disorder³								
All deaths	2.21	1.90	1.16	0.72-1.90	6.78	3.23	3.23	1.07-9.72
Cardiac deaths	0.57	0.57	1.00	0.40-2.51	4.51	0.52	8.61	1.10-67.23
Cardiovascular medication use⁴								
All deaths	2.73	2.15	1.27	0.73-2.20	2.84	1.60	1.77	0.87-3.60
Cardiac deaths	1.03	0.49	2.11	0.73-6.08	1.08	0.67	1.62	0.53-4.95

IR=incidence rate (per 100 patient years)

¹n=499 tio R5, n=476 placebo with history of cardiac disease

²n=207 tio R5, n=228 placebo with history of coronary artery disease

³n=247 tio R5, n=215 placebo with history of rhythm disorder

⁴n=809 tio R5, n=828 placebo with baseline use of cardiovascular medication

Reviewer comment:

The Applicant correctly points out that there are a number of inherent difficulties in distinguishing the cause from the mode of death, such as in the patients admitted with a COPD exacerbation who had a fatal cardiac event during hospitalization. In addition, some of the fatal events listed under the preferred terms of death and sudden death, could have been cardiac in origin. Also, even for a reasonable sized study, such as this one, subgroup analyses of mortality are limited by the number of events.

In order to address some of these issues, the Applicant performed an analysis of a composite cardiac endpoint at FDA request. The composite cardiovascular endpoint included fatal events in the cardiac and vascular SOCs, non-fatal MI, and non-fatal stroke, along with the preferred terms of sudden death, cardiac death, and sudden cardiac death. The combined cardiovascular endpoint was balanced between the groups, with a RR=1.12 (95% CI 0.67, 1.86), although when non-fatal events were excluded there were an increased number of events in the tiotropium group (22 versus 12; RR=1.80; 95% CI 0.89, 3.63) and confidence intervals are wide.

6.2.2.3 Protocol 205.372 conclusions

Study 205.327, a one year trial of Spiriva Respimat in patients with moderate to severe COPD, met both primary endpoints for the study, increase in trough FEV₁ response and time to first COPD exacerbation. At the end of 48 weeks of treatment, the adjusted mean FEV₁ trough value was 1.111L for the tio R5 group as compared to 1.106L in the placebo group (p<0.0001). Tio R5 also showed a significant benefit on time to first COPD exacerbation, regardless of LABA use (HR=0.693; 95% CI 0.625, 0.769; p<0.0001).

With regards to mortality, this trial showed a small imbalance in favor of placebo. There were 49 deaths during treatment, 30 (1.5%) in the tio R5 group and 19 (1.0%) in the placebo group. Including vital status out to Day 337, there were 52 deaths (2.7%) in the tio R5 group and 38 deaths (1.9%) in the placebo group.

The most frequent causes of death were death of unknown cause, sudden death, COPD exacerbation, and pneumonia. Of the most frequent causes of death, death of unknown cause, sudden death, lung cancer, other cancer, and myocardial infarction occurred more frequently in the tio R5 group. COPD exacerbation, pneumonia, and sepsis occurred more frequently in the placebo group.

There was a notable interaction between LABA use and mortality. This change was primarily driven by differences in the preferred terms of “death” and “sudden death”, with 12 fatal events in the tio R5 group versus 3 in placebo for LABA users compared to 7 fatal events (tio R5) versus 9 (placebo) for non-LABA users. While some interaction for mortality with LABA use appears to be occurring in this trial, the nature of the interaction is complex.

Subgroup analyses of mortality by baseline cardiac history showed an increase in both treatment groups in overall fatal adverse events for patients with a known baseline history of cardiac disease (RR=4.03), and cardiac rhythm disorder (RR=8.61), but not for patients with baseline use of cardiovascular medications, or history of coronary artery disease. A combined cardiovascular endpoint including fatal events in the cardiac and

vascular SOCs, non-fatal MI, and non-fatal stroke, along with the preferred terms of sudden death, cardiac death, and sudden cardiac death was balanced between the groups, with a RR=1.12 (95% CI 0.67, 1.86), although the confidence intervals are wide.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCE
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA: 21-395/N024 and N029

Name of drug: Spiriva HandiHaler (tiotropium bromide)

Indication: Maintenance treatment of bronchospasms associated with COPD, including chronic bronchitis and emphysema

Applicant: Boehringer Ingelheim

Dates: Letter November 17, 2008; PDUFA September 17, 2009

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Spiriva HandiHaler (tiotropium bromide inhalation powder) was approved on January 30, 2004 for long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

The primary objective of the clinical program is to supplement the Clinical Studies section of the product information with additional information to prescribers concerning the long-term (4 year) efficacy and safety of tiotropium in the treatment of patients with COPD, based on the results from the UPLIFT study. The requested efficacy claims are: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure.

From a statistical perspective, because of multiplicity issue in the UPLIFT study, there is insufficient evidence that tiotropium 18 mcg is effective in reducing risk of COPD exacerbation and delaying the onset of COPD exacerbation. On the other hand, there is evidence from the UPLIFT study supporting the labeling claim for long-term effect on lung function. On July 22, 2009, the Applicant amended the efficacy supplement to remove the mortality claim. As noted in the clinical review, reduction in respiratory failure is not supported because the improvement is marginally significant and is not predefined.

A Pulmonary and Allergy Drug Advisory Committee meeting is scheduled on November 19, 2009. The Division plans to discuss the results from the UPLIFT study along with the RESPIMAT data.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

On November 17, 2008, the Applicant, Boehringer Ingelheim (BI), submitted an efficacy supplement to the Spiriva Handihaler NDA 21-395 (under Serial No. 029). In this submission, they provided the clinical trial report from the 4-year multi-center study, titled 'A randomized double-blind, placebo-controlled, parallel group trial assessing the rate of decline of lung function with tiotropium 18 mcg inhalation capsule once daily in patients with COPD' and the associated draft labeling based on the results of this study. Of note, this 4-year multi-national clinical trial is also referred to as the UPLIFT Study, i.e., Understanding Potential Long-term Impacts on Function with Tiotropium.

On January 30, 2009, the Applicant submitted a Complete Response to the FDA November 13, 2008 Complete Response letter for NDA 21-395 Serial No. 024. In this submission, they referred to the data and summaries from the UPLIFT clinical trial (Serial No. 029) to address the Division's comments regarding the reduction in COPD exacerbations, as well as stroke. On June 24, 2009, the Applicant formally withdrew the unapproved supplement Serial No. 024, and formally submitted the information supporting the proposed indication for the reduction of COPD exacerbations from Serial No. 24 to Serial No. 29. On July 22, 2009, the Applicant amended the efficacy supplement to remove the mortality claim to maintain consistency with global labeling. According to the Applicant, there was no new Spiriva Handihaler data contributing to this decision.

The UPLIFT study evaluated 5,992 patients with COPD. Study treatment (tiotropium or placebo) was administered to these patients in addition to their usually prescribed therapy for COPD (including short- and long-term inhaled beta-adrenergics, steroids, or theophyllines but excluding inhaled anticholinergics).

1.3 STATISTICAL ISSUES AND FINDINGS

The Applicant proposed to add 'Long-Term Effect of Lung Function', 'Exacerbation' and 'Survival and Respiratory Failure' in the Clinical Section of the SPIRIVA Handihaler label.

On January 11, 2008, the Applicant submitted the results of a six-month clinical trial with Spiriva HandiHaler (Study 266 or VA study) as pivotal evidence to support inclusion of the 'exacerbation' language in the labeling of Spiriva Handihaler. After careful review of the application, the Division concluded that the submitted data failed to provide substantial evidence of efficacy to support labeling claim for reduction of exacerbation in patients with COPD. In the Action Letter, it stated the following deficiency that precludes approval of the application.

The submitted data do not provide substantial evidence of efficacy to support the labeling claim for reduction of exacerbation in COPD patients. Replicate findings from two adequate and well controlled studies are necessary to support a COPD exacerbation labeling claim. The results from combined analysis of clinical studies 205.254 and 205.255 are not acceptable for replication because these studies were conducted with Spiriva Respimat, 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 HandiHaler compared to placebo.

The Division Director's Memo summarized the results from Study 266

The submitted data failed to show substantial evidence to support a reduction of COPD exacerbation claim for Spiriva HandiHaler. Results of the co-primary efficacy variables for study 266 are shown in Table 13. One of the two co-primary efficacy variables was met in this study and the other efficacy variable showed positive trend. Secondary efficacy variable generally trended in the right direction, but the results were not consistent (additional data not shown in this review). This study, while it may be considered positive, is not sufficiently robust to support approval of the labeling claim.

On January 30, 2009, the Applicant submitted a Complete Response to the FDA November 13, 2008 Complete Response letter for NDA 21-395 Serial No. 024. In this submission, they referred to the data and summaries from the UPLIFT clinical trial (Serial No. 029) to address the Division's comments regarding the reduction in COPD exacerbations, as well as stroke.

In the UPLIFT Study Report, the Applicant claimed the following:

Tiotropium did result in significant improvement in lung functions (i.e. FEV₁, FVC, and SVC, and this improvement was maintained over the four years of the trial. They also claimed that tiotropium reduced the risk of the first COPD exacerbation and the risk of the first COPD exacerbation leading to hospitalization by 14% each. Tiotropium significantly reduced the number of COPD exacerbations by 14%, and reduced the number of exacerbation days by 11%. The two treatment groups had comparable numbers of COPD exacerbations leading to hospitalization and comparable numbers of hospitalization days.

In the UPLIFT study, the co-primary endpoints directly relate to the study objective and these were the focus of the design and power of the study. However, statistical significance was not achieved in favor of tiotropium for these co-primary endpoints in order to continue testing the 'key' secondary endpoints (i.e. time to the first COPD exacerbation and time to the first COPD exacerbation leading to hospitalization) and 'other' endpoints (i.e. estimated mean pre- and post-bronchodilators FEV₁ by

visit), based on a pre-specified multiplicity adjustment strategy. In the strictest sense of alpha spending, all the alpha has been spent by the primary efficacy analyses. Furthermore, evaluating the secondary endpoints (i.e. COPD exacerbation) is “to provide additional clinical characterization of the treatment effect”. Although the observed results (i.e. reduction in risk of COPD exacerbation) were in favor of tiotropium, the evidence from this study is insufficient to support the result from the VA study and to warrant a claim ‘for reduction of exacerbation in patients with COPD’. In the VA study, only one of the two ‘co-primary’ endpoints achieved statistical significance. Similar to the UPLIFT Study, the secondary endpoint (i.e. time-to-first COPD exacerbation) is the basis of the labeling claim ‘for reduction of exacerbation in patients with COPD’. Like the UPLIFT study, multiplicity is a problem in interpreting the result of the secondary endpoint analysis because not all primary endpoints achieved statistical significance. However, as Dr. Davi pointed out in her review, there is a correlation between the primary analysis and secondary analysis of the same outcome (i.e. COPD exacerbation) such that it is unlikely the result of the time-to-first COPD exacerbation analysis is a spurious finding. Nevertheless, the overall conclusion by the Division was that the evidence is insufficient to warrant a claim from the VA study.

Therefore the statistical evidence taken collectively from the VA Study and the UPLIFT study, in particular because of the multiplicity issue in the UPLIFT study, does not support labeling claim for reduction of exacerbation in patients with COPD.

Aside from ‘COPD exacerbation’, the Applicant proposed to add the long-term effect in lung function (FEV₁) in the Clinical Section of the label. They claimed that “SPIRIVA HandiHaler maintained improvements in pulmonary function throughout 4 years. Specifically, SPIRIVA HandiHaler sustained improvements in trough (pre-dose) FEV₁ (adjusted means over time: 87 – 103 mL) throughout the 4 years of the study.” Like COPD exacerbation, multiplicity is a problem in interpreting the results of these secondary analyses (i.e. estimated mean pre- or post-bronchodilator FEV₁). Furthermore, ‘maintenance’ and ‘sustainability’ are hard to quantify when group means are used instead of individual response. In other words, there are no pre-defined criteria that would allow us to determine ‘maintenance’ of effect.

Nonetheless, the current approved label indicated that

SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (forced expiratory volume in one second, FEV₁), with peak effect occurring within 3 hours following the first dose.

In addition, the label described the results from the one-year and the six-month placebo controlled studies. It stated that there is evidence that improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year and the 6-month treatment period, respectively.

The result from UPLIFT study was consistent with the one-year and six-month studies when the mean trough FEV₁ scores were calculated throughout the 4-year period. When continuous responder analyses were performed for each Visit until Month 48, there is evidence that a higher proportion of patients treated with tiotropium responded better compared to the placebo as early as Month 1. Visually, the difference was maintained until Month 48 for the pre-bronchodilator FEV₁, and until at least until Month 24 for the post-bronchodilator FEV₁. Therefore the evidence from the UPLIFT study does support labeling claim for long-term effect in lung function.

The Applicant also proposed to include the following result in the Clinical Section of the label:

Improvement in symptom scores was also seen in patients treated with SPIRIVA HandiHaler compared to placebo.

Based on statistical review of the UPLIFT study, the evidence that there is improvement in symptom score is insufficient to warrant inclusion in the Clinical Section of the Label.

Lastly, the Applicant proposed to add mortality and respiratory failure claims in the Clinical Section of the label. The following is the proposed language:

In the 4-year multicenter trial, there was a 16% reduction in the risk of death while on treatment with SPIRIVA HandiHaler compared to placebo. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.78 per 100 patient years in the placebo group [Hazard Ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97]. Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00].

Like COPD exacerbation and long-term effect in lung function, mortality and respiratory failure are classified as secondary endpoints. However, unlike COPD exacerbation and lung function, the general consensus is that mortality can reach the status of a primary endpoint, if analyzed properly and supported by other study. In papers written by Dr. D'Agostino Sr.¹ and Dr. O'Neill² and several other researchers, they have alluded that a statistically significant finding on mortality has clinical impact. They also stated that the usual reason for designating mortality as a secondary endpoint is that the trialist believes *a priori* that there is little chance a treatment effect will be observed, given the sample sizes and the power to detect a clinically important effect on mortality.

In the UPLIFT Study, there is evidence of a benefit of tiotropium on on-treatment mortality. However, because a different result was observed in another SPIRIVA application using RESPIMAT delivery system, the result from UPLIFT needs to be explored further. Of note, in the RESPIMAT application, an increased number of deaths were observed in the Spiriva Respimat treatment groups compared to placebo for 1-year pivotal trials. As stated in the overview, the Applicant amended the efficacy supplement to remove the mortality claim to maintain consistency with global labeling.

The following is from Dr. Michele's review about the 'respiratory failure claim.

Based on the SAE data, the applicant is requesting a claim for reduction in respiratory failure. BI proposes the following language for the clinical studies section of the label: "In the 4-year multicenter trial. Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI 0.65, 1.00]."

While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term "respiratory failure" is undefined and subject to investigator interpretation. Inclusion of the term respiratory failure may be appropriate as part of adverse event reporting for the study; however, there is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

¹ Ralph D'Agostino Sr., "Controlling alpha in a clinical trial: the case for secondary endpoints", Statistics in Medicine, 2000 19: 763-766

² Robert T. O'Neill, "Secondary Endpoints Cannot be Validly Analyzed if the Primary Endpoint Does Not Demonstrate Clear Statistical Significance", Controlled Clinical Trials, 1997 18: 550-556

2 INTRODUCTION

2.1 OVERVIEW

Spiriva HandiHaler (tiotropium bromide inhalation powder) was approved on January 30, 2004 for long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

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. The recommended dose is inhalation of one Spiriva capsule, once-daily, with the HandiHaler inhalation device. One Spiriva capsule contains 18 mcg tiotropium, which is equivalent to 22.5 mcg tiotropium bromide monohydrate.

On January 11, 2008, Boehringer Ingelheim (BI) submitted an efficacy supplement (Serial No. 024) for Spiriva HandiHaler to add the following labeling claim to the Clinical Studies Section of the product label:

In a 6-month clinical trial of COPD patients in a Veterans Affairs setting, Spiriva HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo and significantly delayed the time to first exacerbation. These findings are supported by a pre-specified combined analysis of two one-year clinical trials using Spiriva Respimat.

The Applicant submitted the results of a six-month clinical trial with Spiriva HandiHaler (Study 266 or VA study) as pivotal evidence to support inclusion of the following language in the labeling of Spiriva Handihaler. In addition, the sponsor references two one-year phase 3 clinical studies with Spiriva Respimat (studies 254 and 255) as supportive evidence; however, the Division of Pulmonary and Allergy Products has determined that these studies are not adequate to support labeling of Spiriva Handihaler as the efficacy performance can be different for different formulations and/or devices. The efficacy results and safety profile from the VA study were reviewed by Ruthanna Davi, Ph.D., a mathematical statistician within the Office of Biostatistics, and Theresa Michele, M.D. and Sally Seymour, M.D. of the Division of Pulmonary and Allergy Products. A Complete Response letter was issued on November 13, 2008. In that letter, the Division provided two comments. Comment 1 identifies the deficiency that precludes approval of this application. Comment 2 is an additional comment, which is not a deficiency that precludes approval of this application.

1. The submitted data do not provide substantial evidence of efficacy to support the labeling claim for reduction of exacerbation in COPD patients. Replicate findings from two adequate and well controlled studies are necessary to support a COPD exacerbation labeling claim. The results from combined analysis of clinical studies 205.254 and 205.255 are not acceptable for replication because these studies were conducted with Spiriva Respimat, 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 HandiHaler compared to placebo.

2. 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. Provide data from an adequate and well-controlled study to address the concerns of stroke. The study should be of adequate duration and power that will allow evaluation of the safety concern.

On November 17, 2008, the Applicant submitted an efficacy supplement to the Spiriva Handihaler NDA 21-395 (under Serial No. 029). In this submission, they provided the clinical trial report from the 4-year multi-center study, titled 'A randomized double-blind, placebo-controlled, parallel group trial assessing the rate of decline of lung function with tiotropium 18 mcg inhalation capsule once daily in patients with COPD' and the associated draft labeling based on the results of this study. Of note, this 4-year multi-national clinical trial is also referred to as the UPLIFT Study, i.e., Understanding Potential Long-term Impacts on Function with Tiotropium.

On January 30, 2009, the Applicant submitted a Complete Response to the FDA November 13, 2008 Complete Response letter for NDA 21-395 Serial No. 024. In this submission, they referred to the data and summaries from the UPLIFT clinical trial (Serial No. 029) to address the Division's comments regarding the reduction in COPD exacerbations, as well as stroke. On June 24, 2009, the Applicant formally withdrew the unapproved supplement Serial No. 024, and formally submitted the information supporting the proposed indication for the reduction of COPD exacerbations from Serial No. 24 to Serial No. 29. On July 22, 2009, the Applicant amended the efficacy supplement to remove the mortality claim to main consistency with global labeling. According to the Applicant, there was no new Spiriva Handihaler data contributing to this decision.

2.2 DATA SOURCES

The electronic submission of this NDA can be found at:

[\\Fdswa150\nonectd\N21395\S_029\2008-11-17\](#)
[\\Fdswa150\nonectd\N21395\S_024\2009-01-30\](#)

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 DESIGN AND ANALYSIS PLAN

The primary objective of the clinical program is to supplement the Clinical Studies section of the product information with additional relevant information to prescribers concerning the long-term (4 year) efficacy and safety of tiotropium in the treatment of patients with COPD, based on the results from the UPLIFT study.

In the original efficacy supplement dated January 11, 2008, the Applicant included reports from one 6-month clinical trial with Spiriva HandiHaler (Study 266). In addition, the sponsor references two one-year phase 3 clinical studies with Spiriva Respimat (studies 254 and 255) as supportive evidence; however, the Division of Pulmonary and Allergy Products has determined that these studies are not adequate to support labeling of Spiriva Handihaler as the efficacy performance can be different for different formulations and/or devices. Statistical review of the efficacy results was conducted by Ruthanna Davi, Ph.D. Please refer to Dr. Davi's review of the design, analysis plan, and efficacy

results of Study 266. Any additional claims by the Applicant in the updated label that were not included in Dr. Davi's review will be presented in this review.

The following is taken from Dr. Davi's review (Conclusions and Recommendations Section).

Study 266 provides evidence that the odds of a COPD exacerbation are reduced by Spiriva Handihaler relative to placebo. The percent of patients with a COPD exacerbation (i.e., one of the primary efficacy endpoints) was statistically significantly lower for Spiriva Handihaler compared to placebo (28% and 32%, respectively with $p=0.04$). The proportion of patients with hospitalization for exacerbation (i.e., the second primary efficacy endpoint) was numerically lower for those patients receiving Spiriva Handihaler than those receiving placebo; however, with a strict alpha of 0.05, the comparison did not reach statistical significance (7% and 10%, respectively with $p=0.06$).

Time-to-event analyses of the primary efficacy endpoints were supportive of the efficacy of Spiriva Handihaler. Analysis of the time-to-first COPD exacerbation endpoint is of particular interest in this submission as the sponsor is proposing this claim in labeling. Because of the expected and observed correlation between this secondary analysis and the primary analysis and because this analysis was a selection from one of a limited number of secondary efficacy endpoints, it is unlikely that the significant result for the time-to-first COPD exacerbation analysis is an artifact of multiplicity. In addition, this type of analysis may be considered more appropriate than the primary analysis in that patients who dropped out of the study are censored.

Numerical results for the primary efficacy endpoints sub-grouped by race and age did not reveal any substantively differing treatment effects.

In this submission, the document provides results from a four-year, multinational, randomized, double-blind, placebo-controlled, Phase 3 study (Study 235), comparing the rate of decline in FEV1 in patients with COPD receiving tiotropium to those receiving placebo in addition to their usual care for COPD (including short- and long-acting inhaled beta-adrenergics, steroids, and theophyllines but excluding inhaled anticholinergics). The study design is summarized as follows:

Following an initial screening period, qualifying patients were randomized to tiotropium or placebo at Visit 2 (allocation ratio of 1:1). The randomization was in blocks of four by country and by site in sequence to prevent imbalanced allocation.

Patients were seen after 1 month on treatment (Visit 3), at 3 months (Visit 4), and then every 3 months until study drug termination (at 4 years). At study drug termination, patients received open-label ipratropium for 30 days. The final visit occurred approximately 30 days post-treatment.

Pulmonary function testing was conducted at the screening visit (Visit 1), randomization visit (Visit 2), Day 30 (Visit 3), and then every 6 months (Visits 5, 7, 9, 11, 13, 15, 17, and 19) until the end of treatment. Final pulmonary function testing was performed 30 days post-treatment.

The St. George's Respiratory Questionnaire (SGRQ) was completed at the randomization visit (Visit 2) and then every 6 months (Visits 5, 7, 9, 11, 13, 15, 17, and 19) until the end of treatment. COPD exacerbations, concomitant therapies, and adverse events were monitored throughout the screening period and the 4-year treatment period.

Of note that with the exception of inhaled anticholinergic agents, randomized patients were permitted to continue to use all of their previously prescribed respiratory medications during the treatment period. These concomitant respiratory medications included stable doses of inhaled corticosteroids, theophyllines, short-acting and long-acting beta agonists, and modest doses of oral corticosteroids.

Two primary efficacy endpoints were examined, which the Applicant referred to as 'co-primary endpoints'. They are:

1. Yearly rate of decline in trough FEV1 from day 30 (steady state) until completion of double-blind treatment. Trough FEV1 is the pre dose value measured approximately 24 hours after the previous dose of study drug.
2. Yearly rate of decline in FEV1 measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after inhalation of salbutamol) from day 30 (steady state) until completion of double-blind treatment.

The key secondary endpoints were time to first COPD exacerbation and time to first COPD exacerbation leading to hospitalization. A COPD Exacerbation was defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular or intravenous) steroids. According to the Applicant,

This is based on data contained in the COPD module of the AE case report form. This will be confined to on-treatment exacerbation only, i.e. the starting date of exacerbation is after the treatment start day, and before the treatment end date (not including the 30-day washout period). All events recorded in the exacerbation module will be included in the efficacy analyses whether or not they meet all components of the protocol definition. Overlapping exacerbations were collapsed into one event. Unless otherwise specified, two exacerbations were considered distinct events if there was at least seven exacerbation-free days between the end of one event and the start of the next.

Other secondary endpoints the Applicant examined were:

1. Yearly rate of decline in trough FVC and slow vital capacity (SVC) from day 30 until completion of double-blind treatment. Trough FVC and SVC are the pre dose values measured approximately 24 hours after the previous dose of study drug.
2. Yearly rate of decline in FVC and SVC measured 90 minutes after inhalation of study drug and ipratropium (and 30 minutes after salbutamol) from day 30 until completion of double-blind treatment.
3. Yearly rate of decline in FEV1, FVC, and SVC prior to ipratropium and salbutamol inhalation from day 1 until completion of the trial (30 days post study drug treatment).
4. Yearly rate of decline in FEV1, FVC, and SVC measured 90 minutes after inhalation of ipratropium (and 30 minutes after inhalation of salbutamol) from day 1 until completion of the trial (30 days post study drug treatment).
5. Estimated mean pre- and post-bronchodilator FEV1, FVC, and SVC from day 30 until completion of double-blind treatment.
6. The rate of decline in trough FEV1, representing lung function 24 hours after inhalation of tiotropium, was chosen as one
7. Yearly rate of decline in St. George's Respiratory Questionnaire (SGRQ) total, impact, symptom, and activity scores from 6 months until completion of double-blind treatment.
8. Estimated mean SGRQ total, impact, symptom, and activity scores from 6 months until completion of double-blind treatment.
9. Some additional endpoints for COPD exacerbations and associated hospitalizations

The analysis plan is described as follows:

Unless otherwise specified for specific analyses, all treated patients with at least 3 acceptable

spirometry test sets from Day 30 onward were included in the analyses for the pulmonary function testing endpoints. Sensitivity analyses were performed for decline in pre- and post-bronchodilator FEV1, FVC, and SVC in patients with at least 1 PFT measurement from Day 30 onward.

The co-primary endpoints of the yearly rate of decline in trough (pre-bronchodilator) FEV1 and the yearly rate of decline in post-bronchodilator FEV1 from Day 30 (steady state) to the end of double-blind treatment were analyzed using the random-effects model with center included as random effects. The pre- and post-bronchodilator FEV1 were assumed to follow linear trends over time. In the random-effects model, the intercept and slope were random coefficients, and their covariance matrix was assumed to be unstructured. Additional analyses for these endpoints include using the two-sample Wilcoxon (Mann-Whitney) rank sum test to compare the treatment groups from Day 1 until completion of the trial, and using a repeated measures ANOVA model with visit as a discrete variable to estimate and compare the mean of pre- and post-bronchodilator FEV1 at each visit from Day 30 between the two treatment groups.

As part of secondary analyses to the primary endpoints, a piecewise linear model with random effects was used to analyze the change of FEV1 from Day 1 to Day 30, and the rate of decline from Day 30 onward. The primary analysis was also carried out with adjusting for baseline covariates. In addition, to accommodate the FDA comments dated May 29, 2008, individual rate of decline from day 30 until completion of double-blind treatment will be calculated by taking the difference between the last on-treatment visit and visit 3 (day 30) divided by the time difference and this difference will be compared using Wilcoxon rank sum test.

The primary endpoint was also analyzed for the subgroups (age, gender, smoking status, baseline concomitant medication use, COPD severity according to GOLD stages, race, region, reversibility, BMI) using a random-effects model. Tables of baseline and demographic data and COPD background characteristics were created for each category of the subgroup analyses.

The two key secondary endpoints of time to the first COPD exacerbation and time to the first COPD exacerbation leading to hospitalization were compared between treatment groups using the log rank test. Additional analyses for these endpoints include: an estimate of the hazard ratio between treatment groups using Cox regression with a single covariate of treatment; the Kaplan-Meier estimate of the probability of not having the event (first COPD exacerbation or first COPD exacerbation requiring hospitalization) for each treatment group.

It was specified in the protocol that the number of COPD exacerbations and the number of hospitalizations for exacerbations will be compared between tiotropium and placebo using the Wilcoxon rank-sum test. For the interim analysis, the Poisson regression adjusted for overdispersion and exposure to treatment was requested for analyzing these two variables. Therefore, for the trial report, in addition to the specified analysis in the protocol, Poisson regression adjusted for overdispersion and exposure to treatment will be performed. In addition to the protocol-specified Wilcoxon rank sum test, the number of exacerbation days and number of days hospitalized due to exacerbation will be analyzed with the Poisson regression adjusted for overdispersion.

To accommodate the FDA comments dated May 29, 2008, all the exacerbation endpoints will be analyzed using the exacerbation data with seven days between distinct events. This data would allow for clear distinction between events. Number of exacerbation and number of exacerbations leading to hospitalization based on the Poisson model will also be analyzed using an exacerbation data with 1 day between events as sensitivity analysis.

Other spirometric endpoints (i.e. FVC or SVC) and SGRQ will be analyzed similar to the co-primary endpoints. Time-to-event will be analyzed using log-rank test and hazard ratio estimated using Cox regression. Count data between treatment groups, calculated by patient-year, will be estimated and compared using Poisson regression adjusting for overdispersion with Pearson's method. Treatment exposure was adjusted as the offset of the model. Count data between treatment groups, calculated per patient will be estimated and compared using Wilcoxon (Mann-Whitney) rank-sum test. For other count data (e.g. number of patients with at least one COPD exacerbation) will be compared using Fisher's exact test.

Of note, missing data were not imputed for the efficacy analyses.

In consideration of multiplicity in hypothesis testing, the following multiple testing strategies were used:

1. As defined in the protocol, hierarchical testing was performed for the co-primary endpoints. First, the rate of decline in pre-bronchodilator FEV1 was compared between the tiotropium and the placebo groups at a significance level of 0.049. If significance was achieved in favor of tiotropium, the rate of decline in postbronchodilator FEV1 results was compared between groups at a significance level of 0.049.
2. In parallel with the testing of the co-primary endpoints, the number of COPD exacerbations leading to hospitalizations per patient year was compared between treatment groups at the significance level of 0.001.
3. If statistical significance was achieved in favor of tiotropium for the co-primary endpoints, hierarchical testing of two key secondary endpoints, time to the first COPD exacerbation and time to the first COPD exacerbation leading to hospitalization, was performed using the log-rank test. First, the time to first exacerbation was tested at 0.049 level of significance. If significance was achieved, the time to the first COPD exacerbation leading to hospitalization was tested at 0.049 level of significance.
4. P-values for testing the co-primary endpoints, the number of COPD exacerbations leading to hospitalizations per patient year, and the two key secondary endpoints were adjusted for interim looks. For the other endpoints, p-values are reported at nominal p-values.

By following this procedure, the overall probability of type I error is protected at 0.05 for the two co-primary endpoints, the number of COPD exacerbations leading to hospitalization per patient year, and the two key secondary endpoints.

Interim analyses were not planned in the protocol. However, after the protocol was finalized, a DSMB Charter was developed and interim analyses were planned. In their report, they stated that

As specified in the DSMB Charter, independent interim safety analyses were conducted and reviewed by the DSMB at approximately 12 months, 24 months, 36 months, 48 months, and 54 months after trial initiation. Also as specified in the DSMB Charter, independent interim efficacy analyses were conducted and reviewed by the DSMB at approximately 24 and 36 months after the trial initiation. At 48 and 54 months, efficacy analyses were conducted and data packages were provided to the DSMB for review in the event they felt it was necessary.

For the final efficacy analyses, the p-values for the co-primary endpoints, number of exacerbations leading to hospitalization, and the two key secondary endpoints were adjusted accordingly (for the DSMB efficacy data reviews at 24 and 36 months).

For the interim analyses, stopping rules were based on the following efficacy endpoints: rates of decline in trough and 90 minutes post-bronchodilator FEV1 (co-primary endpoints) and the number of hospitalizations due to COPD exacerbations. As specified in the DSMB Charter, the type I error for the two co-primary endpoints was controlled at 0.049 level (two-tailed). The type I error for the number of hospitalizations due to COPD exacerbations per patient year was controlled at 0.001 level (two-tailed). The Lan-DeMets spending function for generating O'Brien-Fleming type stopping boundaries was used.

The sample size of 2916 patients per group (or 5832 total) was estimated to detect a difference of 15 mL in the rate of decline in FEV1 between tiotropium and placebo (standard deviation 90 mL) with 90% power assuming 35% patients dropout or without adequate data, and in order to conduct subgroup analyses with adequate power (e.g. 40% current smokers). The assumptions were based on data from previous long-term studies in patients with COPD and data from the one-year and six-month studies of tiotropium. Thus, a total of 6000 patients were planned.

During the course of the trial, the protocol was amended on three occasions. Amendment 1 (dated May 16, 2003) was made to include a validated generic quality of life instrument, the EQ-5D questionnaire. However, because this was added more than midway through the recruitment period, only the last 1235 patients from 13 countries with significant enrollment remaining were included in the study. Amendment 2 (dated November 15, 2005) was made to include the monitoring of long-term outcomes, specifically vital status information (i.e. 4-year mortality follow-up) on all randomized patients who prematurely discontinued from the study. Amendment 3 (dated April 25, 2007) was made to establish an external committee to independently assess the primary cause of death for all fatal cases. Changes in the planned analysis are summarized in Appendix 1.

3.1.2 DISPOSITION OF PATIENTS, DEMOGRAPHY AND BASELINE CHARACTERISTICS

In Study 235, a total of 8020 patients from 490 centers worldwide were screened for participation in the study. Of this, 5,993 patients were randomized into the study and took at least from 487 centers in 37 countries. The first patient was randomized on January 9, 2003. The last patient completed February 22, 2008. According to the Applicant,

Several patients that had completed Visit 1 (screening) assessments and failed the screening period were incorrectly reported as randomizations. As a result, recruitment was stopped December 2003 and re-opened in January 2004 in order to reach the overall recruitment goal. Complete enrollment was achieved in 14 months.

One eligible patient withdrew at the randomization visit, prior to receiving study medication. One patient was randomized twice in error: once to placebo for 18 days (patient number 24741) and once to tiotropium for approximately 3 years (patient number 24780). For this patient, data have been included separately for both treatment exposures.

Table 1 summarizes the patient disposition and Appendix 2 summarizes the treatment exposure.

A total of 2457 (41%) patients prematurely discontinued study medication. Of note, patients were considered 'not prematurely discontinued' if they completed at least 1350 days of treatment and were not discontinued due to adverse events. Like in Study 266 (VA study), fewer patients in the tiotropium group (1,099 patients, 37%) prematurely discontinued trial medication than in the placebo group (1,358 patients, 45%). The highest percentage of discontinuations occurred in the first year of treatment (14% tiotropium, 20% placebo). In the tiotropium group there were 627 (21%) discontinuations due to adverse events and 412 (14%) discontinuations due to administrative reasons; while in the placebo group there were 746 (25%) patients who discontinued due to adverse events and 554 (18%) for administrative reasons. The most common adverse event is the worsening of the disease (i.e. COPD).

Table 1: Patient Disposition

	Placebo N (%)	Tio 18 mcg N (%)	Total N (%)
Screened	--	--	8016 ¹
Not entered / randomized	--	--	2023 ¹
Entered / randomized	3006	2987	5993 ²
Not treated	0	1	1
Treated	3006 (100.0)	2986 (100.0)	5992 (100.0)
Not prematurely discontinued from trial medication ³	1648 (54.8)	1887 (63.2)	3535 (59.0)
Prematurely discontinued from trial medication	1358 (45.2)	1099 (36.8)	2457 (41.0)
Adverse event	746 (24.8)	627 (21.0)	1373 (22.9)
Worsening of disease under study	368 (12.2)	238 (8.0)	606 (10.1)
Worsening of other pre-existing disease	41 (1.4)	40 (1.3)	81 (1.4)
Other adverse event	337 (11.2)	349 (11.7)	686 (11.4)
Administrative	554 (18.4)	412 (13.8)	966 (16.1)
Non compliant with protocol	75 (2.5)	48 (1.6)	123 (2.1)
Lost to follow up	76 (2.5)	64 (2.1)	140 (2.3)
Consent withdrawn	403 (13.4)	300 (10.0)	703 (11.7)
Other	58 (1.9)	60 (2.0)	118 (2.0)

Source data: [Table 15.1.1: 2](#)

¹Reflects the number of patients with case report form data available. Four additional patients were registered in IVRS. Actual total number of patients screened = 8020; actual total number of patients not entered = 2027.

²One patient was randomized twice in error.

³Patients were considered "not prematurely discontinued" if they completed at least 1350 days of treatment and were not discontinued due to an adverse event.

The following patients discontinued the trial due to 'Worsening of disease under study', but did not have an adverse event leading to treatment discontinuation coinciding with the date of termination of trial medication: Tiotropium: 18251, 21672, 21758, 23103, 23166, 26577. Placebo: 17991, 18479, 19013, 19018, 21499, 21812, 26130, 26143

Source: Clinical Study Report page 96 and Table 15.1.1:2, page 166

When patient disposition was analyzed using data provided by the Applicant, there is a discrepancy with patient 22842. In the report, patient 22842 was classified as 'Not prematurely discontinued from trial'. When the data was summarized according to the disposition, although this patient is classified as 'not stopped medication', this patient's extent of exposure is 1330 days and is classified as 'non-completer'. Therefore, there should be 1100 patients who prematurely discontinued from the study not 1099 as reported.

There are total of 93 subjects who dropped out of the study after 1350 days (Table 2). Of these, 43 subjects discontinued due to AE and these subjects are included in Table 1 and 50 subjects dropped out for other reasons. These 50 subjects are classified as 'not prematurely discontinued from trial medication' according to the definition provided by the Applicant. Of note, there are slightly more subjects in Tiotropium group who discontinued after 1350 days compared to placebo; but these proportions are very small.

Table 2: Patient Disposition – Discontinued from trial medication after 1350 days

	Placebo N=3006	Tio 18 mcg N = 2986	Total N = 5992
Administrative	9 (0.3%)	19 (0.6%)	28 (0.5%)
Lost to follow-up	2	4	6
Non compliance to Protocol	3	4	7
Refused to continue medication	4	11	15
Other	7 (0.2%)	15 (0.5%)	22 (0.4%)
AE*	31 (1%)	33 (1%)	64 (1%)
Worsening of disease under study	10	7	17
Worsening of other pre-existing disease	2	2	4
Other AE	19	24	43

* Discontinued due to AE included in Table 1.

The Applicant reported several protocol violations (see Appendix 3 and Appendix 4). Treatment allocation was unblinded for 22 patients during the study (9 in the tiotropium group and 13 in the placebo group). All these patients had experienced at least one adverse event: 8 were related to exacerbations of COPD (6 in the placebo group and 2 in the tiotropium group) and 2 were due to sudden death (1 in each group). A total of 440 patients were reported to have protocol violations; 8% (223 patients) of the tiotropium group and 7% (217 patients) of the placebo group. The majority of protocol violations were due to use of anticholinergics on at least 2 consecutive visits, improper wash out of medication, failure to meet the inclusion criteria of post-bronchodilator FEV1 <70 % of predicted or post-bronchodilator FEV1 <70% of FVC at Visits 1 and 2, or respiratory infection/COPD exacerbation in the 4 weeks prior to screening (Visit 1) or between Visits 1 and 2.

In the Statistical Analysis Plan, the Applicant reported fraudulent PFT data for the following patients and visits: patient 18956 visits 9 and 10, patient 18933 visit 9, patient 18974 visits 7 and 9, patient 18932 visits 3 and 5. This was revealed during an audit at one of the investigator sites (specifically Site #5555, Dr. Kemmerich in Germany). There are 28 patients enrolled in Site DE005555.

Sensitivity analyses will be performed to the efficacy endpoints by excluding patients from Site 5555, by excluding patients who were unblinded, and by excluding patients with protocol violations.

Demographic characteristics of subjects at baseline were generally well balanced across treatment groups (Appendix 5). The majority of subjects were men (75%) and Caucasian (90%). The mean age was 65 years and median weight was 78 kg. The majority of subjects was ex-smokers (70%) and on average smoked 49 packs per year. The average duration of COPD is 10 years. The disease characteristics at baseline, including spirometric endpoints like FEV₁ (Appendix 6) and SGRQ scores (Appendix 7) were also generally similar across the randomized groups. Use of pulmonary medication at baseline, defined as within 2 months of entry, is displayed in Appendix 8. Patients taking pulmonary medication were balanced between the treatment groups. At baseline, a total of 67% patients were taking inhaled corticosteroids (ICS), and 60% patients were on long-acting beta adrenergics (LABA). Overall, 93% patients were taking a pulmonary medication.

The following criteria are used to identify the study population to be analyzed:

- For the analysis of rate of decline in pre- or post-bronchodilator FEV₁, FVC, or SVC, treated patients with at least three corresponding acceptable PFT measurements after (including) Day 30 (Visit 2) until the completion of double-blinded treatment (Visit 19) were included. As a sensitivity analysis, the analysis of rate of decline was conducted for patients with at least 1 acceptable PFT measurement between Day 30 and completion of double-blinded treatment.
- For the analysis of rate of decline in the SGRQ activity, impact, symptom and total scores, patients with at least 2 measurements between (including) months 6 (Visit 5) and the completion of double-blinded treatment (Visit 19) were included. As a sensitivity analysis, rate of decline for the SGRQ endpoints was estimated for patients with at least 1 measurement between Visits 5 and 19. Turkish patients (N=128, or 2% of the treated set) were not included for the analysis of SGRQ endpoints due to a missing question in the Turkish version of the questionnaire.
- Evaluation of the secondary endpoints associated with COPD exacerbation and COPD exacerbation leading to hospitalization was performed for the treated set defined as all patients who were randomized and treated with at least one dose of the study medication.

The following (Table 3) summarizes the number of patients included for the analysis of the efficacy endpoints.

Table 3: Patients included for the analysis of the efficacy endpoints

	Placebo N (%)	Tio 18 mcg N (%)	Total N (%)
Total treated (treated set)	3006 (100.0)	2986 (100.0)	5992 (100.0)
PFT*			
Post-bronchodilator FEV ₁	2410 (80.2)	2554 (85.5)	4964 (82.8)
Post-bronchodilator FVC	2410 (80.2)	2554 (85.5)	4964 (82.8)
Post-bronchodilator SVC	2383 (79.3)	2527 (84.6)	4910 (81.9)
Pre-bronchodilator FEV ₁	2413 (80.3)	2557 (85.6)	4970 (82.9)
Pre-bronchodilator FVC	2413 (80.3)	2557 (85.6)	4970 (82.9)
Pre-bronchodilator SVC	2374 (79.0)	2531 (84.8)	4905 (81.9)
SGRQ**			
Activity score	2362 (78.6)	2505 (83.9)	4867 (81.2)
Impact score	2362 (78.6)	2505 (83.9)	4867 (81.2)
Symptom score	2364 (78.6)	2512 (84.1)	4876 (81.4)
Total score	2362 (78.6)	2505 (83.9)	4867 (81.2)

Source data: [Table 15.1.3: 1](#).

* Including patients with at least 3 acceptable measurements between Visits 3 and 19;

** Including patients with at least 2 measurements between Visits 5 and 19; excluding Turkish patients.

Source: Clinical Study Report, Table 11.1:1 page 101

3.1.3 PRIMARY EFFICACY ENDPOINTS

The two primary endpoints, rates of decline of pre- and post-bronchodilator FEV₁, did not achieve statistical significance (Table 4). When sensitivity analyses (1 – 3) were performed, similar results of no significant treatment difference were observed. Additional analyses (Sensitivity #4 – #5) were conducted by the Applicant. These are done by applying nonparametric test to compare the change in lung function (i.e. FEV₁) from Day 1 until completion of the trial, and from Day 30 until

completion of the double-blind treatment period. Although the treatment difference for post-bronchodilator was statistically significant when comparing the change in FEV1 from Day 1 until completion of the trial (p-value=0.0145), 44% of patients did not have end of trial visit and were excluded from the analysis. Therefore, the result may not be reliable. I also conducted additional analyses to the primary endpoint (Sensitivity Analyses # 6 to # 8) by excluding patients from Site 5555, by excluding patients who were unblinded, and by excluding patients with protocol violations, respectively. Similar results of no significant treatment difference were observed.

The Applicant also conducted subgroup analyses on the primary endpoints. The subgroups were pre-specified as follows: age (<55; 55-<65; 65-<75; ≥75 years), gender (male; female), smoking status (smoker; ex-smoker), baseline LABA use (yes; no), baseline ICS use, baseline use of ICS and LABA combination, baseline anticholinergic use, GOLD stage (I/II; III; IV), race (Asian; Black; White), region (Asia; Eastern Europe; Western Europe; Latin America; USA), reversibility, and BMI (<20; 20-<25; 25-<30; ≥30 kg/m²). The results from subgroup analyses are summarized in Appendix 9. There were no significant treatment-by-subgroup interactions detected in any subgroups. There was a treatment difference in the rate of decline in post-bronchodilator FEV1 observed in GOLD stage I/II patients. None of the other subgroups showed any treatment difference.

Additional subgroup analysis was conducted by the Applicant based on the change of smoking status (i.e. sustained ex-smokers, sustained smokers, and intermittent smokers/ex-smokers). The rates of decline in pre- or post-bronchodilator were comparable between the treatment groups for all smoker subgroups.

Table 4: Rate of decline in pre- or post-bronchodilator FEV₁ from Day 30 until completion of double-blind treatment

	Placebo		Tiotropium			Difference	
	N	Mean (SE) [ml/yr]	N	Mean (SE) [ml/yr]	Mean (SE) [ml/yr]	95% CI	p-value
Primary							
Pre-BD	2413	-30 (1)	2557	-30 (1)	0 (2)	(-4, 4)	0.9524
Post-BD	2410	-42 (1)	2554	-40 (1)	2 (2)	(-2, 6)	0.2074
Sensitivity #1							
Pre-BD	2863	-29 (1)	2906	-29 (1)	-0 (2)	(-4, 4)	0.9791
Post-BD	2851	-41 (1)	2904	-39 (1)	2 (2)	(-2, 6)	0.2367
Sensitivity #2							
Pre-BD	2413	-30 (1)	2557	-30 (1)	0 (2)	(-4, 4)	0.9017
Post-BD	2410	-43 (1)	2554	-40 (1)	3 (2)	(-1, 7)	0.1662
Sensitivity #3							
Pre-BD	2413	-31 (1)	2557	-31 (1)	0 (2)	(-4, 4)	0.8886
Post-BD	2410	-43 (1)	2554	-41 (1)	3 (2)	(-1, 7)	0.1738
Sensitivity #4							
Pre-BD	2385	-28	2532	-29			0.4357
Post-BD	2389	-41	2534	-38			0.1072
Sensitivity #5							
Pre-BD	1618	-17	1803	-15			0.2488
Post-BD	1613	-32	1805	-27			0.0145
Sensitivity #6							
Pre-BD	2403	-30 (1)	2547	-30 (1)	0 (2)		0.9349
Post-BD	2400	-42 (1)	2544	-40 (1)	3 (2)		0.1886
Sensitivity #7							
Pre-BD	2405	-30 (1)	2549	-30 (1)	0 (2)		0.9293
Post-BD	2403	-42 (1)	2546	-40 (1)	2 (2)		0.1940
Sensitivity #8							
Pre-BD	2233	-31 (1)	2368	-30 (1)	0 (2)	(-4, 4)	0.8626
Post-BD	2229	-42 (1)	2364	-40 (1)	2 (2)	(-2, 6)	0.2026

Pre-BD: pre-bronchodilator FEV₁ Post-PB: post-bronchodilator FEV₁
Statistical Method: Random effects model with intercept and slope as random coefficients, assuming pre- and post-bronchodilator FEV₁ following linear trend and assuming covariance matrix as unstructured.

Primary: treated set with at least 3 measurement after (including) day 30 until completion of double-blind treatment.

Sensitivity #1: analysis of primary endpoint based on treated set with at least 1 measurement after (including) day 30

Sensitivity #2: analysis of primary endpoint with center as random effect

Sensitivity #3: analysis of primary endpoint when adjusted for baseline covariates, including post-bronchodilator FEV₁, age, sex, height and smoking status in the random effect model.

Sensitivity #4: Re-analysis of the rate of decline in FEV₁ from Day 30 until end of treatment using non-parametric approach. Median scores are reported for the difference in FEV₁ at last on-treatment visit and on Day 30, divided by the duration between visits. P-values were calculated based on Wilcoxon Rank Sum test.

Sensitivity #5: Rate of decline in FEV₁ from Day 1 until end of trial using non-parametric approach. Median scores are reported for the difference in FEV₁ at last trial visit and on Day 1, divided by the duration between visits. P-values were calculated based on Wilcoxon Rank Sum test.

Sensitivity #6: Reviewer's excluding site 5555 (Dr. Kemmerich) from the primary analysis

Sensitivity #7: Reviewer's excluding patients that were unblinded from the primary analysis

Sensitivity #8: Reviewer's excluding patients that had protocol violations from the primary analysis

Source: Clinical Study Report, Table 11.4.1.1.1 (page 107), Table 15.2.1.7 (page 386), Table 15.2.1.13 (page 392), and Table 15.2.1.6 (page 385), Table 15.2.1.14 (page 393), and . Table 11.4.1.2.2.1 (page 112)

The following two figures describe the time course of the FEV₁ pre- and post-bronchodilator. Of note, these figures include all available data and are based on raw means.

Figure 1: Time course of FEV₁ prior to bronchodilators on the test days

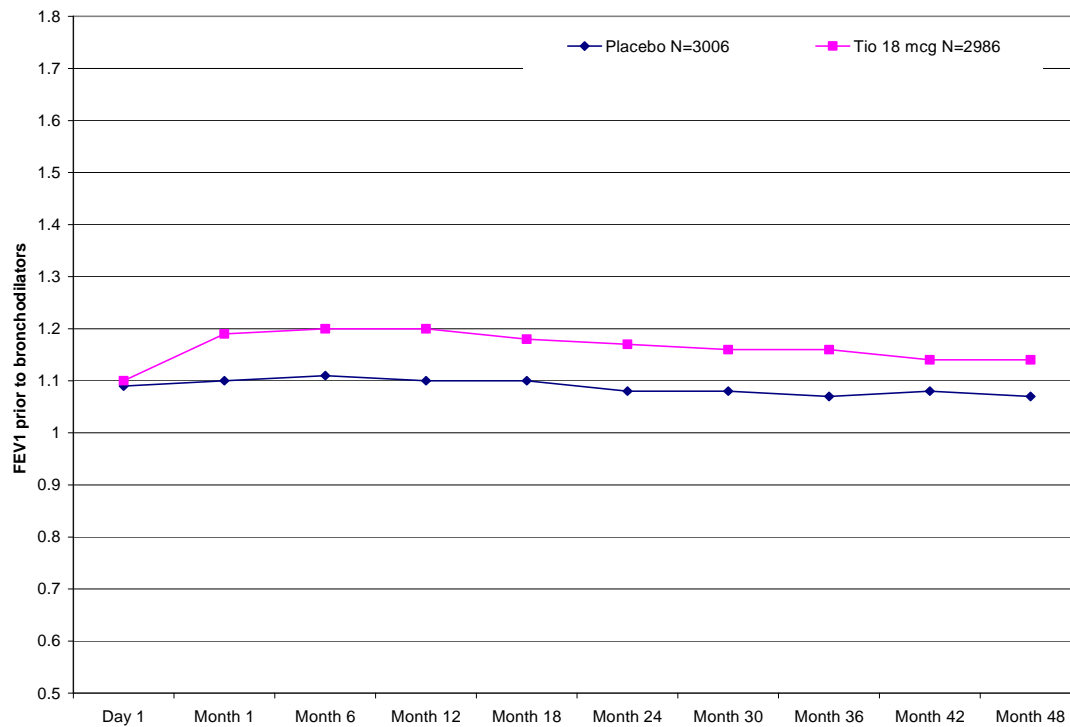
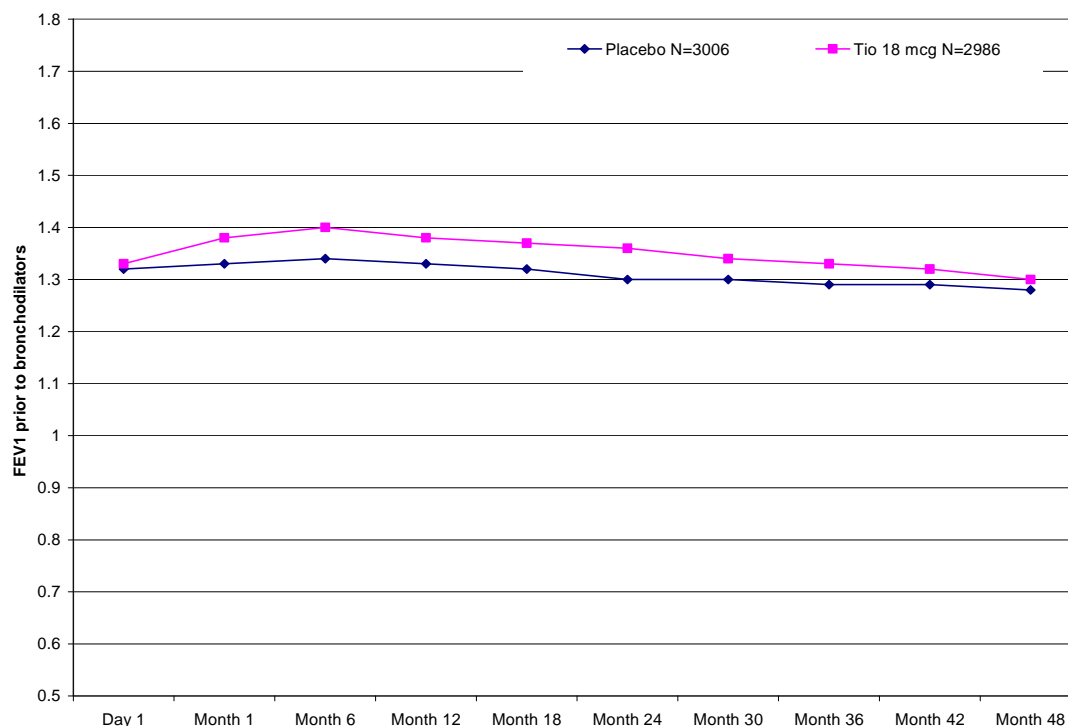


Figure 2: Time course of FEV₁ post-bronchodilators on the test days



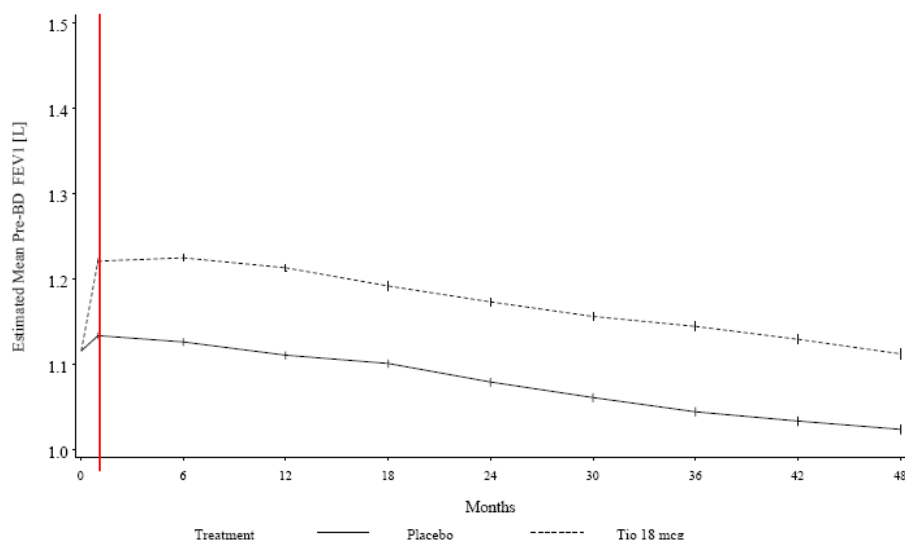
Additional Analyses

The Applicant also assessed the pre- and post-bronchodilators FEV₁ by comparing the overall mean treatment difference and by comparing treatment difference of the mean pre- and post-bronchodilators FEV₁ by visit. The results are presented in Figure 3 and Figure 4 and summarized in Appendix 10. There is an initial increase of 105 ml and 71 ml in mean pre- and post-bronchodilator FEV₁, respectively, at Visit 3 (Day 30 – vertical line) from baseline in the tiotropium group compared to 18 ml and 25 ml in mean pre- and post-bronchodilator FEV₁, respectively, in the placebo group. The treatment difference in the mean pre- and post-bronchodilators FEV₁ was evident as early as Day 30 and was maintained throughout the trial. Despite the concurrent administration of ipatropium and salbutamol in both treatment groups after inhalation of study drug, the mean post-bronchodilators FEV₁ was consistently higher in the tiotropium group compared to the placebo group.

For the mean pre-bronchodilator FEV₁, the estimated mean treatment difference ranged from 87 to 103 ml and an overall mean difference of 94 ml. For the mean post-bronchodilator FEV₁, the estimated mean treatment difference ranged from 47 to 65 ml and an overall mean difference of 57 ml.

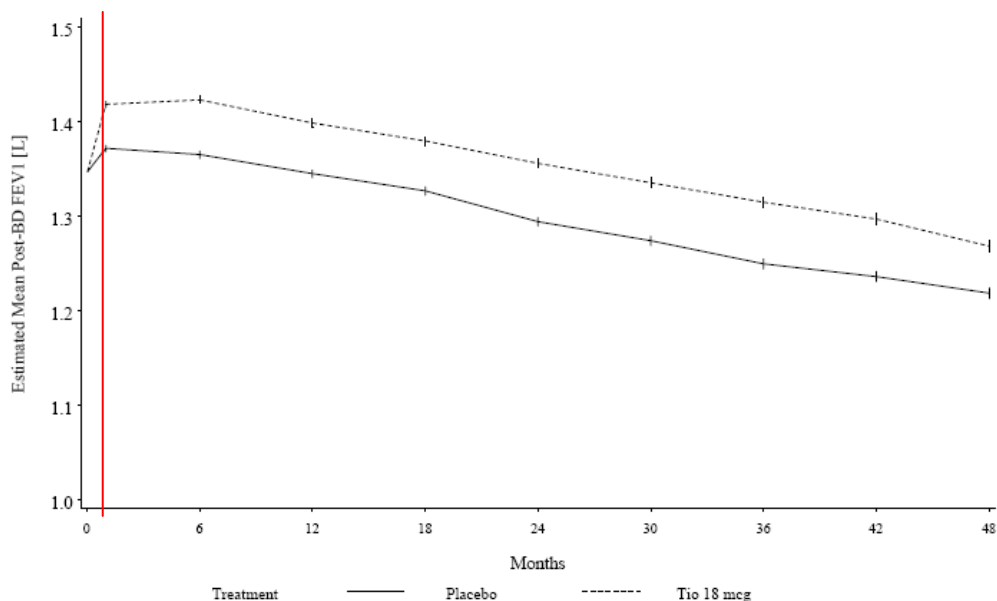
I conducted additional analyses to assess the sensitivity of the results when some patients are removed from the analysis. The results are summarized in Table 5 for the overall mean difference and are in agreement with the Applicant's results.

Figure 3: Estimated* mean FEV₁ pre-bronchodilators by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48)



Source: Clinical Study Report, Figure 11.4.1.2.2:1 page 111; *Estimated (least squares) means are based on repeated measures ANOVA model with visit as a discrete variable and baseline value as a covariate.

Figure 4: Estimated* mean FEV₁ post-bronchodilators by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48)



Source: Clinical Study Report, Figure 11.4.1.2.2:2 page 112; *Estimated (least squares) means are based on repeated measures ANOVA model with visit as a discrete variable and baseline value as a covariate.

Table 5: Estimated* mean pre- or post-bronchodilator FEV₁ from Day 30 until completion of double-blind treatment - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48)

	Treatment		Mean (SE) [ml/yr]	Difference	
	Placebo Mean (SE)	Titropium Mean (SE)		95% CI	p-value
Original					
Pre-BD	1.080 (0.004)	1.174 (0.004)	0.094	(0.084, 0.105)	<0.0001
Post-BD	1.298 (0.004)	1.354 (0.004)	0.057	(0.046, 0.067)	<0.0001
Sensitivity #1					
Pre-BD	1.080 (0.004)	1.174 (0.004)	0.094	(0.084, 0.105)	<0.0001
Post-BD	1.298 (0.004)	1.354 (0.004)	0.057	(0.046, 0.067)	<0.0001
Sensitivity #2					
Pre-BD	1.080 (0.004)	1.175 (0.004)	0.095	(0.084, 0.105)	<0.0001
Post-BD	1.298 (0.004)	1.355 (0.004)	0.057	(0.047, 0.068)	<0.0001
Sensitivity #3					
Pre-BD	1.086 (0.004)	1.180 (0.004)	0.094	(0.084, 0.105)	<0.0001
Post-BD	1.305 (0.004)	1.362 (0.004)	0.057	(0.047, 0.068)	<0.0001
Sensitivity #4					
Pre-BD	1.074 (0.004)	1.168 (0.004)	0.095	(0.085, 0.104)	<0.0001
Post-BD	1.291 (0.004)	1.346 (0.004)	0.055	(0.045, 0.065)	<0.0001

*Estimated (least squares) means are based on repeated measures ANOVA model with visit as a discrete variable and baseline value as a covariate.

Sensitivity #1: Excluding site 5555 (Dr. Kemmerich) from the analysis

Sensitivity #2: Excluding patients that were unblinded from the analysis

Sensitivity #3: Excluding patients that had protocol violations from the analysis

Sensitivity #4: analysis of endpoint based on treated set with at least 1 measurement after (including) day 30

Responder Analyses

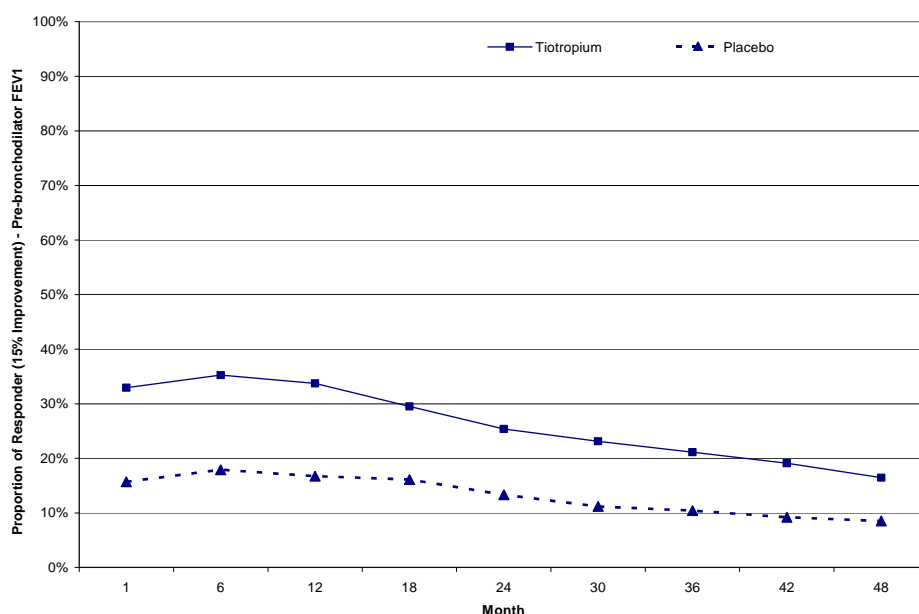
An alternate way to view the treatment effect is to explore the proportion of patients who had at least 15% improvement in pre- and post-bronchodilators FEV₁ at each Visit from baseline. Only patients with baseline score and had at least 3 measurements between Months 1 to 48 are included in the calculation. Patients who discontinued from the study regardless of reason are considered non-responders. Last observed FEV₁ score is imputed to missing post-baseline FEV₁ scores. Of note, patients who responded at one time point do not necessarily respond to other time points.

The results are presented in Figure 5 and Figure 6, for pre- and post-bronchodilators FEV₁, respectively.

At Month 1, 33% of patients treated with tiotropium achieved the level of response (i.e. 15% improvement from baseline) in (trough) pre-bronchodilator FEV₁ compared to 16% in the placebo group (i.e. 17% treatment difference in the proportions of responder). At Month 48, there is roughly 7% difference in the proportions of responder between tiotropium (16%) and placebo (9%).

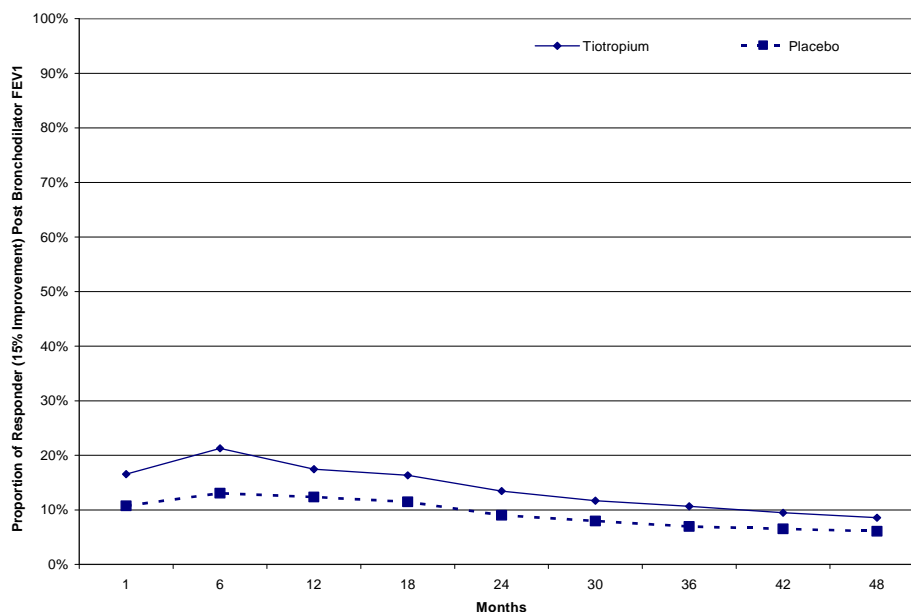
For post-bronchodilator FEV₁, the proportions of responder in both treatment groups are generally smaller compared to when pre-bronchodilator FEV₁ measurements are used. However, the proportion of responder remains higher in the tiotropium group compared to the placebo group across all visits, particularly prior to Year 1 (or Month 12).

Figure 5: Proportion of Responders* (i.e. 15% Improvement from baseline) Pre-Bronchodilator FEV₁ by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score



*Note: Patients who responded at one time point do not necessarily respond across all time points

Figure 6: Proportion of Responders (i.e. 15% Improvement from baseline) Post-Bronchodilator FEV₁ by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score



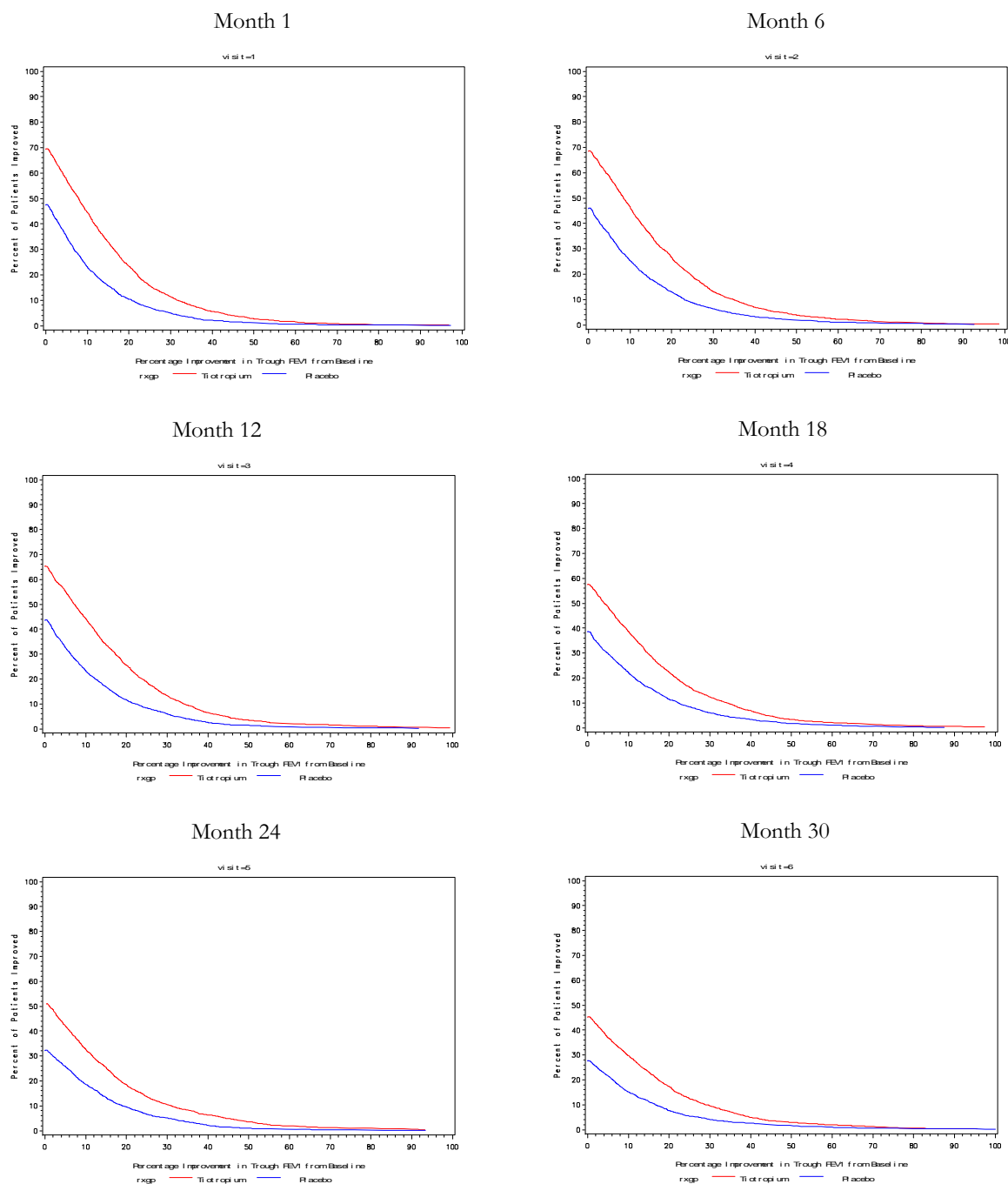
*Note: Patients who responded at one time point do not necessarily respond across all time points

Continuous responder analyses by Visit are explored for the pre- and post-bronchodilators FEV₁ scores (Figure 7 and Figure 8, respectively). In these plots, only patients with baseline score and had at least 3 measurements between Months 1 to 48 are included in the calculation. Patients who discontinued from the study regardless of reason are considered non-responders. Last observed FEV₁ score is imputed to missing post-baseline FEV₁ scores.

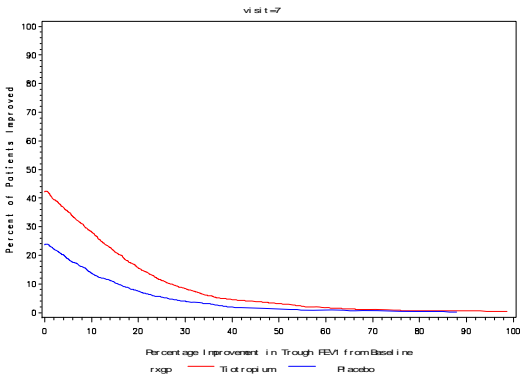
These figures were created to provide a visual display of the relative benefit of tiotropium across the entire range of response, as well over the period of double-blind treatment. The x-axis shows the percent improvement in FEV₁ score from baseline to endpoint, and the y-axis shows the corresponding percentage of patients achieving that level of response.

From the plots for pre- and post-bronchodilators FEV₁ scores there is clear evidence that a higher proportion of patients treated with tiotropium responded better compared to the placebo as early as Month 1. Visually, the difference was maintained until Month 48 for the pre-bronchodilator FEV₁, and until at least until Month 24 for the post-bronchodilator FEV₁.

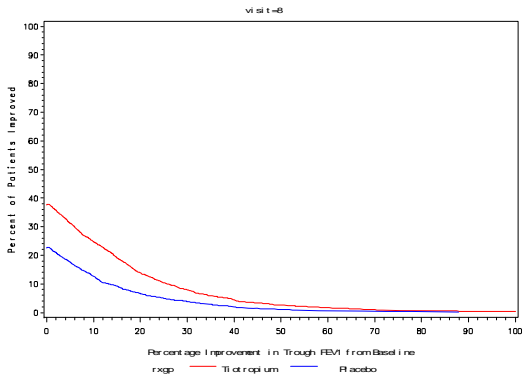
Figure 7: Response Profile Pre-Bronchodilator FEV₁ by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score



Month 36



Month 42



Month 48/EOT

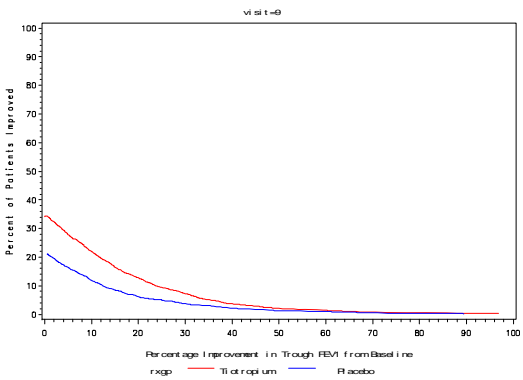
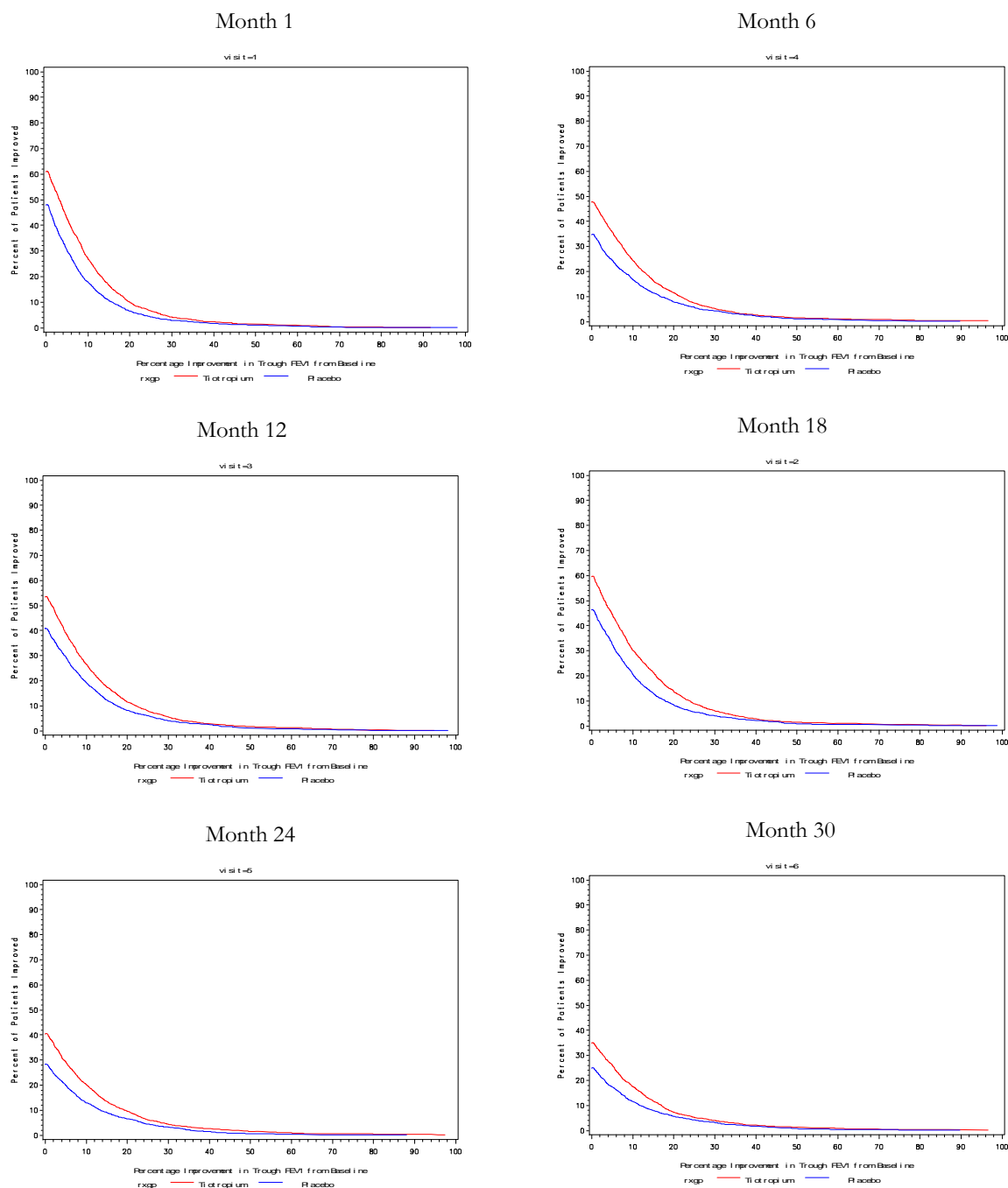
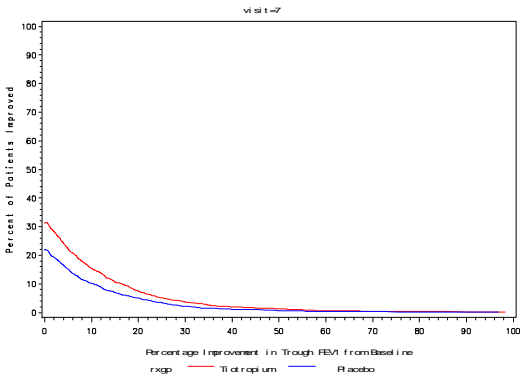


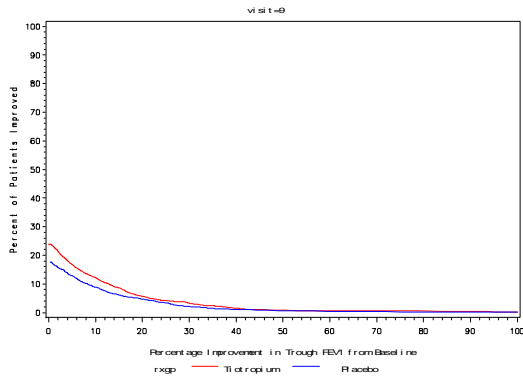
Figure 8: Response Profile Post-Bronchodilator FEV₁ by Visits – treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score



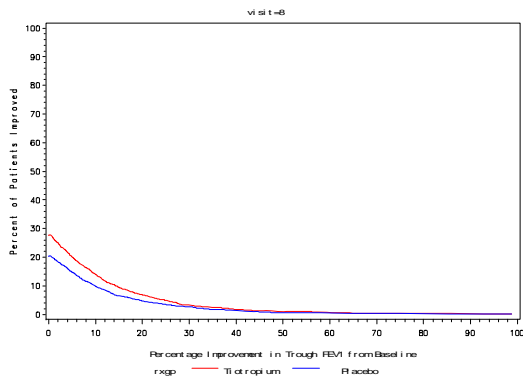
Month 36



Month 42



Month 48/EOT



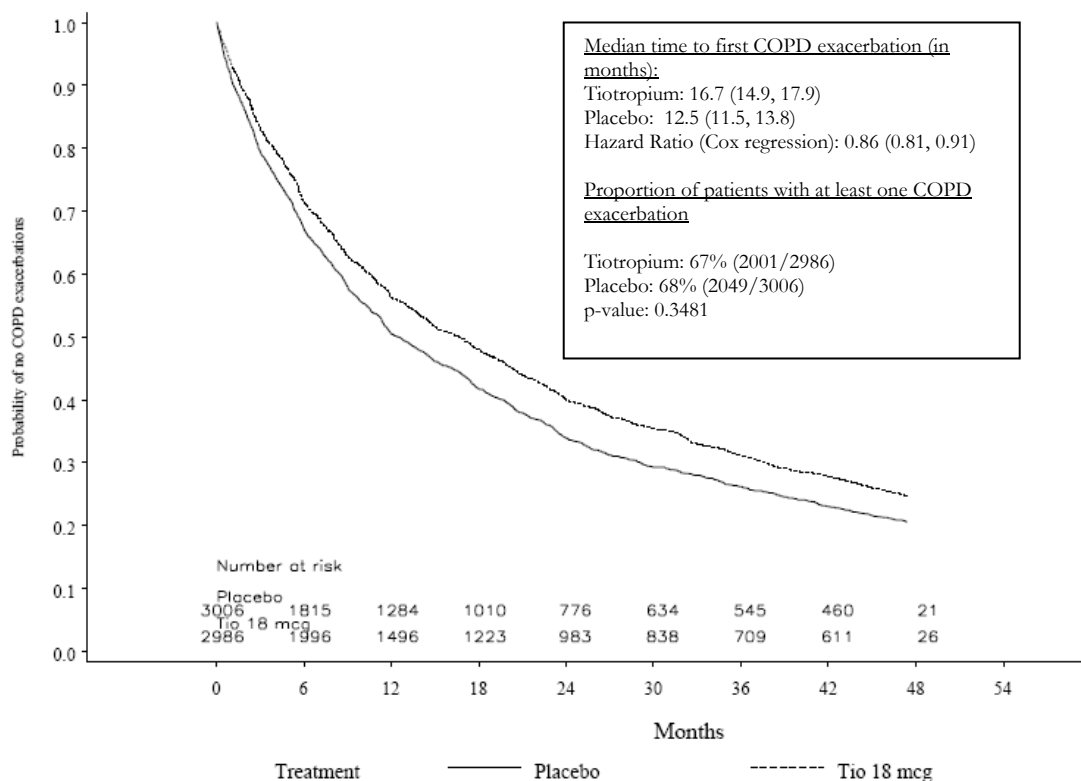
3.1.4 KEY SECONDARY ENDPOINTS

Time to the first COPD exacerbation

Figure 9 presents the Kaplan-Meier estimates of the probability of no COPD exacerbation. Although there is no treatment difference in the proportion of patients with at least one COPD exacerbation, data suggests that tiotropium reduced the risk of COPD exacerbation by 14% compared with placebo. This is based on the estimated hazard ratio (using Cox model) of 0.86 [95% CI: (0.81, 0.91)] between tiotropium and placebo. Furthermore, based on Kaplan-Meier estimates, the median time to first COPD exacerbation in the tiotropium group is 16.7 months compared to 12.5 months in the placebo group. This implies a four-month delay in the time to first exacerbation in the tiotropium-treated patients compared to placebo-treated patients.

Additional analyses were conducted to assess the COPD exacerbations and the results are summarized in Table 6. The results that tiotropium reduced the risk of COPD exacerbation by about 14% were consistent when patient-year is applied or when COPD exacerbation were explored in patients treated with steroids or treated with antibiotics.

Figure 9: Kaplan-Meier estimates of the probability of no COPD exacerbation – treated set



Source: Clinical Study Report, Figure 11.4.1.2.1:1, page 109, Table 15.2.5.1:2 page 427, Table 14.2.5.2:4 page 434

Table 6: Analysis of COPD exacerbation

	Placebo N=3006 PY=8499.46	Tiotropium N=2986 PY=9222.31	Ratio or Difference 95% CI	p-value
Median time to first exacerbation (months)*	12.5	16.7	HR: 0.86 (0.81, 0.91)	<0.0001
No. of patients with at least one exacerbation†	2049 (68%)	2001 (67%)		0.3481
Estimated no. (rate) of COPD exacerbations per patient year ‡	7183 (0.85)	6691 (0.73)	Ratio: 0.86 (0.81, 0.91)	<0.0001
Patients treated with steroids				
Median time to first exacerbation (months)*	26.4	36.5	HR: 0.84 (0.78, 0.90)	<0.0001
No. of patients with at least one Exacerbation†	1561 (52%)	1490 (50%)		
Estimated no. (rate) of COPD exacerbations per PY‡	4432 (0.52)	4051 (0.44)	Ratio: 0.84 (0.78, 0.91)	<0.0001
Patients treated with antibiotics				
Median time to first exacerbation (months)*	16.2	19.8	HR: 0.87 (0.81, 0.93)	<0.0001
No. of patients with at least one Exacerbation†	1917 (64%)	1887 (63%)		
Estimated no. (rate) of COPD exacerbations per PY‡	6076 (0.71)	5741 (0.62)	Ratio: 0.87 (0.82, 0.93)	<0.0001

*Hazard ratio based on Cox model with single covariate treatment; p-value was obtained using log-rank test.

†p-value was calculated using Fisher's exact test

‡Ratio and p-value were calculated using Poisson regression adjusting for overdispersion with Pearson's method. Treatment exposure was adjusted as the offset of the model. Of note, two exacerbation events were considered distinct if there were a 7-day gap.

Source: Clinical Study Report Table 15.2.5.1:2, page 427; Table 15.2.5.2:4, page 434, Table 11.4.1.2.2:4, page 121, Table 15.2.5.1:3 page 428, Table 14.2.5.2 :6, page 436, Table 15.2.5.1:4 page 429, Table 14.2.5.2 :7, page 437

When comparing time to first COPD exacerbation between treatment groups, patients who dropped out of the study are considered 'censored' observations, and assume they are noninformative. In fact, the results generated in Figure 9 and Table 6 all considered dropouts as being noninformative. However, COPD exacerbation is an adverse event and most likely correlated with other adverse events. This implies that patients who discontinued from the study due to adverse events and did not have exacerbation may likely to exacerbate if they continue from the study. In Table 7, with and without COPD exacerbation are explored by patient disposition. The objective is to explore if there is a difference in the proportion of discontinued patients (particularly due to AE) among those with exacerbation and without exacerbation. Although a higher proportion of patients in the 'without exacerbation' group discontinued from the study, the magnitude of the difference between treatment groups are the same in the 'with exacerbation' group and the 'without exacerbation' group. In particular, the magnitude of the difference between treatment groups in the proportion that discontinued due to AEs is almost the same in the 'with exacerbation' group and the 'without exacerbation' group. Thus, additional analysis assigning patients who discontinued as 'with exacerbation' will most likely yield the same conclusion.

Table 7: Patient with at least one exacerbation by Disposition

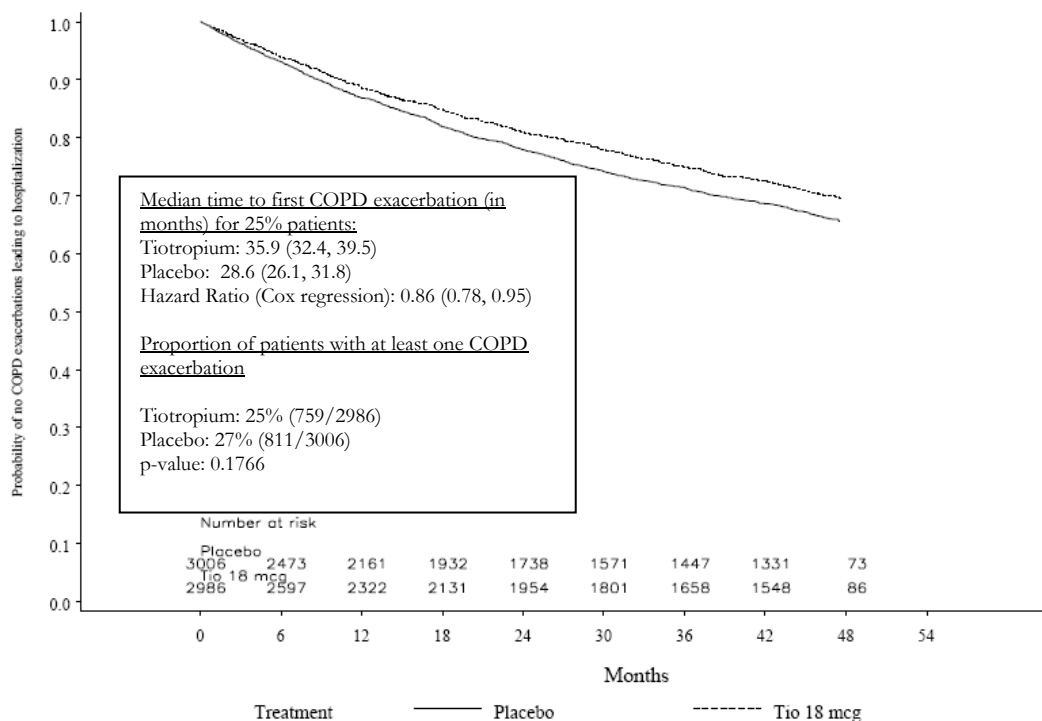
	With Exacerbation		Without Exacerbation	
	Placebo N=2049	Tiotropium N=2001	Placebo N=957	Tiotropium N=985
Completed	1245 (61%)	1356 (68%)	403 (42%)	531 (54%)
Discontinued	804 (39%)	645 (32%)	554 (58%)	454 (46%)
AE	502 (25%)	421 (21%)	244 (26%)	206 (21%)
Lost to Follow-Up	26 (1%)	22 (1%)	50 (5%)	42 (4%)
Refused to Continue Medication	203 (10%)	149 (7%)	200 (21%)	151 (15%)
Other	73 (4%)	53 (3%)	60 (6%)	55 (6%)

Time to the first COPD exacerbation leading to hospitalization

The Kaplan-Meier estimates of the probability of no COPD exacerbation leading to hospitalization is presented in Figure 10. This includes a subset of patients with COPD exacerbation (i.e. patients that were hospitalized), thus the sample (numerator) is smaller. Similar to COPD exacerbation, although there is no treatment difference in the proportion of patients with at least one COPD exacerbation leading to hospitalization, there is some evidence that tiotropium reduced the risk of COPD exacerbation leading to hospitalization by 14% compared with placebo (Table 8). This is based on the estimated hazard ratio (using Cox model) of 0.86 [95% CI: (0.78, 0.95)] between tiotropium and placebo. Based on Kaplan-Meier estimates, the median time to first COPD exacerbation leading to hospitalization in 25% patients in the tiotropium group is 35.9 months compared to 28.6 months in the placebo group. This implies a seven-month delay in the time to first exacerbation leading to hospitalization in the tiotropium-treated patients compared to placebo-treated patients.

A Poisson model with adjustment for overdispersion was used to estimate the mean number of exacerbation leading to hospitalization. Log-exposure was used in the model as the offset. The treatment difference measured by rate ratio, 0.94 [95% CI (0.82, 1.07)] for tiotropium vs. placebo, was not significant (p-value=0.3413).

Figure 10: Kaplan-Meier estimates of the probability of no COPD exacerbation leading to hospitalization – treated set



Source: Clinical Study Report, Figure 11.4.1.2.1:2, page 110, Table 15.2.6.1:2 page 444

Table 8: Analysis of COPD exacerbation leading to hospitalization

	Placebo N=3006 PY=8499.46	Tiotropium N=2986 PY=9222.31	Ratio or Difference 95% CI	p-value
Median time to first exacerbation (months) For 25% patients	28.6	35.9	HR: 0.86 (0.78, 0.95)	0.0024
No. of patients with at least one exacerbation	811 (27%)	759 (25%)		0.1766
Estimated no. (rate) of COPD exacerbations per patient year	1379 (0.16)	1403 (0.15)	Ratio: 0.94 (0.82, 1.07)	0.3413

Source: Clinical Study Report Table 15.2.6.1:2 page 444, Table 14.2.6.2:3 page 448, Table 15.2.6.2:1 page 446

3.1.5 ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

For SGRQ endpoints, an increase in scores indicated worsening of quality of life, while a decrease indicated improved quality of life.

Random effects model was used to estimate the rate of decline in SGRQ scores (Table 10). There was no treatment difference in SGRQ activity, impact and total scores. For symptom scores, tiotropium group showed a higher rate of increase (or worsening) than the placebo group did. According to the Applicant, this was due to the different change of symptom score between months 42 and 48, which can be attributed to higher dropout rate in the placebo group.

Table 9: Rate of increase in SGRQ scores from Month 6 until completion of treatment – treated set with at least 2 acceptable measurements

Time point	N	Placebo	N	Tio 18 mcg	Difference (Tio 18 mcg - Placebo)		
		Mean (SE) [per year]		Mean (SE) [per year]	Mean (SE) [per year]	95% CI	P-value
Activity	2362	1.51 (0.11)	2505	1.40 (0.11)	-0.11 (0.15)	(-0.4, 0.2)	0.4717
Impact	2362	1.18 (0.10)	2505	1.18 (0.10)	-0.00 (0.14)	(-0.3, 0.3)	0.9889
Symptom	2364	0.55 (0.14)	2512	1.00 (0.13)	0.45 (0.19)	(0.1, 0.8)	0.0171
Total	2362	1.21 (0.09)	2505	1.25 (0.09)	0.04 (0.13)	(-0.2, 0.3)	0.7840

Source data: [Table 15.2.4: 2](#).

Source: Clinical Study Report Tabl 11.4.1.2.2:3 page 117

3.1.6 OTHER PULMONARY FUNCTION TESTING

Like the primary endpoint pre- and post-bronchodilator FEV₁, similar analyses are conducted to compare the yearly decline of pre- and post-bronchodilator Forced Vital Capacity (FVC) and pre- and post-bronchodilator Slow Vital Capacity (SVC) between tiotropium 18 mcg and placebo.

3.1.6.1 Forced Vital Capacity (FVC)

The results for the analyses of yearly rate of decline of pre- and post-bronchodilator FVC are summarized in Table 10. There were no significant treatment differences in the yearly rate of decline of pre- and post-bronchodilator FVC.

Table 10: Rate of decline in pre- or post-bronchodilator FVC

	Placebo		Tiotropium		Mean (SE) [ml/yr]	Difference 95% CI	p-value
	N	Mean (SE) [ml/yr]	N	Mean (SE) [ml/yr]			
Random Effects Model							
Pre-BD	2413	-39 (3)	2557	-43 (3)	4 (4)	(-4, 12)	0.2990
Post-BD	2410	-61 (3)	2554	-61 (3)	1 (4)	(-7, 9)	0.8375
Sensitivity #1							
Pre-BD	2863	-37 (3)	2906	-42 (3)	4 (4)	(-4, 12)	0.2463
Post-BD	2851	-59 (3)	2904	-61 (3)	1 (4)	(-7, 9)	0.7600
Sensitivity #2							
Pre-BD	1618	-12	1803	-10			0.2705
Post-BD	1613	-40	1805	-40			0.3060

Pre-BD: pre-bronchodilator FVC Post-PB: post-bronchodilator FVC

Primary: treated set with at least 3 measurement after (including) day 30 until completion of double-blind treatment

Sensitivity #1: analysis of primary endpoint based on treated set with at least 1 measurement after (including) day 30

Sensitivity #2: Rate of decline in FVC from Day 1 until end of trial using non-parametric approach. Median scores are reported for the difference in FVC at last trial visit and on Day 1, divided by the duration between visits. P-values were calculated based on Wilcoxon Rank Sum test.

Source: Clinical Study Report, Table 11..4.1.2.2:2 (page 113), Table 15.2.2:4 (page 400), Table 15.2.2.: 3 (page 399)

3.1.6.2 Slow Vital Capacity

The results for the analyses of yearly rate of decline of pre- and post-bronchodilator SVC are summarized in Table 11. There were no significant treatment differences in the yearly rate of decline of pre- and post-bronchodilator SVC.

Table 11: Rate of decline in pre- or post-bronchodilator SVC

	Placebo		Tiotopium		Mean (SE) [ml/yr]	Difference 95% CI	p-value
	N	Mean (SE) [ml/yr]	N	Mean (SE) [ml/yr]			
Random Effects Model							
Pre-BD	2374	-41 (3)	2531	-47 (3)	6 (4)	(-2, 14)	0.1143
Post-BD	2383	-65 (3)	2527	-66 (3)	1 (4)	(-7, 9)	0.7870
Sensitivity #1							
Pre-BD	2851	-40 (3)	2895	-47 (3)	6 (4)	(-2, 14)	0.0928
Post-BD	2842	-64 (3)	2894	-65 (3)	1 (4)	(-7, 9)	0.8022
Sensitivity #2							
Pre-BD	1562	-17	1706	-17			0.8103
Post-BD	1540	-46	1711	-42			0.9814

Pre-BD: pre-bronchodilator SVC Post-PB: post-bronchodilator SVC

Primary: treated set with at least 3 measurement after (including) day 30 until completion of double-blind treatment

Sensitivity #1: analysis of primary endpoint based on treated set with at least 1 measurement after (including) day 30

Sensitivity #2: Rate of decline in SVC from Day 1 until end of trial using non-parametric approach. Median scores are reported for the difference in SVC at last trial visit and on Day 1, divided by the duration between visits. P-values were calculated based on Wilcoxon Rank Sum test.

Source: Clinical Study Report, Table 11..4.1.2.2:2 (page 113), Table 15.2.3:4 (page 408), Table 15.2.3.: 3 (page 407)

3.1.7 EFFICACY CONCLUSION

After careful review of the UPLIFT Study, the following are the results from the analyses of the primary and secondary endpoints.

1. The two primary endpoints, rates of decline of pre- and post-bronchodilator FEV₁, did not achieve statistical significance when tiotropium was compared to placebo.
2. Additional analyses on the lung function FEV₁ produced the following results:
 - a. When mean pre- or post-bronchodilator FEV₁ were estimated in the UPLIFT study, there is an initial increase of 105 and 71 ml, respectively, at Visit 3 (or Day 30) from baseline in the tiotropium group. Numerically, the treatment difference in mean pre- or post-bronchodilator FEV₁ was evident at Visit 3, and the difference was maintained throughout the trial. The overall mean treatment difference in mean pre-bronchodilator FEV₁ was 94 ml and 57 ml in mean post-bronchodilator FEV₁.
 - b. Based on responder analysis, defined as 15% improvement in mean pre- or post-bronchodilator FEV₁ from baseline across all timepoints, 33% of patients treated with tiotropium achieved the level of response at Visit 3 (Day 30) in pre-bronchodilator FEV₁ compared to 16% in the placebo group (i.e. 17% treatment difference in the proportions of responder). At Month 48, there is roughly 7% difference in the proportions of responder between tiotropium (16%) and placebo (9%). For post-bronchodilator FEV₁, the proportions of responder in both treatment groups are generally smaller compared to when pre-bronchodilator FEV₁ measurements are used. However, the proportion of responder remains higher in the tiotropium group compared to the placebo group across all visits, particularly prior to Year 1 (or Month 12).
3. The following are results from the analyses of COPD exacerbation. Of note, the pre-specified multiplicity adjustment (i.e. hierarchical strategy) by the Applicant requires that the co-primary endpoints needs to achieve statistical significance prior to considering the 'key' secondary endpoints. Because the primary endpoints did not achieve statistical significance, caution needs to be exercised in making inferences for secondary endpoints. I will discuss this further in Section 5.1.
 - a. There is no treatment difference in the proportion of patients with at least one COPD exacerbation. However when treatment exposure is taken into account, the estimated rate of COPD exacerbation per patient year is lower in the tiotropium group (rate=0.73) compared to the placebo group (rate=0.85). The rate ratio of 0.86 suggested a 14% reduction of COPD exacerbation events in the tiotropium group. In addition, there is evidence that tiotropium-treated patients experienced a delay in the time to first exacerbation compared to placebo-treated patients.
 - b. There is no treatment difference in the proportion of patients with at least one COPD exacerbation leading to hospitalization. When treatment exposure is taken into account, the estimated rate of COPD exacerbation per patient year in the tiotropium group (rate=0.15) is not different to the placebo group (rate=0.16).
 - c. In Table 12, I explored the exacerbation endpoints in the UPLIFT study following the exacerbation endpoints used in the VA study. At six months, the results from the UPLIFT study are similar to the VA study with the percentage of patients with a

COPD exacerbation meeting the protocol definition was lower for tiotropium compared to placebo, with an odds ratio of 0.84. The calculated hazard ratio in the VA study is also similar to the UPLIFT study at 0.83. Thus, at six months, there is a relative risk reduction of about 16% in the tiotropium group compared to the placebo group. For 25% of patients, the median time to first COPD exacerbation in the tiotropium group is 5 months compared to 4 months in the placebo group.

4. There was no treatment difference in the rate of decline of SGRQ total score, yearly rate of decline of pre- and post-bronchodilator FVC, and yearly rate of decline of pre- and post-bronchodilator SVC.

Table 12: Analysis of COPD exacerbation – UPLIFT Study

	Placebo N=3006 PY=8499.46	Tiotropium N=2986 PY=9222.31	Ratio or Difference 95% CI	Unadjusted p-value
At Six Months				
No. of patients with at least one exacerbation	933 (31%)	821 (27%)	OR= 0.84	0.0026
No. of patients with at least one exacerbation meeting protocol definition	923 (31%)	810 (27%)	OR= 0.84	0.0023
No. of patients with at least one exacerbation leading to Hospitalization	192 (6%)	173 (6%)	OR= 0.90	0.3369
Median time to first exacerbation (months) for 25% patients	4.2	5.3	HR: 0.83 (0.76, 0.92)	0.0001
Median time to first exacerbation (months)*	N/A	N/A	HR: 0.87 (0.71, 1.07)	0.1987
At 48 Months				
No. of patients with at least one exacerbation	2049 (68%)	2001 (67%)		0.3481
No. of patients with at least one exacerbation leading to Hospitalization	811 (27%)	759 (25%)		0.1766
Estimated no. (rate) of COPD exacerbations per patient year ‡	7183 (0.85)	6691 (0.73)	Ratio: 0.86 (0.81, 0.91)	<0.0001
Estimated no. (rate) of COPD exacerbations per patient year leading to hospitalization‡	1379 (0.16)	1403 (0.15)	Ratio: 0.94 (0.82, 1.07)	0.3413

The following results are taken from the Clinical Review and Statistics Review of Study 266 (VA Study), serial number 024.

1. There were two primary (i.e. 'co-primary') endpoints, percentage of patients with a COPD exacerbation meeting the protocol definition and the percentage of patients with a hospitalization due to COPD exacerbation. Only one of the two 'co-primary' endpoints was met, that is, the percentage of patients with a COPD exacerbation meeting the protocol definition was significantly lower for tiotropium compared to placebo ($p=0.04$), with an odds ratio of 0.806 (Table 13).
2. One of the secondary endpoints the Applicant examined was the time-to-first COPD exacerbation. The Applicant reports that patients in the tiotropium group had a "significantly" longer time to event than patients in the placebo group with a hazard ratio of 0.834. The p-value of 0.04 was unadjusted. Similarly, patients in the tiotropium group had a longer time to first hospitalization due to COPD exacerbation compared to placebo, and the unadjusted p-value was 0.05.
3. The Applicant also explored the treatment effect in lung function. The following results are taken from Dr. Michele's review:
 - a. When mean pre- or post-bronchodilator FEV₁ were estimated, the mean treatment difference in mean pre-bronchodilator FEV₁ was 100 ml and 160 ml in mean post-bronchodilator FEV₁ at 3 months.
 - b. At 6 months, the mean treatment difference in mean pre-bronchodilator FEV₁ was 90 ml and 170 ml in mean post-bronchodilator FEV₁.
 - c. Unlike the UPLIFT study, this study did not require administration of open-labeled inhaled salbutamol (albuterol) 400 mcg and ipratropium bromide 80 mcg in addition to study medication (tiotropium or placebo) to achieve optimal bronchodilation for post-bronchodilator lung function measurements; Thus, the mean difference in post-bronchodilator FEV₁ is higher compared to the mean difference in the UPLIFT study.

In Study 266 (VA study), sequential testing was conducted only on the 'co-primary' endpoints. Multiplicity correction was not pre-specified in the secondary endpoints, which includes time-to-first COPD exacerbation. This multiplicity issue was discussed in detail in Dr. Ruthanna Davi's review. In summary Dr. Davi wrote that

Because of the expected and observed correlation between this secondary analysis and the primary analysis and because this analysis was a selection from one of a limited number of secondary efficacy endpoints, it is unlikely that these result of the time-to-first COPD exacerbation analysis is a spurious finding. Rather it is likely that the statistical significance observed in this comparison is a true representation of the treatment effect on this endpoint. In addition, this type of analysis may be considered more appropriate than the primary analysis in that subjects who dropped out of the study are censored.

The following is taken from the Clinical Review (VA Study) describing the efficacy conclusion:

These results, while positive, are not sufficiently robust to allow approval on the basis of the single study submitted. A second placebo-controlled clinical trial demonstrating a reduction in COPD exacerbations with Spiriva HandiHaler is required to confirm efficacy. The exact wording of the claim will need consideration as various aspects of exacerbation were measured in Protocol 205.266.

Table 13: Analysis of COPD exacerbation –VA Study

	Placebo N=915	Tiotropium N=914	Ratio or Difference 95% CI	p-value
Co-Primary Endpoints (at 6 months)				
No. of patients with at least one exacerbation meeting protocol definition	32%	28%	OR = 0.81	0.0368
No. of patients with at least one exacerbation leading to Hospitalization	10%	7%	OR= 0.72	0.0557
Secondary Endpoints				
Estimated no. (rate) of COPD exacerbations per patient year ‡	0.88	0.71	Ratio: 0.81	0.04
Estimated no. (rate) of COPD exacerbations per patient year leading to hospitalization‡	0.15	0.21	Ratio: 0.70	0.054

Source: Clinical Review and Statistical Review, SE8, S024

3.2 EVALUATION OF SAFETY

The Applicant proposed the inclusion of ‘Survival and Respiratory Failure’ in the Clinical Section of the SPIRIVA Handihaler label. They claimed that there was a 16% reduction in the risk of death while on treatment with SPIRIVA HandiHaler compared to placebo. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.78 per 100 patient years in the placebo group [Hazard Ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97]. Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00].

The following describes the Analysis Plan for the ‘mortality’ and ‘respiratory failure’ endpoints:

Mortality events were analyzed for on-treatment death (onset of the fatal AE is between first drug intake and last drug intake + 30 days), and all deaths including post-discontinuation vital status collection. Causes of deaths were reported by investigator or via vital status collection, and the primary cause of death was also reported. The adjudication committee provided the adjudicated primary cause of death.

Frequency and incidence density tables by SOC and PT for all deaths including vital status included all fatal events collected before 1470 days. Similar tables for on-treatment deaths included all the on-treatment fatal AEs without the 1470-day cut-off. Frequency and incidence density tables were prepared for adjudicated primary cause of death for all deaths including vital status, and on-treatment deaths, as well as for reported causes of on-treatment death.

Time to death was defined as time to the end of a fatal AE. Analyses of time to death using the Kaplan-Meier estimates and Cox regression applied the cut-off Day of 1470 days (i.e., all patients after the planned trial period of 1470 days were censored for these analyses). The time to death analyses were carried out for both adjudicated primary cause of death for all deaths including vital status and on-treatment deaths. The mortality endpoints for these analyses included all cause, lower respiratory, cardiac disorders, stroke, and any fatal AE that occurred in more than 1% (or 60 cases) of the patients.

Subgroup analysis for mortality data was carried out only for all-cause, lower respiratory, and cardiac death for adjudicated all deaths including vital status, and only for the time-to-death analysis. Cox regression with treatment, subgroup and treatment by subgroup interaction was used to assess consistency of treatment effect across subgroups.

The statistical analyses for respiratory mortality were based on the adjudicated primary cause of death. Matching between adjudicated and investigator reported primary cause of death was explored using descriptive statistics. Respiratory mortality specified in the trial protocol was interpreted as lower respiratory mortality, as defined by the SPIRIVA project rules.

Analyses were added to investigate the risk of stroke in response to an FDA early communication. Kaplan-Meier estimates as well as Cox regression were carried out for stroke AE, serious AE, and fatal AEs.

In this review, I will focus on the ‘mortality’ claim. Please refer to Dr. Theresa Michele’s review for a thorough discussion of these and other safety endpoints.

In the Study Report, fatal events are presented in two ways: 1) deaths on-treatment and 2) all deaths including post discontinuation vital status collection. Both 1 and 2 were analyzed with cut-off of 1440 days (4 years), 1470 days (4 years and 30 days) and with no cut-off.

Table 14 presents the summary of all-cause mortality. The total number of deaths from any cause during treatment (including the last day of study drug plus 30 days) was 792; 411

(14%) in the placebo group and 381 (13%) in the treatment group. Additional death information was collected from the post-discontinuation Vital Status (i.e. off-treatment) for 189 patients, totaling the number of deaths from any cause to 981; 514 (17%) in the placebo group and 467 (16%) in the tiotropium group. The hazard ratio for on-treatment death from any cause (tiotropium/placebo) was 0.84 [95% CI: 0.73, 0.97], and 0.89 [95% CI: 0.78, 1.00] for 'on-treatment and off-treatment' death. Of note, the confidence interval and p-value of the hazard ratio are unadjusted for multiplicity.

The Kaplan-Meier estimate of no all-cause mortality (on-treatment) by Day 1470 is presented in Figure 11. There is evidence that the two curves started to separate at Month 12 with the tiotropium curve on top of the placebo group, and the separation is maintained until Month 48.

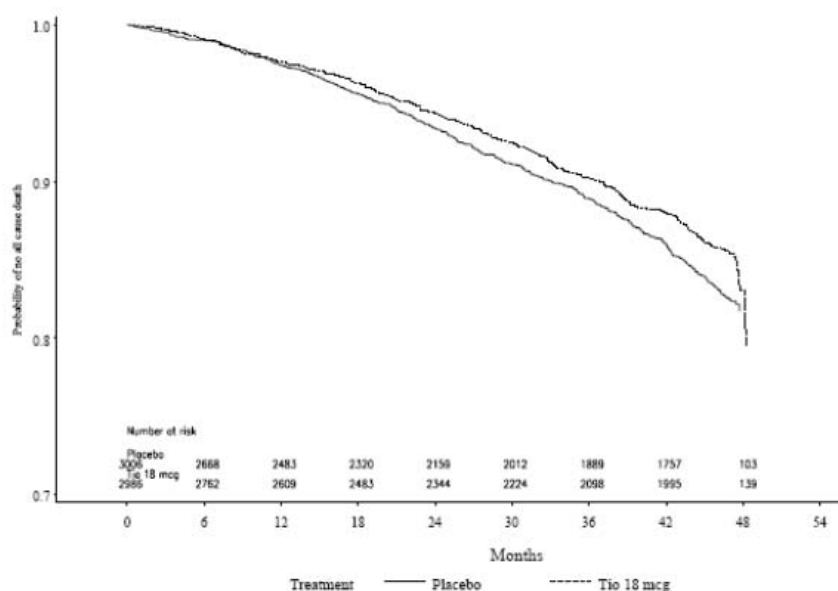
Table 14: Fatal Adverse Event Summary – Treated Set

	Placebo	Tiotropium	Δ Rates	Hazard Ratio Tiotropium vs. Placebo		
	N (%)	N (%)		HR	95% CI	P-value
On-Treatment (Day 1440)	400 (13.3)	361 (12.1)	1.2%	0.83	0.72, 0.95	0.010
On Treatment (Day 1470)	402 (13.4)	374 (12.5)	0.9%	0.85	0.74, 0.98	0.024
On-Treatment (all)	411 (13.7)	381 (12.8)	0.9%	0.84	0.73, 0.97	0.016
Vital Status (Day 1440)	491 (16.3)	430 (14.4)	1.9%	0.87	0.76, 0.99	0.034
Vital Status (Day 1470)	495 (16.5)	446 (14.9)	1.6%	0.89	0.79, 1.02	0.086
Vital Status (all)	514 (17.1)	467 (15.6)	1.5%	0.89	0.78, 1.00	0.058

Source data: Tables 15.3.3: 1 and 15.3.3: 2

Source: Clinical Study Report, Table 12.3:1, page 134; p-value is unadjusted

Figure 11: Kaplan-Meier estimates of the probability of no all-cause mortality – adjudicated; on-treatment deaths-treated set-censored at Day 1470



Source data: Figure 15.3.2.2.2: 1

Source: Clinical Study Report, Figure 12.3:1, page 135

Based on re-analysis of the ‘raw’ mortality data, all deaths were adjudicated. However it appears that 193 deaths were off-treatment (i.e. vital status information) and 788 deaths were on-treatment, as opposed to 189 and 792 deaths, respectively. Four subjects (tiotropium 2, placebo 2) were classified as off-treatment in the raw data (ID=10434, 15167, 21595, and 22955). This discrepancy did not alter the results described in Table 14.

Subgroup analyses were conducted for the on-treatment death with and without 1470 days cut-off. Although there were slight discrepancies in the ‘days on treatment and days censored’, these discrepancies did not alter the conclusion. The results are presented in Appendix 13 and Appendix 14 for the following subgroups: age (<55; 55-<65; 65-<75; ≥75 years), gender (male; female), smoking status (smoker; ex-smoker), baseline LABA use (yes; no), baseline ICS use, baseline use of ICS and LABA combination, baseline anticholinergic use, GOLD stage (I/II; III; IV), race (Asian; Black; White), region (Asia; Eastern Europe; Western Europe; Latin America; USA), reversibility, and BMI (<20; 20-<25; 25-<30; ≥30 kg/m²).

Except for smoking status and BMI, there were no significant treatment-by-subgroup interactions detected in any subgroups on the mortality endpoints. Table 15 presents the subgroup analysis on on-treatment death (with 1470 cut-off) by smoking status and by BMI. There is some evidence of a qualitative interaction between treatment and smoking status, as well as between treatment and BMI in the proportion of death. There is numerically higher proportion of mortality in the placebo group among ex-smokers compared to tiotropium, while a numerically higher proportion of mortality is seen in the tiotropium group among current smokers compared to placebo. There is numerically higher proportion of mortality in the placebo group among patients with BMI between 25 and 30 kg/m² compared to tiotropium. These findings should be explored further in another study.

Table 15: Subgroup Analysis for on-treatment death (with 1470 cut-off) – treated set

	Placebo		Tiotropium		Hazard ratio (Tio vs. Placebo) 95% CI	Subgroup by treatment interaction p-value
	N	No. deaths (%)	N	No. deaths (%)		
Total treated with on-treatment fatal AE events	3006	402 (13.4)	2986	374 (12.5)	0.85 (0.74, 0.98)	
Smoking Status						0.0562
Ex-Smoker	2108	292 (13.9)	2112	252 (11.9)	0.78 (0.66, 0.92)	
Current Smoker	898	110 (12.2)	874	122 (14.0)	1.05 (0.81, 1.36)	
BMI						0.0562
<20	352	72 (20.5)	297	74 (24.9)	1.07 (0.77, 1.47)	
≥20, < 25	1024	128 (12.5)	1074	138 (12.8)	0.91 (0.72, 1.16)	
≥25, < 30	1033	141 (13.6)	1039	101 (9.7)	0.66 (0.51, 0.85)	
≥30	597	61 (10.2)	576	61 (10.6)	0.96 (0.67, 1.37)	0.0883

Table 16 and Table 17 present a summary of the most common causes of death (reported in >1% of patients in either treatment group) during study drug treatment as assessed by the adjudication committee, on-treatment death and on-treatment plus vital status, respectively. Like the subgroup analyses using Cox regression model in calculating the hazard ratio, there are also some discrepancies in the calculation of patient-year. However, this discrepancy did not alter the conclusion.

With the exception of pneumonia and sudden death, the incidence of fatal AE by selected preferred terms in the placebo group is higher or almost equal to the tiotropium group. The incidence of death caused by pneumonia and sudden death appears to be slightly higher (numerically) in the tiotropium group compared to the placebo group with a risk ratio that corresponds to a less favorable outcome in the tiotropium group. However, the confidence interval includes the null value and values that correspond to a more favorable outcome with tiotropium, so that the direction of the difference in risk, if any, is not known with much confidence. Similarly, the confidence interval across all other causes of death includes the null value, thus, the direction of the difference is not known with much confidence either.

Table 16: Incidence density of fatal AE by treatment, selected preferred terms – adjudicated primary cause; on-treatment death – treated set

	Placebo N=3006		Tiotropium N=2986		Risk Ratio (Tio vs. Placebo) 95% CI
	Pt-Year at risk	n (incidence)	Pt-Year at risk	n (incidence)	
Total treated with on-treatment fatal AE events	8575	411 (4.8)	9281	381 (4.1)	0.86 (0.75, 0.98)
COPD exacerbation	8702	121 (1.4)	9418	103 (1.1)	0.79 (0.60, 1.02)
Lung cancer	8718	66 (0.8)	9425	73 (0.8)	1.02 (0.73, 1.43)
Death (unknown cause)	8718	36 (0.4)	9452	29 (0.3)	0.74 (0.53, 1.07)
Sudden cardiac death	8742	23 (0.3)	9464	15 (0.2)	0.60 (0.31, 1.15)
Pneumonia	8740	18 (0.2)	9453	27 (0.3)	1.39 (0.76, 2.52)
Congestive heart failure	8740	14 (0.2)	9463	15 (0.2)	0.99 (0.48, 2.05)
Sudden death	8743	12 (0.1)	9466	14 (0.2)	1.08 (0.50, 2.33)
Cerebrovascular Accident (CVA) or Stroke	8740	13 (0.2)	9467	12 (0.1)	0.85 (0.39, 1.87)

Source: Clinical Study Report, Table 15.3.2.2.1.2:2 page 1046 - 1050

Table 17: Incidence density of fatal AE by treatment, selected preferred terms – adjudicated primary cause; on-treatment death including Vital Status (1470 cut-off) – treated set

	Placebo N=3006		Tiotropium N=2986		Risk Ratio (Tio vs. Placebo) 95% CI
	Pt-Year at risk	n (incidence)	Pt-Year at risk	n (incidence)	
Total treated with on-treatment fatal AE events	10718	495 (4.6)	10821	446 (4.1)	0.89 (0.79, 1.01)
COPD exacerbation	10950	150 (1.4)	11025	120 (1.1)	0.79 (0.62, 1.01)
Lung cancer	10984	70 (0.6)	11037	78 (0.7)	1.11 (0.80, 1.53)
Death (unknown cause)	10989	59 (0.5)	11092	56 (0.5)	0.94 (0.65, 1.36)
Sudden cardiac death	11052	25 (0.2)	11110	18 (0.2)	0.72 (0.39, 1.31)
Pneumonia	11039	21 (0.2)	11088	32 (0.3)	1.52 (0.87, 2.63)
Congestive heart failure	11044	17 (0.2)	11109	15 (0.1)	0.88 (0.44, 1.76)
Sudden death	11051	18 (0.2)	11114	15 (0.1)	0.8308 (0.42, 1.64)
Cerebrovascular Accident (CVA) or Stroke	11046	17 (0.2)	11112	14 (0.1)	0.82 (0.40, 1.66)

Source: Clinical Study Report, Table 15.3.2.2.1.1:2 page 1031 - 1044

The incidence of fatal death caused by pneumonia is further examined by evaluating the treatment effect in subgroup of patients with or without baseline ICS or LABA used. The results are presented in Table 18. Of note, when calculating the patient-year at risk, there is a slight difference in the result. However, this did not affect the overall conclusion.

There is some evidence of a qualitative interaction between treatment group and baseline ICS and/or LABA use. Numerically, there is slightly higher proportion of mortality due to pneumonia in patients with baseline ICS or LABA who are taking tiotropium compared to those taking placebo. In contrast, there is no difference in the proportion of mortality due to pneumonia in patients without baseline ICS or LABA. Because the number of events is small and the confidence interval for the risk ratio includes the null value, therefore the direction of the difference is not known with much confidence either.

Table 18: Subgroup Analyses of Pneumonia - on-treatment death – treated set

	Placebo		Tiotropium		Risk Ratio (Tio vs. Placebo) 95% CI
	N (Pt-Year at risk)	N (incidence)	Pt-Year at risk	N (incidence)	
Overall	3006 (8740)	18 (0.2)	2986 (9453)	27 (0.3)	1.39 (0.76, 2.52)
Baseline ICS: Yes	1860 (5335)	10 (0.2)	1840 (5797)	19 (0.3)	1.75 (0.81, 3.76)
No	1146 (3411)	8 (0.2)	1146 (3663)	8 (0.2)	0.93 (0.35, 2.48)
Baseline LABA: Yes	1808 (5214)	8 (0.2)	1796 (5695)	17 (0.3)	1.95 (0.84, 4.51)
No	1198 (3532)	10 (0.3)	1190 (3765)	10 (0.3)	0.94 (0.39, 2.25)
Baseline ICS/LABA: Yes	1462 (4197)	7 (0.2)	1464 (4610)	15 (0.3)	1.95 (0.80, 4.78)
No	1544 (4549)	11 (0.2)	1522 (4850)	12 (0.2)	1.02 (0.45, 2.32)

In conclusion, although there is some suggestion of a benefit of tiotropium for on-treatment mortality, this needs to be explored further. In particular, a different result was observed in a different SPIRIVA application using RESPIMAT delivery system. In that application, an increased number of deaths are observed in the Spiriva Respimat treatment groups compared to placebo for 1-year pivotal trials, resulting in a Complete Response action for the Spiriva Respimat NDA. On July 22, 2009, the Applicant amended the efficacy supplement to remove the mortality claim to main consistency with global labeling. According to the Applicant, there was no new Spiriva Handihaler data contributing to this decision.

Furthermore, according to the EMEA guidance

If not defined as primary variables, clinically very important variables (e.g. mortality) need further study when significant benefits are observed, but the primary objective has not been achieved. Variables that have the potential of being indicative of a major clinical benefit or may in a different situation present an important safety issue (e.g. mortality) may be relegated to secondary variables because there is an *a priori* belief that the size of the planned trial is too small (and thus the power too low) to show a benefit. *If, however, the observed beneficial effect is much higher than expected but the study fell short of achieving its primary objective, this would be a typical situation where information from further studies would be needed which can be used in support of the observed beneficial effect.*

4 FINDINGS IN SUBGROUPS AND SPECIAL POPULATIONS

On January 7, 2009, an information request was sent to the Applicant requesting subgroup analyses for the following endpoints:

- Time to first COPD exacerbation
- Time to first COPD exacerbation leading to hospitalization
- Number of COPD exacerbations per patient year
- Adverse events: individual, serious, cardiovascular events, stroke events

On February 17, 2009, the Applicant submitted their responses to the analyses request for the following subgroups (age, gender, smoking status, baseline concomitant medication use, COPD severity according to GOLD stages, race, region, reversibility, BMI). The results are presented in this Section. Of note, the Cox model was used for the time to first event analysis and the Poisson model adjusting for overdispersion was used to estimate the number of COPD exacerbations per patient year. Meanwhile, the incidence rate and rate ratio were reported for the adverse event analyses.

In addition to the four endpoints reported by the Applicant, I conducted additional subgroup analyses on the estimated mean pre- and post-bronchodilators FEV₁ scores at each visit. The repeated measures ANOVA model was used to conduct these analyses.

Because the two primary endpoints (i.e. the rates of decline of pre- and post-bronchodilator FEV₁) did not achieve statistical significance, I did not perform additional analyses other than what was conducted by the Applicant and summarized in Section 3.1.3.

Note that because these subgroup analyses are done post-hoc, these should be considered exploratory.

4.1 COPD EXACERBATION

The Applicant conducted subgroup analyses on the exacerbation endpoints. The subgroups were specified as follows: age (<55; 55-<65; 65-<75; ≥75 years), gender (male; female), smoking status (smoker; ex-smoker), baseline LABA use (yes; no), baseline ICS use, baseline use of ICS and LABA combination, baseline anticholinergic use, GOLD stage (I/II; III; IV), race (Asian; Black; White), region (Asia; Eastern Europe; Western Europe; Latin America; USA), reversibility, and BMI (<20; 20-<25; 25-<30; ≥30 kg/m²).

The results from subgroup analyses of COPD exacerbation, COPD exacerbation leading to hospitalization, COPD exacerbation per patient year are summarized in Table 19, Table 20, and Table 21, respectively.

There were no significant treatment-by-subgroup interactions detected in any subgroups on the exacerbation endpoints.

Table 19: Analysis of COPD exacerbation – Number of Patients with Exacerbation (%) and Median Time to First Exacerbation (in months)

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	2049/3006 (68%) 13 months	2001/2986 (67%) 17 months	0.86 (0.81, 0.91)	
Sex: Female	539/784 (69%) 10 months	496/735 (68%) 15 months	0.83 (0.74, 0.94)	
Male	1510/2222 (68%) 13 months	1505/2251 (67%) 17 months	0.87 (0.81, 0.93)	0.5632
Gold Stage: I/II	883/1356 (65%) 17 months	824/1386 (60%) 23 months	0.82 (0.75, 0.90)	
III	942/1331 (71%) 10 months	944 /1304 (72%) 13 months	0.87 (0.79, 0.95)	
IV	188/271 (69%) 9 months	200/250 (80%) 10 months	0.99 (0.81, 1.21)	0.2341
Baseline Smoking Status	1458/2108 (69%) 12 months	1437/2112 (68%) 16 months	0.86 (0.80, 0.93)	
Ex-Smoker	591/898 (66%) 14 months	564/874 (65%) 18 months	0.85 (0.76, 0.95)	0.8680
Reversibility: Yes	1036/1513 (69%) 13 months	1021/1520 (67%) 17 months	0.86 (0.79, 0.94)	
No	946/1393 (68%) 12 months	913/1357 (67%) 16 months	0.86 (0.79, 0.94)	0.9854
Baseline ICS: Yes	1338/1860 (72%) 10 months	1302/1840 (71%) 13 months	0.85 (0.79, 0.92)	
No	711/1146 (62%) 18 months	699/1146 (61%) 23 months	0.86 (0.78, 0.96)	0.8068
Baseline LABA: Yes	1302/1808 (72%) 11 months	1275/1796 (71%) 13 months	0.85 (0.79, 0.92)	
No	747/1198 (62%) 17 months	726/1190 (61%) 22 months	0.87 (0.78, 0.96)	0.7171
Baseline ICS/LABA: Yes	1066/1462 (73%) 10 months	1052/1464 (72%) 12 months	0.86 (0.79, 0.93)	
No	983/1544 (64%) 17 months	949/1522 (62%) 21 months	0.86 (0.78, 0.94)	0.9146
Race: White	1845/2697 (68%) 12 months	1817/2691 (68%) 16 months	0.87 (0.81, 0.92)	
Black	36/53 (68%) 18 months	19/38 (50%) 41 months	0.48 (0.28, 0.85)	
Asian	118/185 (64%) 13 months	119/192 (62%) 18 months	0.81 (0.63, 1.05)	0.2310

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	2049/3006 (68%) 13 months	2001/2986 (67%) 17 months	0.86 (0.81, 0.91)	
Region: Asia	114/178 (64%) 13 months	113/184 (61%) 18 months	0.81 (0.62, 1.05)	
E. Europe	402/597 (67%) 20 months	367/590 (62%) 21 months	0.88 (0.76, 1.01)	
Latin America	163/207 (79%) 9 months	142/198 (72%) 15 months	0.78 (0.63, 0.98)	
USA	489/767 (64%) 12 months	477/767 (62%) 18 months	0.80 (0.71, 0.91)	
W. Europe	881/1257 (70%) 11 months	902/1247 (72%) 13 months	0.90 (0.82, 0.99)	0.5122
Age: <55	254/382 (67%) 12 months	248/384 (65%) 18 months	0.83 (0.70, 0.99)	
55 – 65	716/1055 (68%) 14 months	714/1054 (68%) 17 months	0.90 (0.81, 0.99)	
65 – 75	825/1198 (69%) 13 months	810/1208 (67%) 17 months	0.86 (0.78, 0.95)	
≥ 75	254/371 (69%) 9 months	229/340 (67%) 13 months	0.76 (0.64, 0.91)	0.4440
BMI: <20	263/352 (75%) 10 months	216/297 (73%) 13 months	0.76 (0.64, 0.91)	
20 – 25	673/1024 (66%) 12 months	709/1074 (66%) 16 months	0.86 (0.78, 0.96)	
25 – 30	704/1033 (68%) 14 months	705/1039 (68%) 17 months	0.91 (0.82, 1.01)	
≥ 30	407/597 (68%) 13 months	371/576 (64%) 19 months	0.82 (0.71, 0.94)	0.4118
Anticholinergic Use:	922/1350 (68%) 11 months	950/1366 (70%) 14 months	0.87 (0.79, 0.95)	
Yes	1127/1656 (68%) 15 months	1051/1620 (65%) 18 months	0.85 (0.78, 0.92)	0.7960
No				

*Hazard ratio based on Cox model with treatment, baseline covariate and baseline covariate by treatment interaction; p-value was obtained using log-rank test.

Table 20: Analysis of COPD exacerbation leading to Hospitalization – Number of Patients with Exacerbation (%) and Median Time to First Exacerbation for 25% patients (in months)

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	811/3006 (27%) 29 months	759/2986 (25%) 36 months	0.86 (0.78, 0.95)	0.0024
Sex: Female	199/784 (25%) 27 months	162/735 (22%) 43 months	0.77 (0.62, 0.94)	
Male	612/2222 (28%) 29 months	597/2251 (27%) 34 months	0.89 (0.79, 0.99)	0.2100
Gold Stage: I/II	265/1356 (20%) N/A months	211/1386 (15%) N/A months	0.74 (0.61, 0.88)	
III	413/1331 (31%) 23 months	421/1304 (32%) 25 months	0.93 (0.81, 1.06)	
IV	116/271 (43%) 11 months	112/250 (45%) 14 months	0.85 (0.66, 1.10)	0.1362
Baseline Smoking Status	570/2108 (27%) 29 months	530/2112 (25%) 37 months	0.84 (0.75, 0.95)	
Ex-Smoker	241/898 (27%) 29 months	229/874 (26%) 34 months	0.90 (0.75, 1.07)	0.5589
Reversibility: Yes	370/1513 (25%) 36 months	365/1520 (24%) 40 months	0.91 (0.78, 1.05)	
No	412/1393 (30%) 24 months	365/1357 (27%) 32 months	0.82 (0.71, 0.94)	0.2915
Baseline ICS: Yes	556/1860 (30%) 24 months	492/1840 (27%) 32 months	0.80 (0.71, 0.90)	
No	255/1146 (22%) 41 months	267/1146 (23%) 43 months	0.98 (0.83, 1.17)	0.0504
Baseline LABA: Yes	529/1808 (29%) 25 months	484/1796 (27%) 33 months	0.83 (0.73, 0.94)	
No	282/1198 (24%) 36 months	275/1190 (23%) 42 months	0.91 (0.77, 1.08)	0.3596
Baseline ICS/LABA: Yes	442/1462 (30%) 24 months	398/1464 (27%) 32 months	0.80 (0.70, 0.92)	
No	369/1544 (24%) 35 months	361/1522 (24%) 40 months	0.92 (0.79, 1.06)	0.1801
Race: White	709/2697 (26%) 30 months	664/2691 (25%) 37 months	0.85 (0.77, 0.95)	
Black	17/53 (32%) 18 months	11/38 (29%) 42 months	0.73 (0.34, 1.56)	
Asian	72/185 (39%) 15 months	68/192 (35%) 18 months	0.82 (0.59, 1.15)	0.9243

	Placebo	Tiotropium	Hazard Ratio 95% CI	p-value*
Overall	811/3006 (27%) 29 months	759/2986 (25%) 36 months	0.86 (0.78, 0.95)	0.0024
Region: Asia	69/178 (39%) 16 months	66/184 (36%) 18 months	0.85 (0.61, 1.19)	
E. Europe	159/597 (27%) 33 months	154/590 (26%) 35 months	0.97 (0.78, 1.22)	
Latin America	61/207 (30%) 25 months	49/198 (25%) 45 months	0.75 (0.52, 1.10)	
USA	173/767 (23%) 33 months	164/767 (21%) 38 months	0.84 (0.68, 1.04)	
W. Europe	349/1257 (28%) 28 months	326/1247 (26%) 36 months	0.83 (0.72, 0.97)	0.7561
Age: <55	78/382 (20%) N/A months	79/384 (21%) N/A months	0.93 (0.68, 1.27)	
55 – 65	273/1055 (26%) 32 months	251/1054 (24%) 43 months	0.85 (0.71, 1.01)	
65 – 75	343/1198 (29%) 27 months	323/1208 (27%) 32 months	0.87 (0.74, 1.01)	
≥ 75	117/371 (32%) 18 months	106/340 (31%) 27 months	0.81 (0.62, 1.05)	0.9337
BMI: <20	141/352 (40%) 17 months	119/297 (40%) 19 months	0.88 (0.69, 1.13)	
20 – 25	276/1024 (27%) 24 months	271/1074 (25%) 35 months	0.81 (0.68, 0.96)	
25 – 30	250/1033 (24%) 37 months	242/1039 (23%) 43 months	0.91 (0.77, 1.09)	
≥ 30	144/597 (24%) 37 months	127/576 (22%) 45 months	0.86 (0.68, 1.09)	0.8073
Anticholinergic Use:	411/1350 (30%)	401/1366 (29%)	0.85 (0.74, 0.97)	
Yes	23 months	27 months		
No	400/1656 (24%) 38 months	358/1620 (22%) 45 months	0.85 (0.74, 0.98)	0.9418

*Hazard ratio based on Cox model with treatment, baseline covariate and baseline covariate by treatment interaction; p-value was obtained using log-rank test.

Table 21: Estimated Rate of Patients with Exacerbation per Patient-Year

	Placebo	Tiotropium	Ratio 95% CI	p-value*
Overall	0.85	0.73	0.86 (0.81, 0.91)	
Sex: Female	0.92	0.77	0.84 (0.74, 0.94)	0.6084
Male	0.82	0.71	0.87 (0.81, 0.93)	
Gold Stage: I/II	0.70	0.56	0.80 (0.72, 0.88)	0.2462
III	0.97	0.85	0.88 (0.80, 0.95)	
IV	1.15	1.05	0.92 (0.76, 1.12)	
Baseline Smoking Status				0.3930
Ex-Smoker	0.87	0.73	0.84 (0.78, 0.91)	
Smoker	0.79	0.71	0.90 (0.80, 1.01)	
Reversibility: Yes	0.82	0.69	0.85 (0.78, 0.92)	0.7430
No	0.87	0.76	0.87 (0.79, 0.95)	
Baseline ICS: Yes	0.96	0.82	0.85 (0.79, 0.92)	0.8834
No	0.67	0.57	0.86 (0.77, 0.96)	
Baseline LABA: Yes	0.96	0.81	0.84 (0.78, 0.91)	0.4690
No	0.68	0.60	0.89 (0.79, 0.99)	
Baseline ICS/LABA: Yes	1.00	0.85	0.85 (0.78, 0.92)	0.7915
No	0.71	0.61	0.86 (0.79, 0.95)	
Race: White	0.84	0.73	0.87 (0.81, 0.93)	0.2324
Black	0.62	0.39	0.63 (0.33, 1.19)	
Asian	0.92	0.66	0.72 (0.56, 0.93)	
Region: Asia	0.92	0.68	0.73 (0.57, 0.94)	0.2959
E. Europe	0.61	0.58	0.95 (0.82, 1.11)	
Latin America	1.09	0.82	0.82 (0.61, 0.92)	
USA	0.75	0.65	0.65 (0.75, 0.98)	
W. Europe	0.97	0.83	0.86 (0.79, 0.94)	
Age: <55	0.75	0.64	0.86 (0.72, 1.03)	0.9933
55 – 65	0.84	0.72	0.86 (0.77, 0.95)	
65 – 75	0.85	0.74	0.87 (0.79, 0.95)	
≥ 75	0.96	0.81	0.84 (0.70, 1.01)	
BMI: <20	1.12	0.88	0.78 (0.65, 0.93)	0.3807
20 – 25	0.83	0.73	0.88 (0.79, 0.98)	
25 – 30	0.79	0.72	0.90 (0.81, 1.00)	
≥ 30	0.81	0.66	0.81 (0.70, 0.93)	
Anticholinergic Use:				0.3745
Yes	0.93	0.81	0.88 (0.80, 0.96)	
No	0.79	0.65	0.83 (0.76, 0.91)	

*Estimated mean and Ratio were calculated based on Poisson model with overdispersion adjusting for time at risk

4.2 PRE- AND POST-BRONCHODILATOR FEV₁

Additional subgroup analyses were conducted on the estimated mean pre- and post-bronchodilators FEV₁ scores at each visit. The results are summarized in Table 22 and Table 23, respectively. There appears to be a quantitative interaction between treatment and baseline ICS in the estimated mean pre- and post-bronchodilators FEV₁ scores. This implies that the treatment effect in each subgroup is in the same direction, but of ‘slightly’ different magnitude. The results from these subgroup analyses also were consistent with the overall treatment effect. Like baseline ICS, there is also a quantitative interaction between treatment and baseline anticholinergic in the estimated mean post-bronchodilators FEV₁ scores. The results from this subgroup analysis also were consistent with the overall treatment effect.

Table 22: Estimated* mean pre-bronchodilator FEV₁ from Day 30 until completion of double-blind treatment - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48)

	Treatment		Mean (SE) [ml/yr]	Difference	
	Placebo Mean (SE)	Titropium Mean (SE)		95% CI	p-value*
Pre-BD	1.080 (0.004)	1.174 (0.004)	0.094	(0.084, 0.105)	<0.0001
Sex: Female	0.875 (0.007)	0.955 (0.007)	0.080	(0.062, 0.099)	0.1742
Male	1.144 (0.005)	1.242 (0.004)	0.099	(0.087, 0.111)	
Gold Stage: I/II	1.293 (0.006)	1.403 (0.006)	0.110	(0.093, 0.126)	0.2388
III	0.903 (0.005)	0.991 (0.005)	0.088	(0.074, 0.103)	
IV	0.624 (0.010)	0.659 (0.010)	0.035	(0.008, 0.063)	
Baseline Smoking Status: Ex-Smoker	1.059 (0.004)	1.152 (0.004)	0.093	(0.081, 0.105)	0.2833
Smoker	1.131 (0.007)	1.228 (0.007)	0.097	(0.077, 0.117)	
Reversibility: Yes	1.113 (0.005)	1.221 (0.005)	0.108	(0.094, 0.122)	0.6380
No	1.040 (0.005)	1.120 (0.005)	0.080	(0.065, 0.095)	
Baseline ICS: Yes	1.064 (0.005)	1.153 (0.005)	0.089	(0.075, 0.102)	0.0319
No	1.104 (0.006)	1.207 (0.006)	0.103	(0.088, 0.119)	
Baseline LABA: Yes	1.052 (0.005)	1.120 (0.006)	0.093	(0.080, 0.106)	0.3031
No	1.146 (0.005)	1.216 (0.006)	0.096	(0.080, 0.113)	
Baseline ICS/LABA: Yes	1.045 (0.005)	1.143 (0.005)	0.098	(0.083, 0.113)	0.2051
No	1.111 (0.005)	1.202 (0.005)	0.091	(0.077, 0.106)	
Race: White	1.099 (0.004)	1.194 (0.004)	0.095	(0.084, 0.106)	0.7327
Black	0.941 (0.020)	1.026 (0.022)	0.085	(0.026, 0.144)	
Asian	0.823 (0.011)	0.917 (0.011)	0.094	(0.064, 0.125)	

	Treatment		Mean (SE) [ml/yr]	Difference	
	Placebo Mean (SE)	Titropium Mean (SE)		95% CI	p-value*
Pre-BD	1.080 (0.004)	1.174 (0.004)	0.094	(0.084, 0.105)	<0.0001
Region: Asia	0.815 (0.012)	0.910 (0.011)	0.095	(0.064, 0.127)	
E. Europe	1.168 (0.010)	1.245 (0.010)	0.077	(0.051, 0.104)	
Latin America	0.947 (0.012)	1.029 (0.012)	0.082	(0.049, 0.116)	
USA	1.062 (0.007)	1.155 (0.007)	0.094	(0.075, 0.113)	
W. Europe	1.106 (0.006)	1.212 (0.006)	0.106	(0.090, 0.122)	0.9936
Age: <55	1.217 (0.012)	1.320 (0.012)	0.104	(0.070, 0.138)	
55 – 65	1.106 (0.007)	1.199 (0.007)	0.093	(0.075, 0.111)	
65 – 75	1.039 (0.005)	1.135 (0.005)	0.096	(0.081, 0.111)	
≥ 75	0.958 (0.009)	1.043 (0.009)	0.085	(0.060, 0.110)	0.4898
BMI: <20	0.861 (0.010)	0.941 (0.010)	0.080	(0.053, 0.107)	
20 – 25	1.027 (0.006)	1.123 (0.006)	0.096	(0.077, 0.115)	
25 – 30	1.124 (0.007)	1.223 (0.006)	0.099	(0.081, 0.117)	
≥ 30	1.199 (0.009)	1.289 (0.009)	0.090	(0.066, 0.114)	0.1740
Anticholinergic:					
Yes	1.031 (0.006)	1.122 (0.006)	0.092	(0.076, 0.108)	
No	1.117 (0.005)	1.214 (0.005)	0.097	(0.083, 0.110)	0.0757

*Estimated (least squares) means are based on repeated measures ANOVA model with visit as a discrete variable and baseline value as a covariate.

Table 23: Estimated* mean post-bronchodilator FEV₁ from Day 30 until completion of double-blind treatment - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48)

	Treatment		Mean (SE) [ml/yr]	Difference	
	Placebo Mean (SE)	Titropium Mean (SE)		95% CI	p-value
Post-BD	1.298 (0.004)	1.354 (0.004)	0.057	(0.046, 0.067)	<0.0001
Sex: Female	1.053 (0.007)	1.106 (0.007)	0.053	(0.034, 0.071)	
Male	1.375 (0.005)	1.433 (0.004)	0.058	(0.045, 0.070)	0.4672
Gold Stage: I/II	1.544 (0.006)	1.613 (0.005)	0.069	(0.054, 0.084)	
III	1.098 (0.006)	1.148 (0.006)	0.050	(0.034, 0.065)	
IV	0.753 (0.012)	0.771 (0.011)	0.018	(-0.014, 0.049)	0.5848
Baseline Smoking Status: Ex-Smoker	1.276 (0.004)	1.326 (0.004)	0.050	(0.038, 0.062)	
Smoker	1.351 (0.008)	1.424 (0.007)	0.072	(0.052, 0.093)	0.4070
Reversibility: Yes	1.387 (0.005)	1.446 (0.005)	0.059	(0.045, 0.072)	
No	1.196 (0.006)	1.248 (0.006)	0.052	(0.036, 0.068)	0.4913

	Treatment		Mean (SE) [ml/yr]	Difference	
	Placebo Mean (SE)	Titropium Mean (SE)		95% CI	p-value
Post-BD	1.298 (0.004)	1.354 (0.004)	0.057	(0.046, 0.067)	<0.0001
Baseline ICS: Yes	1.278 (0.005)	1.329 (0.005)	0.051	(0.038, 0.065)	
No	1.329 (0.006)	1.394 (0.006)	0.065	(0.049, 0.080)	0.0467
Baseline LABA: Yes	1.268 (0.005)	1.326 (0.005)	0.058	(0.045, 0.072)	
No	1.342 (0.006)	1.396 (0.006)	0.054	(0.038, 0.070)	0.7631
Baseline ICS/LABA:					
Yes	1.260 (0.006)	1.322 (0.005)	0.062	(0.047, 0.078)	
No	1.333 (0.005)	1.384 (0.005)	0.051	(0.037, 0.065)	0.4761
Race: White	1.321 (0.004)	1.379 (0.004)	0.057	(0.046, 0.069)	
Black	1.137 (0.018)	1.151 (0.021)	0.013	(-0.041, 0.068)	
Asian	1.004 (0.012)	1.062 (0.011)	0.058	(0.026, 0.090)	0.5805
Region: Asia	0.998 (0.012)	1.056 (0.011)	0.057	(0.025, 0.089)	
E. Europe	1.373 (0.010)	1.429 (0.011)	0.056	(0.029, 0.084)	
Latin America	1.171 (0.013)	1.202 (0.013)	0.032	(-0.003, 0.067)	
USA	1.295 (0.007)	1.344 (0.006)	0.049	(0.031, 0.066)	
W. Europe	1.327 (0.006)	1.394 (0.006)	0.066	(0.050, 0.082)	0.9726
Age: <55	1.456 (0.013)	1.537 (0.012)	0.081	(0.046, 0.116)	
55 – 65	1.332 (0.007)	1.391 (0.006)	0.060	(0.041, 0.078)	
65 – 75	1.252 (0.005)	1.300 (0.005)	0.048	(0.033, 0.063)	
≥ 75	1.140 (0.009)	1.189 (0.009)	0.050	(0.025, 0.075)	0.3673*
BMI: <20	1.044 (0.009)	1.100 (0.010)	0.056	(0.030, 0.081)	
20 – 25	1.238 (0.006)	1.302 (0.006)	0.064	(0.047, 0.081)	
25 – 30	1.352 (0.007)	1.406 (0.006)	0.054	(0.036, 0.072)	
≥ 30	1.426 (0.009)	1.475 (0.009)	0.048	(0.024, 0.073)	0.3165
Anticholinergic:					
Yes	1.248 (0.006)	1.296 (0.006)	0.049	(0.032, 0.065)	
No	1.336 (0.005)	1.399 (0.005)	0.063	(0.049, 0.076)	0.0225

By-subgroup estimated (least squares) means are based on repeated measures ANOVA model with visit as a discrete variable and baseline value as a covariate

p-value based on test of interaction using repeated measures ANOVA with treatment, visit, subgroup, and treatment by subgroup interaction

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

The Applicant proposed to add 'Long-Term Effect of Lung Function', 'Exacerbation' and 'Survival and Respiratory Failure' in the Clinical Section of the SPIRIVA Handihaler label.

On January 11, 2008, the Applicant submitted the results of a six-month clinical trial with Spiriva HandiHaler (Study 266 or VA study) as pivotal evidence to support inclusion of the 'exacerbation' language in the labeling of Spiriva Handihaler. After careful review of the application, the Division concluded that the submitted data failed to provide substantial evidence of efficacy to support labeling claim for reduction of exacerbation in patients with COPD. In the Action Letter, it stated the following deficiency that precludes approval of the application.

The submitted data do not provide substantial evidence of efficacy to support the labeling claim for reduction of exacerbation in COPD patients. Replicate findings from two adequate and well controlled studies are necessary to support a COPD exacerbation labeling claim. The results from combined analysis of clinical studies 205.254 and 205.255 are not acceptable for replication because these studies were conducted with Spiriva Respimat, 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 HandiHaler compared to placebo.

The Division Director's Memo summarized the results from Study 266

The submitted data failed to show substantial evidence to support a reduction of COPD exacerbation claim for Spiriva HandiHaler. Results of the co-primary efficacy variables for study 266 are shown in Table 13. One of the two co-primary efficacy variables was met in this study and the other efficacy variable showed positive trend. Secondary efficacy variable generally trended in the right direction, but the results were not consistent (additional data not shown in this review). This study, while it may be considered positive, is not sufficiently robust to support approval of the labeling claim.

On January 30, 2009, the Applicant submitted a Complete Response to the FDA November 13, 2008 Complete Response letter for NDA 21-395 Serial No. 024. In this submission, they referred to the data and summaries from the UPLIFT clinical trial (Serial No. 029) to address the Division's comments regarding the reduction in COPD exacerbations, as well as stroke. In the UPLIFT Study Report, the Applicant claimed the following:

Tiotropium did result in significant improvement in lung functions (i.e. FEV₁, FVC, and SVC, and this improvement was maintained over the four years of the trial. They also claimed that tiotropium reduced the risk of the first COPD exacerbation and the risk of the first COPD exacerbation leading to hospitalization by 14% each. Tiotropium significantly reduced the number of COPD exacerbations by 14%, and reduced the number of exacerbation days by 11%. The two treatment groups had comparable numbers of COPD exacerbations leading to hospitalization and comparable numbers of hospitalization days.

In the UPLIFT study, the co-primary endpoints directly relate to the study objective and these were the focus of the design and power of the study. However, statistical significance was not achieved in favor of tiotropium for these co-primary endpoints in order to continue testing the 'key' secondary endpoints (i.e. time to the first COPD exacerbation and time to the first COPD exacerbation leading to hospitalization) and 'other' endpoints (i.e. estimated mean pre- and post-bronchodilators FEV₁ by visit), based on a pre-specified multiplicity adjustment strategy. In the strictest sense of alpha spending, all the alpha has been spent by the primary efficacy analyses. Furthermore, evaluating the secondary endpoints (i.e. COPD exacerbation) is "to provide additional clinical characterization of

the treatment effect”. Although the observed results (i.e. reduction in risk of COPD exacerbation) were in favor of tiotropium, the evidence from this study is insufficient to support the result from the VA study and to warrant a claim ‘for reduction of exacerbation in patients with COPD’.

In the VA study, only one of the two ‘co-primary’ endpoints achieved statistical significance. Similar to the UPLIFT Study, the secondary endpoint (i.e. time-to-first COPD exacerbation) is the basis of the labeling claim ‘for reduction of exacerbation in patients with COPD’. Like the UPLIFT study, multiplicity is a problem in interpreting the result of the secondary endpoint analysis because not all primary endpoints achieved statistical significance. However, as Dr. Davi pointed out in her review, there is a correlation between the primary analysis and secondary analysis of the same outcome (i.e. COPD exacerbation) such that it is unlikely the result of the time-to-first COPD exacerbation analysis is a spurious finding. Nevertheless, the overall conclusion by the Division was that the evidence is insufficient to warrant a claim from the VA study.

Therefore the statistical evidence taken collectively from the VA Study and the UPLIFT study, in particular because of the multiplicity issue in the UPLIFT study, does not support labeling claim for reduction of exacerbation in patients with COPD.

Aside from ‘COPD exacerbation’, the Applicant proposed to add the long-term effect in lung function (FEV₁) in the Clinical Section of the label. They claimed that “SPIRIVA HandiHaler maintained improvements in pulmonary function throughout 4 years. Specifically, SPIRIVA HandiHaler sustained improvements in trough (pre-dose) FEV₁ (adjusted means over time: 87 – 103 mL) throughout the 4 years of the study.” Like COPD exacerbation, multiplicity is a problem in interpreting the results of these secondary analyses (i.e. estimated mean pre- or post-bronchodilator FEV₁). Furthermore, ‘maintenance’ and ‘sustainability’ are hard to quantify when group means are used instead of individual response. In other words, there are no pre-defined criteria that would allow us to determine ‘maintenance’ of effect.

Nonetheless, the current approved label indicated that

SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (forced expiratory volume in one second, FEV₁), with peak effect occurring within 3 hours following the first dose.

In addition, the label described the results from the one-year and the six-month placebo controlled studies. It stated that there is evidence that improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year and the 6-month treatment period, respectively.

The result from UPLIFT study was consistent with the one-year and six-month studies when the mean trough FEV₁ scores were calculated throughout the 4-year period. When continuous responder analyses were performed for each Visit until Month 48, there is evidence that a higher proportion of patients treated with tiotropium responded better compared to the placebo as early as Month 1. Visually, the difference was maintained until Month 48 for the pre-bronchodilator FEV₁, and until at least until Month 24 for the post-bronchodilator FEV₁. Therefore the evidence from the UPLIFT study does support labeling claim for long-term effect in lung function.

The Applicant also proposed to include the following result in the Clinical Section of the label:

Improvement in symptom scores was also seen in patients treated with SPIRIVA HandiHaler compared to placebo.

Based on statistical review of the UPLIFT study, the evidence that there is improvement in symptom score is insufficient to warrant inclusion in the Clinical Section of the Label.

Lastly, the Applicant proposed to add mortality and respiratory failure claims in the Clinical Section of the label. The following is the proposed language:

In the 4-year multicenter trial, there was a 16% reduction in the risk of death while on treatment with SPIRIVA HandiHaler compared to placebo. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.78 per 100 patient years in the placebo group [Hazard Ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97]. Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00].

Like COPD exacerbation and long-term effect in lung function, mortality and respiratory failure are classified as secondary endpoints. However, unlike COPD exacerbation and lung function, the general consensus is that mortality can reach the status of a primary endpoint, if analyzed properly and supported by other study. In papers written by Dr. D'Agostino Sr.³ and Dr. O'Neill⁴ and several other researchers, they have alluded that a statistically significant finding on mortality has clinical impact. They also stated that the usual reason for designating mortality as a secondary endpoint is that the trialist believes *a priori* that there is little chance a treatment effect will be observed, given the sample sizes and the power to detect a clinically important effect on mortality.

In the UPLIFT Study, there is evidence of a benefit of tiotropium on on-treatment mortality. However, because a different result was observed in another SPIRIVA application using RESPIMAT delivery system, the result from UPLIFT needs to be explored further. Of note, in the RESPIMAT application, an increased number of deaths were observed in the Spiriva Respimat treatment groups compared to placebo for 1-year pivotal trials, resulting in a Complete Response action for the Spiriva Respimat NDA. Although there is evidence of a benefit of tiotropium on on-treatment mortality, a different result was observed in another SPIRIVA application using the RESPIMAT delivery system which complicates the mortality claim. On July 22, 2009, the Applicant amended the efficacy supplement to remove the mortality claim to main consistency with global labeling. According to the Applicant, there was no new Spiriva Handihaler data contributing to this decision.

The following is from Dr. Michele's review about the 'respiratory failure claim.

Based on the SAE data, the applicant is requesting a claim for reduction in respiratory failure. BI proposes the following language for the clinical studies section of the label: "In the 4-year multicenter trial....Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI 0.65, 1.00]."

While the incidence of SAEs of respiratory failure is reduced in the tio HH18 group, the difference is marginally significant and there are multiple related preferred terms that have been analyzed separately. Unlike mortality, which is a hard endpoint and was pre-specified in the protocol as an event of interest (including vital status collection and an independent adjudication committee), the term "respiratory failure" is undefined and subject to investigator interpretation. Inclusion of the term respiratory failure may be appropriate as part of adverse event reporting for the study; however, there is insufficient evidence to justify a specific claim that Spiriva HandiHaler reduces respiratory failure.

³ Ralph D'Agostino Sr., "Controlling alpha in a clinical trial: the case for secondary endpoints", Statistics in Medicine, 2000 19: 763-766

⁴ Robert T. O'Neill, "Secondary Endpoints Cannot be Validly Analyzed if the Primary Endpoint Does Not Demonstrate Clear Statistical Significance", Controlled Clinical Trials, 1997 18: 550-556

5.2 CONCLUSIONS AND RECOMMENDATIONS

Spiriva HandiHaler (tiotropium bromide inhalation powder) was approved on January 30, 2004 for long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

The primary objective of the clinical program is to supplement the Clinical Studies section of the product information with additional information to prescribers concerning the long-term (4 year) efficacy and safety of tiotropium in the treatment of patients with COPD, based on the results from the UPLIFT study. The requested efficacy claims are: 1) description of the long-term effects on lung function, 2) reduction in exacerbations, 3) reduction in mortality, and 4) reduction in respiratory failure.

From a statistical perspective, because of multiplicity issue in the UPLIFT study, there is insufficient evidence that tiotropium 18 mcg is effective in reducing risk of COPD exacerbation and delaying the onset of COPD exacerbation. On the other hand, there is evidence from the UPLIFT study supporting the labeling claim for long-term effect on lung function. On July 22, 2009, the Applicant amended the efficacy supplement to remove the mortality claim. As noted in the clinical review, reduction in respiratory failure is not supported because the improvement is marginally significant and is not predefined.

A Pulmonary and Allergy Drug Advisory Committee meeting is scheduled on November 19, 2009. The Division plans to discuss the results from the UPLIFT study along with the RESPIMAT data.

6 LABELING

The following are the proposed changes and comments to the label.

1 INDICATIONS AND USAGE

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

14 CLINICAL STUDIES

The SPIRIVA HandiHaler clinical development program consisted of six Phase 3 studies in 2,663 patients with COPD (1,308 receiving SPIRIVA HandiHaler): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had an FEV₁ less than or equal to 60 or 65% of predicted, and a ratio of FEV₁/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (forced expiratory volume in one second, FEV₁), with peak effect occurring within 3 hours following the first dose.

Two additional trials evaluated exacerbations: a 6-month, randomized, double-blind, placebo-controlled, multicenter clinical trial of 1,829 COPD patients in a US Veterans Affairs setting and a 4-year, randomized, double-blind, placebo-controlled, multicenter, clinical trial of 5,993 COPD patients. Long-term effects on lung function and other outcomes were also evaluated in the 4 year multicenter trial. **Reviewer: These sentences in red are new and are acceptable**

Lung Function

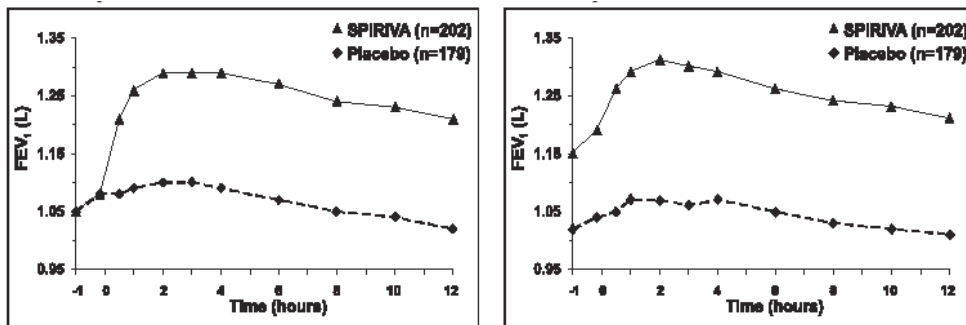
In the 1-year, placebo-controlled trials, the mean improvement in FEV₁ at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the first dose (Day 1). Further improvements in FEV₁ and FVC were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV₁, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV₁ values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV₁) with SPIRIVA HandiHaler, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

Figure 1 Mean FEV₁ Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*

Day 1

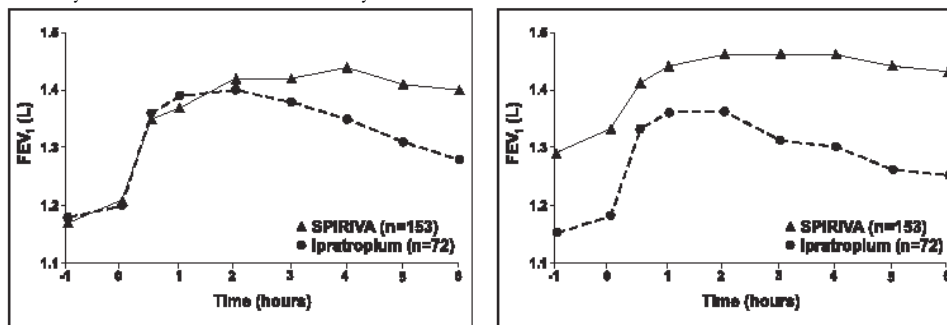
Day 169



*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HandiHaler and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

Results of each of the one-year ipratropium-controlled trials were similar to the results of the one-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV₁ Over Time (0 to 6 hours post-dose) on Days 1 and 92, respectively for one of the two Ipratropium-Controlled Studies*



*Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HandiHaler and ipratropium groups, respectively, completed through three months of observation. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

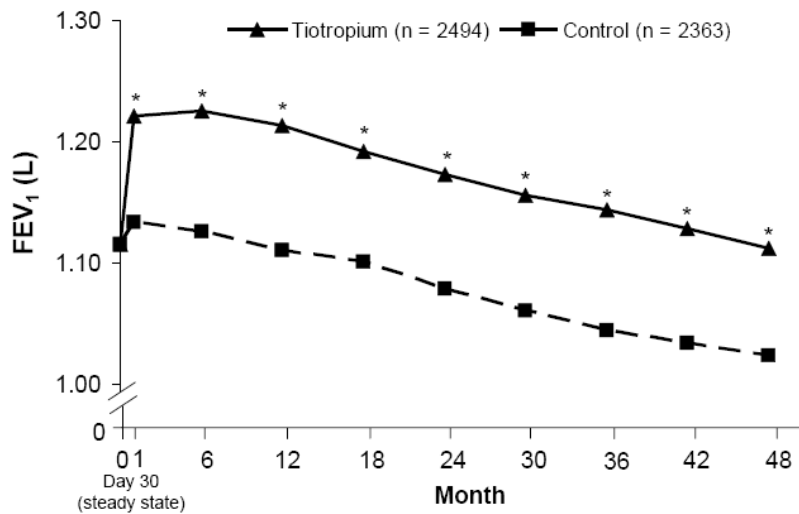
A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HandiHaler was administered in the morning or in the evening.

Throughout each week of the one-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HandiHaler had a reduced requirement for the use of rescue short-acting beta₂-agonists. Reduction in the use of rescue short-acting beta₂-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

Long-Term Effects on Lung Function

A 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial involving 5,993 COPD patients was conducted to evaluate the long-term effects of SPIRIVA HandiHaler. Patients were permitted to use all respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. The patients were 40 to 88 years of age with a diagnosis of COPD and a post-bronchodilator FEV₁ ≤70% of predicted at study entry. The co-primary efficacy endpoints, yearly rate of decline in pre- and post-bronchodilator FEV₁, were not significantly different between the two groups. [SPIRIVA HandiHaler maintained improvements in pulmonary function throughout 4 years.] [Reviewer: I suggest deleting the previous sentence because (1) it is not clear what improvement means and what criterion was maintained; and (2) it seems redundant with the next sentence. In fact, the next sentence gave a better description of what 'improvement' means.] Specifically, SPIRIVA HandiHaler sustained improvements in trough (pre-dose) FEV₁ (adjusted means over time: 87-103 mL) throughout the 4 years of the study. (Figure 3)

Figure 3 Trough FEV₁ - Mean values at each time point



*P<0.0001 vs. placebo. [I suggest removing the p-values] Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV₁ (observed mean) = 1.116. Patients with ≥ 3 acceptable PFTs after day 30 and non-missing baseline value were included in the analysis.

Exacerbations

In a 6-month clinical trial of COPD patients in a Veterans Affairs setting, SPIRIVA HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo and significantly delayed the time to first exacerbation. These findings are supported by a pre-specified combined analysis of two one-year clinical trials using SPIRIVA RESPIMAT.

Exacerbations were evaluated as a secondary outcome in the 4-year multicenter trial. In this trial, COPD exacerbations were defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular or intravenous) steroids. SPIRIVA HandiHaler reduced the risk of an exacerbation by 14% (Hazard Ratio 0.86, 95% CI = 0.81, 0.91, p<0.001) and exacerbation-related hospitalization by 14% (Hazard Ratio 0.86, 95% CI = 0.78, 0.95, p<0.002) compared to placebo. [I recommend removing this paragraph because there is insufficient evidence that tiotropium 18 mcg reduces the risk of COPD exacerbation, from a statistical perspective] Improvement in symptom scores was also seen in patients treated with SPIRIVA HandiHaler compared to placebo. [The last sentence should be removed because there is no statistical basis for this claim i.e. improvement in symptom scores]

Survival and Respiratory Failure

In the 4-year multicenter trial, there was a 16% reduction in the risk of death while on treatment with SPIRIVA HandiHaler compared to placebo. The incidence rate of death was 4.10 per 100 patient years in the tiotropium group vs. 4.78 per 100 patient years in the placebo group [Hazard Ratio (tiotropium/placebo) = 0.84, 95% CI = 0.73, 0.97]. Treatment with tiotropium reduced the risk of respiratory failure by 19% (2.09 vs. 1.68 cases per 100 patient years [relative risk (tiotropium/placebo) = 0.81, 95% CI = 0.65, 1.00]). [The claim of respiratory failure should be removed because as noted in the clinical review, reduction in respiratory failure is not supported. The improvement is marginally significant and is not predefined.]

7 APPENDIX

Appendix 1: Changes in Planned Analyses

- The co-primary endpoints, yearly rate of decline in trough FEV1 and yearly rate of decline in FEV1 90 minutes post-bronchodilators were tested at the 0.049 overall significance level (two-sided), adjusted for all interim evaluations, for the final trial analysis.
- In the protocol, it was stated that the yearly rate of decline in FEV1, FVC, and SVC pre- and post-bronchodilator from Day 1 until completion of the trial (30 days post-study drug treatment) would be compared using ANOVA, or equivalently a two-sample t-test. For robustness, the test was changed to a Wilcoxon rank sum test.
- Based on comments from the FDA (29 May 2008), the individual rate of decline from Day 30 until completion of double blinded treatment was calculated for trough (pre-bronchodilator) and post-bronchodilator FEV1 by taking the difference between the last on-treatment visit and visit 3 (Day 30) divided by the time difference. Treatment groups were compared using Wilcoxon rank sum test.
- Two secondary endpoints, time to the first exacerbation and time to the first COPD exacerbation leading to hospitalization, were identified as key secondary endpoints. In addition, a gate-keeping strategy for statistical hypothesis testing was established to test the co-primary endpoints, number of hospitalizations due to an exacerbation of COPD, and the two key secondary endpoints and the TSAP. P-value adjustment for interim analyses was planned for the number of hospitalizations due to an exacerbation of COPD and the co-primary endpoints.
- Based on comments from the FDA (29 May 2008), all the exacerbation endpoints were analyzed using the exacerbation data with seven days between distinct events. This data allowed for clear distinction between events. Number of COPD exacerbations and number of COPD exacerbations leading to hospitalization based on the Poisson model were also analyzed using an exacerbation data with 1 day between events as sensitivity analysis.
- For the number of COPD exacerbations and the number of COPD exacerbations leading to hospitalization, Poisson regression adjusted for overdispersion and exposure to treatment was performed in addition to the protocol-specified Wilcoxon rank-sum test.
- For the number of COPD exacerbation days and number of days hospitalized due to COPD exacerbation, Poisson regression adjusted for overdispersion was performed in addition to the protocol-specified Wilcoxon rank sum test.
- For the analysis of COPD exacerbations, the following endpoints were added: time to the first COPD exacerbation treated with steroids, number of exacerbations treated with steroids per patient year, time to the first COPD exacerbation treated using antibiotics, and number of exacerbations treated with antibiotics per patient year.

- The number of days between exacerbations was included as a secondary endpoint in the protocol. However, for the first and the last exacerbations, it was impossible to accurately estimate the number of days from the previous exacerbation to the first event during the trial, and from the last exacerbations in the trial to the next post-trial event. Consequently, if calculated, this endpoint would have been highly biased, especially for those patients with 0 or 1 exacerbation, thus this endpoint was not analyzed.
- The statistical analyses for respiratory mortality were based on the adjudicated primary cause of death. Matching between adjudicated and investigator reported primary cause of death was explored using descriptive statistics. Respiratory mortality specified in the trial protocol was interpreted as lower respiratory mortality, as defined by the SPRIVA® project rules.
- Analyses were added to investigate the risk of stroke in response to an FDA early communication. Kaplan-Meier estimates as well as Cox regression were carried out for stroke AE, serious AE, and fatal AEs.
- In addition to SGRQ total scores, the declines in SGRQ impact, symptom, and activity scores were analyzed.
- All the exacerbation endpoints were analyzed using the exacerbation data with seven days between distinct events. This data would allow for clear distinction between events. Number of exacerbation and number of exacerbations leading to hospitalization based on the Poisson model were also analyzed using exacerbation data with 1 day between events as sensitivity analysis.
- Individual rate of decline from Day 30 until completion of double-blinded treatment was calculated for trough and peak FEV1 by taking the difference between the last on-treatment visit and visit 3 (Day 30) divided by the time difference. Treatment groups were compared using Wilcoxon rank sum test.
- Post-unblinding analyses:
 - Assuming a patient had one rate of decline of FEV1 while on LABA or ICS (either monoproduct or combination), and another rate of decline when he/she was off LABA or ICS (not on either), a random-effects model was used to estimate treatment difference for the on- and off-LABA/ICS periods.
 - A random-effects model was used to compare treatment difference of the rate of decline of FEV1 in patients not treated with either LABA or ICS (monoproduct or combination) at baseline.
 - A random-effects model was used to compare treatment difference of the rate of decline of FEV1 in completers and in non-completers
 - To explore the sensitivity of the hazard ratio and p-values to cut-off days, different cut-off days and no cut-off were used in the Cox-regression of on-treatment deaths and all deaths including vital status. In particular, Day 1440 was planned in accordance with the designed length of the vital status collection.

- Subgroup analyses were conducted for on-treatment deaths using Cox regression with 1440-day and 1470-day cut-offs, or without any cut-off day.
- Responder analysis of SGRQ total scores was included after unblinding. A patient was considered a responder if there was a decrease of at least 4 units in SGRQ total score from the baseline. A logistic regression was used to calculate the odds ratio of responder between treatment groups at years 1, 2, 3 and 4 while adjusting for baseline covariates. The frequency table was provided for the portion of responders at these time points. Similarly, a deteriorator was defined as someone with an increase of at least 4 units in SGRQ total score from the baseline. Similar analyses of proportion of deteriorator were carried out at years 1, 2, 3, and 4.

Appendix 2: Treatment exposure – Treated Set

	Placebo	Tio 18 mcg	Total
Total treated	3006 (100.0)	2986 (100.0)	5992 (100.0)
Exposure [Months]			
>=1	2867 (95.4)	2915 (97.6)	5782 (96.5)
>=3	2740 (91.2)	2816 (94.3)	5556 (92.7)
>=6	2618 (87.1)	2726 (91.3)	5344 (89.2)
>=9	2513 (83.6)	2634 (88.2)	5147 (85.9)
>=12	2418 (80.4)	2565 (85.9)	4983 (83.2)
>=15	2344 (78.0)	2496 (83.6)	4840 (80.8)
>=18	2249 (74.8)	2432 (81.4)	4681 (78.1)
>=21	2161 (71.9)	2363 (79.1)	4524 (75.5)
>=24	2090 (69.5)	2293 (76.8)	4383 (73.1)
>=27	2013 (67.0)	2236 (74.9)	4249 (70.9)
>=30	1947 (64.8)	2177 (72.9)	4124 (68.8)
>=33	1891 (62.9)	2117 (70.9)	4008 (66.9)
>=36	1831 (60.9)	2060 (69.0)	3891 (64.9)
>=39	1779 (59.2)	2001 (67.0)	3780 (63.1)
>=42	1723 (57.3)	1970 (66.0)	3693 (61.6)
>=45	1665 (55.4)	1904 (63.8)	3569 (59.6)
Treatment Exposure [days]			
Mean	1032.7	1128.1	1080.3
Min	1	1	1
Max	1550	1655	1655
SD	533.0	466.5	512.5

Source: Clinical Study Report, Table 15.3.1.1:1 page 463

Appendix 3: Unblinded Patients – Treated Set

Country	Site Number	Patient Number	Treatment Allocation (tiotropium or placebo)	Adverse Event
Argentina	0107	10181	tiotropium	Interstitial lung disease
Brazil	0514	10591	placebo	Fecal impaction
Denmark	0801	17543	placebo	Acute laryngitis
Germany	1110	18852	tiotropium	COPD exacerbation
Greece	1201	19016	placebo	Dysphonia, pharyngeal disorder
Hungary	1304	16123	placebo	COPD exacerbation
Italy	1629	19800	tiotropium	Pneumonia
Mexico	2002	10680	tiotropium	Hyperplasia of prostate, Bladder neck obstruction
Netherlands	2109	20602	tiotropium	Shortness of breath, COPD exacerbation
New Zealand	0212	23831	placebo	Increased shortness of breath on exertion, Wheeze, Sub-acute exacerbation of COPD with asthmatic component
Singapore	1906	27043	placebo	COPD exacerbation
Spain	3027	21600	placebo	COPD exacerbation
Switzerland	3203	24308	tiotropium	Ventricular fibrillation
Thailand	3404	26645	placebo	Chest tightness, Sudden death
Thailand	3404	26639	tiotropium	Acute myocardial infarction
Turkey	3512	22812	placebo	COPD exacerbation
Turkey	3512	22815	placebo	Type 2 respiratory failure, COPD exacerbation
United States	3787	13557	placebo	Atrial flutter
United States	3788	13581	tiotropium	Atrial flutter
United States	3789	13606	placebo	Prolonged ileus
United States	3789	13615	tiotropium	Sudden death, presumably arrhythmic
United States	3789	13685	placebo	Atrial fibrillation

Source data: Patients were unblinded via IVRS. Data on file in BI Drug Safety Database.

Source: Study Report, Table 10.1.2, page 97

Appendix 4: Protocol Violations – Treated Set

	Placebo N (%)	Tio 18 mcg N (%)	Total N (%)
Treated patients	3006 (100.0)	2986 (100.0)	5992 (100.0)
Total with important PV ¹	217 (7.2)	223 (7.5)	440 (7.3)
PV Category ¹			
Known active tuberculosis	0 (0.0)	1 (0.0)	1 (0.0)
History of excluded pulmonary disease	10 (0.3)	7 (0.2)	17 (0.3)
History of thoracotomy with resection	1 (0.0)	4 (0.1)	5 (0.1)
Respiratory infection/COPD exacerbation	26 (0.9)	29 (1.0)	55 (0.9)
Unstable respiratory medication use	7 (0.2)	10 (0.3)	17 (0.3)
Known narrow-angle glaucoma	1 (0.0)	3 (0.1)	4 (0.1)
Symptomatic prostatic hyperplasia/bladder-neck obstruction	0 (0.0)	1 (0.0)	1 (0.0)
Malignancy treated in the last 5 years	5 (0.2)	2 (0.1)	7 (0.1)
Anticholinergic drug hypersensitivity	0 (0.0)	1 (0.0)	1 (0.0)
Involved in other trials	0 (0.0)	1 (0.0)	1 (0.0)
FEV ₁ >70% of predicted or FEV ₁ >70% of FVC	28 (0.9)	32 (1.1)	60 (1.0)
Informed consent signed late	2 (0.1)	2 (0.1)	4 (0.1)
Incorrect trial medication taken	1 (0.0)	0 (0.0)	1 (0.0)
Improper medication washout	39 (1.3)	43 (1.4)	82 (1.4)
Anticholinergic use for at least two consecutive visits	115 (3.8)	112 (3.8)	227 (3.8)

Source data: [Table 15.1.2: 1](#)

¹ Percentages are based on treated patients

Source: Clinical Study Report, Table 10.2:1 page 98

Appendix 5: Summary of demographic characteristics – Treated Set

	Placebo		Tio 18 mcg		Total	
	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)
Total treated	3006 (100)		2986 (100)		5992 (100)	
Sex [N (%)]						
Male	2222 (73.9)		2251 (75.4)		4473 (74.6)	
Female	784 (26.1)		735 (24.6)		1519 (25.4)	
Race [N (%)]						
White	2697 (89.7)		2691 (90.1)		5388 (89.9)	
Black	53 (1.8)		38 (1.3)		91 (1.5)	
Asian	185 (6.2)		192 (6.4)		377 (6.3)	
Missing	71 (2.4)		65 (2.2)		136 (2.3)	
GOLD stage [N(%)]						
Stage I	1 (0.0)		2 (0.1)		3 (0.1)	
Stage II	1355 (45.1)		1384 (46.3)		2739 (45.7)	
Stage III	1331 (44.3)		1304 (43.7)		2635 (44.0)	
Stage IV	271 (9.0)		250 (8.4)		521 (8.7)	
Missing	48 (1.6)		46 (1.5)		94 (1.6)	
Age [years]	3006	64.5 (8.5)	2986	64.5 (8.4)	5992	64.5 (8.5)
Height [cm]	3006	169.1 (8.7)	2986	169.3 (8.6)	5992	169.2 (8.7)
Weight [kg]	3006	74.4 (17)	2986	74.9 (17.2)	5992	74.7 (17.1)
BMI	3006	25.9 (5.1)	2986	26.0 (5.1)	5992	26 (5.1)
Smoking history [N(%)]						
Ex-Smoker	2108 (70.1)		2112 (70.7)		4220 (70.4)	
Smoker	898 (29.9)		874 (29.3)		1772 (29.6)	
Smoking history [pack years]	3006	48.4 (27.9)	2986	49 (28.0)	5992	48.7 (27.9)
COPD duration [years]	3006	9.7 (7.4)	2986	9.9 (7.6)	5992	9.8 (7.5)

Source data: [Table 15.1.4.1: 1](#)

Source: Clinical Study Report, Table 11.2:1, page 102

Appendix 6: Summary of baseline disease characteristics – Treated Set

	Pre-bronchodilator			Post-bronchodilator		
	Placebo	Tio 18 mcg	Total	Placebo	Tio 18mcg	Total
Total Treated	3006	2986	5992	3006	2986	5992
FEV ₁ [liters]						
N	2937	2908	5845	2958	2940	5898
Mean	1.092	1.101	1.096	1.315	1.328	1.322
SD	0.4	0.403	0.401	0.441	0.438	0.44
FEV ₁ increase [%]*						
N	-	-	-	2906	2877	5783
Mean	-	-	-	23.4	23.4	23.4
SD	-	-	-	18	18	18
%Predicted FEV ₁						
N	2937	2908	5845	2958	2940	5898
Mean	39.3	39.5	39.4	47.4	47.7	47.6
SD	11.9	12	12	12.6	12.7	12.7
FEV ₁ /FVC [%]						
N	2937	2908	5845	2958	2940	5898
Mean	42.1	42.4	42.3	43.3	43.6	43.4
SD	10.5	10.5	10.5	10.7	10.8	10.7
FVC [liters]						
N	2937	2908	5845	2958	2940	5898
Mean	2.626	2.625	2.625	3.09	3.09	3.09
SD	0.83	0.807	0.819	0.902	0.863	0.882
%Predicted FVC						
N	2937	2908	5845	2958	2940	5898
Mean	74.9	74.7	74.8	88.3	88.1	88.2
SD	18	18.1	18.1	18.8	18.7	18.7
SVC [liters]						
N	2925	2882	5807	2930	2909	5839
Mean	2.798	2.802	2.8	3.195	3.213	3.204
SD	0.827	0.817	0.822	0.902	0.88	0.891

Source: [Table 15.1.4.1.2](#)

* FEV₁ increase refers to % increase in FEV₁ following maximal bronchodilation, i.e., 100*(post-BD - pre-BD)/pre-BD.

Source: Clinical Study Report, Table 11.2:2, page 103

Appendix 7: Summary of baseline SGRQ scores – Treated Set

	Placebo		Tio 18 mcg		Total	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Total treated	3006		2986		5992	
Activity score*	2909	61.64 (19.3)	2888	61.44 (19.67)	5797	61.54 (19.48)
Impact score*	2909	35.68 (19.55)	2888	35.37 (18.89)	5797	35.53 (19.22)
Symptom score*	2941	50.49 (22.45)	2920	49.9 (22.64)	5861	50.2 (22.55)
Total score*	2909	46.03(17.22)	2888	45.7 (17)	5797	45.87 (17.11)

Source data: [Table 15.1.4.1: 6](#)

* ~~See footnote 1~~ ~~See footnote 2~~

Source: Clinical Study Report, Table 11.2:3, page 104

Appendix 8: Summary of pulmonary medication use at baseline – Treated Set

	Placebo		Tio 18 mcg		Total	
	N	(%)	N	(%)	N	(%)
Total treated	3006	(100.0)	2986	(100.0)	5992	(100.0)
Total taking pulmonary medication	2800	(93.1)	2788	(93.4)	5588	(93.3)
Anticholinergic (Long-Acting/Inhaled)	49	(1.6)	60	(2.0)	109	(1.8)
Anticholinergic (Short-Acting/Inhaled)	1325	(44.1)	1342	(44.9)	2667	(44.5)
Beta Adrenergics (Long-Acting/Inhaled)	1808	(60.1)	1796	(60.1)	3604	(60.1)
Beta Adrenergics (Oral/Short-Acting/Inhaled)	2047	(68.1)	2044	(68.5)	4091	(68.3)
Leukotriene Receptor Antagonists	94	(3.1)	98	(3.3)	192	(3.2)
Mucolytics	208	(6.9)	222	(7.4)	430	(7.2)
Oxygen	57	(1.9)	68	(2.3)	125	(2.1)
Steroids(Inhaled)	1860	(61.9)	1840	(61.6)	3700	(61.7)
Steroids(Other)	251	(8.3)	251	(8.4)	502	(8.4)
Xanthines	858	(28.5)	848	(28.4)	1706	(28.5)
Xanthines/Beta Adrenergics Combination	1	(0.0)	2	(0.1)	3	(0.1)

Source data: [Table 15.1.4.1: 4](#)

Source: Clinical Study Report, Table 11.2:4, page 105

Appendix 9: Subgroup Analyses for the mean slope of FEV₁ from day 30 until completion of treatment – Treated Set

Subgroup		N	Placebo Mean (SE) [ml/year]	N	Tio 18 mcg Mean (SE) [ml/year]	Subgroup by treatment interaction p-value	Difference (Tio 18 mcg - Placebo) Mean (SE) [ml/year]	F-value
Pre-BD	Age					0.5125		
	< 55	322	-41 (4)	340	-40 (3)		1 (5)	0.8302
	>= 55, <65	861	-36 (2)	908	-34 (2)		2 (3)	0.4669
	>= 65, <75	976	-24 (2)	1029	-27 (2)		-3 (3)	0.2678
	>= 75	254	-21 (4)	280	-17 (4)		4 (6)	0.4800
	Gender					0.8017		
	Male	1815	-31 (2)	1946	-31 (1)		0 (2)	0.8549
	Female	598	-27 (3)	611	-27 (3)		-1 (4)	0.8530
	Smoking status					0.1924		
	Ex-smoker	1706	-25 (2)	1818	-26 (1)		-2 (2)	0.4775
	Currently smokes	707	-43 (2)	739	-40 (2)		4 (3)	0.2743
	LABA use					0.6718		
	No	969	-33 (2)	1021	-32 (2)		1 (3)	0.7207
	Yes	1444	-28 (2)	1536	-29 (2)		-1 (2)	0.8163
	ICS use					0.5782		
	No	942	-36 (2)	989	-35 (2)		1 (3)	0.6451
	Yes	1471	-26 (2)	1568	-27 (2)		-1 (2)	0.7533
	LABA/ICS					0.4968		
	No	1254	-32 (2)	1310	-34 (2)		-1 (3)	0.6553
	Yes	1159	-28 (2)	1247	-26 (2)		1 (3)	0.6077
	Antichol inergics					0.5303		
	No	1382	-32 (2)	1409	-31 (2)		1 (2)	0.6692
	Yes	1031	-28 (2)	1148	-29 (2)		-1 (3)	0.6453
	GOLD stage					0.1913		
	I/II	1159	-37 (2)	1221	-35 (2)		2 (3)	0.3794
	III	1033	-26 (2)	1107	-27 (2)		-1 (3)	0.6233
	IV	185	-9 (5)	193	-20 (5)		-11 (7)	0.1293

Random effects model is used: treatment, subgroup and treatment by subgroup interaction for slope and intercept.

Subgroup		N	Placebo Mean (SE) [ml/year]	N	Tio 18 mcg Mean (SE) [ml/year]	Subgroup by treatment interaction p-value	Difference (Tio 18 mcg - Placebo) Mean (SE) [ml/year]	P-value
Pre-BD	Race					0.4419		
		White	2158	-31 (1)	2304		1 (2)	0.6643
		Black	46	-22 (10)	34		-17 (14)	0.2415
	Region	Asian	153	-18 (5)	165	0.7695	-2 (7)	0.7443
		Asia	147	-18 (5)	158		-2 (7)	0.8346
		E. Europe	530	-33 (3)	521		-2 (4)	0.5323
	Reversibility	Latin America	180	-32 (5)	180	0.9956	6 (7)	0.3446
		USA	565	-25 (3)	621		-2 (4)	0.6438
		W. Europe	991	-33 (2)	1077		1 (3)	0.5993
	BMI	No	1084	-31 (2)	1150	0.3721	-0 (3)	0.9666
		Yes	1255	-29 (2)	1319		-0 (3)	0.9696
	Smoking status	<20	280	-36 (4)	245	0.5718	-2 (6)	0.6917
		>=20, <25	784	-37 (2)	915		4 (3)	0.1798
		>=25, <30	852	-27 (2)	904		-0 (3)	0.9260
		>=30	497	-22 (3)	493		-4 (4)	0.2782
Post-BD	Age	< 55	322	-54 (4)	340	0.6289	6 (5)	0.2083
		>= 55, <65	860	-48 (2)	909		3 (3)	0.2877
		>= 65, <75	971	-35 (2)	1027		-1 (3)	0.8391
		>= 75	257	-35 (4)	278		6 (6)	0.3509
	Gender	Male	1812	-43 (2)	1945	0.9011	2 (2)	0.3782
		Female	598	-39 (3)	609		4 (4)	0.2945
	Smoking status	Ex-smoker	1700	-38 (2)	1815	0.9011	2 (2)	0.3432
		Currently smokes	710	-52 (3)	739		3 (4)	0.4515

Random effects model is used: treatment, subgroup and treatment by subgroup interaction for slope and intercept.

Subgroup		N	Placebo Mean (SE) [ml/year]	N	Tio 18 mcg Mean (SE) [ml/year]	Subgroup by treatment interaction p-value	Difference (Tio 18 mcg - Placebo) Mean (SE) [ml/year]	P-value		
Post-BD	LABA use					0.5703				
		No	968	-44 (2)	1018		-40 (2)	4 (3)	0.2165	
	Yes	1442	-41 (2)	1536	-39 (2)	2 (2)	0.5421			
	ICS use					0.6762				
		No	940	-45 (2)	988		-42 (2)	3 (3)	0.2676	
	Yes	1470	-40 (2)	1566	-38 (2)	2 (2)	0.4734			
	LABA/ICS					0.7128				
		No	1252	-43 (2)	1307		-42 (2)	2 (3)	0.5201	
	Yes	1158	-41 (2)	1247	-38 (2)	3 (3)	0.2583			
	Antichol inergics					0.6861				
		No	1383	-42 (2)	1405		-39 (2)	3 (3)	0.2208	
	Yes	1027	-42 (2)	1149	-41 (2)	2 (3)	0.6007			
	GOLD stage					0.0787				
		I/II	1158	-49 (2)	1218		-43 (2)	6 (3)	0.0235	
		III	1031	-38 (2)	1104		-39 (2)	-0 (3)	0.8667	
		IV	185	-23 (5)	194		-32 (5)	-9 (7)	0.2406	
	Race	White	2154	-43 (1)	2301	-40 (1)	0.7543	3 (2)	0.1880	
			Black	46	-36 (10)	34		-44 (11)	-8 (15)	0.5905
			Asian	153	-31 (6)	165		-27 (5)	4 (8)	0.5591
		White	2154	-43 (1)	2301	-40 (1)	0.7543	3 (2)	0.1880	
			Black	46	-36 (10)	34		-44 (11)	-8 (15)	0.5905
Asian			153	-31 (6)	165	-27 (5)		4 (8)	0.5591	
White		2154	-43 (1)	2301	-40 (1)	0.7543	3 (2)	0.1880		
		Black	46	-36 (10)	34		-44 (11)	-8 (15)	0.5905	
		Asian	153	-31 (6)	165		-27 (5)	4 (8)	0.5591	
BMI						0.7736				
Random effects model is used: treatment, subgroup and treatment by subgroup interaction for slope and intercept.										
Subgroup		N	Placebo Mean (SE) [ml/year]	N	Tio 18 mcg Mean (SE) [ml/year]	Subgroup by treatment interaction p-value	Difference (Tio 18 mcg - Placebo) Mean (SE) [ml/year]	P-value		
Post-BD	BMI	<20	280	-55 (4)	242	-53 (4)		1 (6)	0.8456	
		>=20, <25	782	-49 (2)	915	-44 (2)		5 (3)	0.1209	
		>=25, <30	853	-37 (2)	903	-36 (2)		2 (3)	0.5882	
		>=30	495	-34 (3)	494	-34 (3)		-0 (4)	0.9762	

Source: Clinical Study Report , Table 15.2.1:4, page 380 – 382.

Appendix 10: Estimate mean FEV1 using repeated measure ANOVA from day 30 to completion of treatment – treated set with baseline and at least 3 measurements after (including) day 30

	Time Point	Placebo Mean (SE) [L]	Tio 18 mcg Mean (SE) [L]	_Difference (Tio 18 mcg Mean (CI)	- Placebo P-value
Day 1	Pre-BD	1.116	1.116		
	Post-BD	1.347	1.347		
Month 1	Pre-BD	1.134 (0.004)	1.221 (0.004)	0.087 (0.077, 0.098)	<.0001
	Post-BD	1.372 (0.004)	1.418 (0.004)	0.047 (0.037, 0.057)	<.0001
Month 6	Pre-BD	1.126 (0.004)	1.225 (0.004)	0.099 (0.087, 0.110)	<.0001
	Post-BD	1.365 (0.004)	1.423 (0.004)	0.058 (0.047, 0.069)	<.0001
Month 12	Pre-BD	1.111 (0.004)	1.213 (0.004)	0.103 (0.091, 0.115)	<.0001
	Post-BD	1.345 (0.004)	1.398 (0.004)	0.054 (0.042, 0.065)	<.0001
Month 18	Pre-BD	1.101 (0.005)	1.192 (0.005)	0.091 (0.078, 0.104)	<.0001
	Post-BD	1.326 (0.005)	1.379 (0.005)	0.053 (0.040, 0.066)	<.0001
Month 24	Pre-BD	1.079 (0.005)	1.173 (0.005)	0.094 (0.081, 0.107)	<.0001
	Post-BD	1.294 (0.005)	1.356 (0.005)	0.062 (0.049, 0.075)	<.0001
Month 30	Pre-BD	1.061 (0.005)	1.156 (0.005)	0.095 (0.081, 0.109)	<.0001
	Post-BD	1.274 (0.005)	1.335 (0.005)	0.061 (0.047, 0.075)	<.0001
Month 36	Pre-BD	1.045 (0.005)	1.144 (0.005)	0.099 (0.085, 0.114)	<.0001
	Post-BD	1.250 (0.005)	1.315 (0.005)	0.065 (0.051, 0.080)	<.0001
Month 42	Pre-BD	1.034 (0.005)	1.129 (0.005)	0.095 (0.080, 0.110)	<.0001
	Post-BD	1.236 (0.006)	1.297 (0.005)	0.061 (0.045, 0.076)	<.0001
Month 48	Pre-BD	1.024 (0.006)	1.112 (0.005)	0.088 (0.073, 0.103)	<.0001
	Post-BD	1.219 (0.006)	1.268 (0.006)	0.049 (0.033, 0.065)	<.0001
Overall mean	Pre-BD	1.080 (0.004)	1.174 (0.004)	0.094 (0.084, 0.105)	<.0001
	Post-BD	1.298 (0.004)	1.354 (0.004)	0.057 (0.046, 0.067)	<.0001

Pre-BD: before bronchodilator on test day 1; before bronchodilator and study medication on other test days
Post-BD: after bronchodilator on test day 1; after bronchodilator and study medication on other test days
For pre-BD, N = 2363 and 2494 for treatment Placebo and Tio 18 mcg respectively
For post-BD, N = 2374 and 2516 for treatment Placebo and Tio 18 mcg respectively
The mean, standard error and 95% confidence interval are estimated using repeated measure ANOVA model
Model adjusted for baseline measurement. Day 1 (baseline) values are observed overall mean value, not estimated from the mixed model

Source: Clinical Study Report, Table 15.2.1:12 page 391

Appendix 11: Proportion of Responders* ($\geq 15\%$ improvement) in mean pre- or post-bronchodilator FEV₁ at each Visit from Baseline - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score

Month	Pre-Bronchodilator		Post-Bronchodilator	
	Placebo N=2363	Titropium N=2494	Placebo N=2374	Titropium N=2516
1	16%	33%	11%	17%
6	18%	35%	13%	21%
12	17%	33%	12%	17%
18	16%	29%	11%	16%
24	13%	25%	9%	13%
30	11%	23%	8%	12%
36	10%	21%	7%	11%
42	9%	19%	7%	9%
48	8%	16%	6%	9%

* Dropouts are considered non-responder. Last observed value carried forward to missed visit/values.

Appendix 12: Proportion of Responders* ($\geq 15\%$ improvement) in mean pre- or post-bronchodilator FEV₁ at each Visit from Baseline - Treated set with at least 3 measurements between Visits 3 – 19 (or Months 1 – 48) and have baseline score

Month	Pre-Bronchodilator		Post-Bronchodilator	
	Placebo N=2363	Titropium N=2494	Placebo N=2374	Titropium N=2516
1	16%	33%	11%	17%
6	18%	35%	13%	21%
12	17%	33%	12%	17%
18	16%	29%	11%	16%
24	13%	25%	9%	13%
30	11%	23%	8%	12%
36	10%	21%	7%	10%
42	9%	19%	6%	9%
48	8%	16%	6%	8%

* All Missing Data are considered non-responders.

Appendix 13: Subgroup Analysis for On-treatment Death (no cut-off), Cox-Regression – Treated Set

	Placebo		Tio 18 mcg		Subgroup by treatment interaction p-value	Within subgroup Tio 18 mcg vs. Placebo Hazard ratio (95% CI)	P-value
	N	Number of deaths	N	Number of deaths			
Age					0.3348		
< 55	382	26	384	24		0.82 (0.47, 1.43)	0.4873
>= 55, <65	1055	108	1054	96		0.79 (0.60, 1.04)	0.0966
>= 65, <75	1198	191	1208	194		0.95 (0.78, 1.17)	0.6507
>= 75	371	86	340	67		0.69 (0.50, 0.95)	0.0237
Gender					0.8610		
Male	2222	335	2251	310		0.84 (0.72, 0.98)	0.0253
Female	784	76	735	71		0.84 (0.61, 1.16)	0.2946
Smoking status					0.0613		
Ex-smoker	2108	299	2112	256		0.77 (0.65, 0.91)	0.0024
Currently smokes	898	112	874	125		1.04 (0.80, 1.34)	0.7847
LABA use					0.7252		
No	1198	178	1190	168		0.87 (0.70, 1.08)	0.2003
Yes	1808	233	1796	213		0.82 (0.68, 0.99)	0.0403
ICS use					0.7180		
No	1146	169	1146	158		0.87 (0.70, 1.08)	0.2151
Yes	1860	242	1840	223		0.83 (0.69, 0.99)	0.0399
LABA/ICS					0.9098		
No	1544	233	1522	211		0.84 (0.70, 1.01)	0.0640
Yes	1462	178	1464	170		0.85 (0.69, 1.05)	0.1323
Anticholinergics					0.6823		
No	2957	404	2926	375		0.85 (0.73, 0.97)	0.0194
Yes	49	7	60	6		0.71 (0.24, 2.13)	0.5428
GOLD stage					0.8363		
I/II	1356	134	1386	119		0.83 (0.65, 1.07)	0.1525
III	1331	204	1304	200		0.86 (0.71, 1.05)	0.1333
IV	271	66	250	57		0.76 (0.53, 1.09)	0.1325
Race					0.3248		
White	2697	353	2691	339		0.87 (0.75, 1.01)	0.0686
Black	53	5	38	2		0.42 (0.08, 2.19)	0.3068
Asian	185	42	192	30		0.63 (0.40, 1.01)	0.0545
Region					0.3975		
Asia	178	39	184	29		0.66 (0.41, 1.07)	0.0950
E. Europe	597	86	590	86		0.96 (0.71, 1.30)	0.7872
Latin America	207	52	198	35		0.66 (0.43, 1.02)	0.0594
USA	767	86	767	93		0.97 (0.72, 1.30)	0.8264
W. Europe	1257	148	1247	138		0.83 (0.65, 1.04)	0.1060
Reversibility					0.9145		
No	1393	227	1357	210		0.84 (0.70, 1.01)	0.0666
Yes	1513	171	1520	157		0.84 (0.68, 1.05)	0.1270
BMI					0.0782		
<20	352	72	297	75		1.06 (0.77, 1.47)	0.7111
>=20, <25	1024	131	1074	140		0.90 (0.71, 1.14)	0.3714
>=25, <30	1033	145	1039	103		0.65 (0.51, 0.84)	0.0009
>=30	597	63	576	63		0.95 (0.67, 1.35)	0.7866

P-value and hazard ratio are based on Cox regression with treatment, subgroup and treatment by subgroup interaction as covariates.
Time to death is actual death date, not the onset of fatal AE

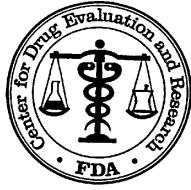
Source: Clinical Study Report, Table 15.3.3:3, page 111

Appendix 14: Subgroup Analysis for On-treatment Death (1470 days cut-off), Cox-Regression – Treated Set

	Placebo		Tio 18 mcg		Subgroup by treatment interaction p-value	Within subgroup Tio 18 mcg vs. Placebo Hazard ratio (95% CI)	P-value
	N	Number of deaths	N	Number of deaths			
Age					0.4051		
< 55	382	26	384	24		0.82 (0.47, 1.43)	0.4873
>= 55, <65	1055	106	1054	92		0.80 (0.61, 1.06)	0.1261
>= 65, <75	1198	185	1208	192		0.95 (0.78, 1.17)	0.6498
>= 75	371	85	340	66		0.70 (0.51, 0.96)	0.0289
Gender					0.9081		
Male	2222	327	2251	305		0.85 (0.72, 0.99)	0.0365
Female	784	75	735	69		0.85 (0.62, 1.18)	0.3453
Smoking status					0.0562		
Ex-smoker	2108	292	2112	252		0.78 (0.66, 0.92)	0.0034
Currently smokes	898	110	874	122		1.05 (0.81, 1.36)	0.7051
LABA use					0.8871		
No	1198	178	1190	164		0.86 (0.70, 1.07)	0.1694
Yes	1808	224	1796	210		0.84 (0.70, 1.02)	0.0762
ICS use					0.9274		
No	1146	166	1146	154		0.86 (0.69, 1.07)	0.1737
Yes	1860	236	1840	220		0.84 (0.70, 1.01)	0.0707
LABA/ICS					0.7397		
No	1544	230	1522	206		0.84 (0.69, 1.01)	0.0605
Yes	1462	172	1464	168		0.87 (0.71, 1.08)	0.2105
Anticholinergics					0.8617		
No	2957	396	2926	368		0.85 (0.74, 0.98)	0.0271
Yes	49	6	60	6		0.78 (0.25, 2.41)	0.6607
GOLD stage					0.8196		
I/II	1356	130	1386	117		0.85 (0.66, 1.09)	0.1970
III	1331	199	1304	195		0.86 (0.71, 1.05)	0.1474
IV	271	66	250	57		0.76 (0.53, 1.09)	0.1325
Race					0.3115		
White	2697	344	2691	332		0.88 (0.76, 1.02)	0.0922
Black	53	5	38	2		0.42 (0.08, 2.19)	0.3068
Asian	185	42	192	30		0.63 (0.40, 1.01)	0.0545
Region					0.4282		
Asia	178	39	184	29		0.66 (0.41, 1.07)	0.0950
E. Europe	597	86	590	84		0.96 (0.71, 1.30)	0.8091
Latin America	207	51	198	34		0.65 (0.42, 1.00)	0.0517
USA	767	85	767	91		0.96 (0.71, 1.29)	0.7738
W. Europe	1257	141	1247	136		0.85 (0.67, 1.08)	0.1854
Reversibility					0.8981		
No	1393	225	1357	208		0.84 (0.70, 1.02)	0.0725
Yes	1513	164	1520	152		0.86 (0.69, 1.07)	0.1668
BMI					0.0863		
<20	352	72	297	74		1.07 (0.77, 1.47)	0.7035
>=20, <25	1024	128	1074	138		0.91 (0.72, 1.16)	0.4637
>=25, <30	1033	141	1039	101		0.66 (0.51, 0.85)	0.0015
>=30	597	61	576	61		0.96 (0.67, 1.37)	0.8111

P-value and hazard ratio are based on Cox regression with treatment, subgroup and treatment by subgroup interaction as covariates. Time to death is actual death date, not the onset of fatal AE

Source: Clinical Study Report, Table 15.3.3:5, page 1116



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

SECONDARY STATISTICAL REVIEW

NDA/Serial Number: 21-395/S-029

Drug Name: Tiotropium Bromide Inhalation Powder (SPIRIVA HandiHaler[®])

Indication(s): Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema in Patients 40 years of age and above

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

Date(s): Received 11/17/08

Review Priority: Goal date: 12/17/09 – Standard clock with 3 month extension subsequent to additional information submission

Biometrics Division: Division of Biometrics II

Secondary Statistical Reviewer: Qian H. Li, Sc.D.

Statistics Supervisor: Thomas Permutt, Ph.D.

Medical Division: Division of Pulmonary and Allergy Products

Clinical Reviewer: Theresa Michele, M.D.

Project Manager: Miranda Raggio

Note: This is a draft review which has not been signed off by reviewer's supervisor.

SUMMARY

This review evaluates whether sufficient evidence exists to support proposed label revisions in clinical study section of tiotropium inhalation powder 18 mcg (tiotropium), also known as Sprivia Handihaler, a drug product approved in 2002 for maintenance treatment to patients with chronic obstructive pulmonary disease (COPD). The currently approved label contains the effect of tiotropium on lung function. The sponsor proposed to add long-term effects on lung functions as well as reduction on exacerbations and respiratory failure in COPD patients treated with tiotropium. The support of the proposed claims is primarily based on the results of a recently completed 4-year randomized, double-blinded, and placebo-controlled study which enrolled about 6,000 COPD patients. This study is referred to as the UPLIFT study, which stands for Understanding Potential Long-term Impacts on Function with Tiotropium.

Dr. Joan Buenconsejo conducted the primary statistical review of the UPLIFT study. Because of the differences of views in interpreting the study results, a secondary review will be written. The key difference is in whether the conclusions should be based on pre-specified decision rules in individual studies or collective evidence from multiple studies.

A closed step-down testing procedure is pre-specified in the UPLIFT study. The procedure required the primary endpoints to show statistically significant treatment difference before testing the secondary endpoints. The primary endpoints were the rates of decline in forced expiratory volume in one second (FEV1) measured before and after the administration of the study drugs. UPLIFT failed to show treatment differences between tiotropium and placebo in the rates of decline in either of the pre- or post-study drug pulmonary function measurements. The study also failed to show reduction in frequency of severe COPD exacerbation leading to hospitalization. The two primary endpoints as well as the rates of severe exacerbation leading to hospitalization are pre-specified to be tested in the first layer of the closed testing hierarchical procedure. Because the study failed on the first layer of the closed testing procedure, the primary reviewer believes no additional claims should be considered to prevent the potential inflation of type I error. Therefore the primary reviewer believes there is insufficient evidence to support the proposed claims, except the long term effect on lung function.

This secondary statistical review emphasizes evidence based evaluation using collective evidence from multiple studies and multiple endpoints. When evidence is evaluated collectively from multiple studies, consistent evidence across studies will ensure the error rate of false claims to be controlled at minimum. Because the error rate can be tightly controlled with collective evidence from multiple studies, the pre-specified multiplicity procedures from individual studies are no longer needed in the evidence based evaluation. The collective evidence from multiple studies with treatment duration ranging from 6 months to 4 years consistently shows that tiotropium maintains better effect on lung function over four-year period in COPD patients compared with placebo. Based on results of two large studies including UPLIFT, tiotropium delayed the onset of the first exacerbation, and reduced the frequency and duration of the exacerbations

compared with placebo. However, there is inconsistent evidence to support the effect of tiotropium on the severe exacerbation leading to hospitalization, which is a subset of the exacerbation. There is not sufficient evidence to support the protective effect of respiratory failure using tiotropium. Although UPLIFT showed statistically significant reduction in mortality risk, overlapping on the hazard functions between tiotropium and placebo makes it less convincing that tiotropium reduced the mortality risk.

This review first provides a brief overview of the design and results of the UPLIFT study, then discusses the problems of pre-specified decision rules and the importance of evidence based decision rules when multiple studies are available. The collective evidence from multiple studies for the effect of long term lung function and reduction in exacerbations is presented next. Notice that the arguments using collective evidence on the long term effect of pulmonary function in this review are now consistent with the primary reviewer's conclusion after a recent revision on the conclusions of the primary review. The section is kept in this review to further support the primary reviewer's conclusion on long term effect in lung function.

OVERVIEW OF THE RESULTS OF THE UPLIFT STUDY

The primary objective of the UPLIFT study is to compare the rates of decline of pulmonary function in patients with COPD treated with tiotropium and placebo. Close to 6,000 COPD patients were randomized in 1:1 ratio to tiotropium and placebo and treated over 4-year duration. The study allowed patients to take their usual pulmonary treatments available on market except the regular use of the approved anticholinergic products. The primary endpoints are the rates of decline measured by pre- and post-study drug FEV1. The uniqueness of the study design is that at the administration of study drugs, 80 mcg ipratropium was co-administrated with the study drugs, and 60 minutes later post-study drugs, 400 mcg salbutamol was also administrated in both treatment groups. Other endpoints include time to the first exacerbation and the frequency and duration of exacerbation assessments as well as endpoints on severe exacerbations leading to hospitalization. Some other pulmonary function parameters were also measured and safety endpoints such as survival and serious adverse events were obtained. A closed step-down testing procedure is pre-specified in the trial statistical analysis plan. The first layer of the procedure is to require tiotropium to show slowing down the deterioration of lung function measured as pre- and post-study drug FEV1 compared with placebo. The significance level for the two co-primary endpoints are set at 0.048. Tiotropium could have another chance passing the first layer if it showed reducing the frequency of severe exacerbation leading to hospitalization at the level of 0.001. Once the first layer is successfully achieved, the second layer is to be tested to see if tiotropium delays the onset of the first exacerbation and the onset of the first severe exacerbation leading to the hospitalization.

The results of the UPLIFT study completely failed at the first layer of the step-down closed testing procedure. There was no difference in the rates of decline of lung function between tiotropium and placebo in almost all pulmonary function assessments. The rates of decline were 30 mL/year for both tiotropium and placebo in pre-study drug (trough)

FEV1 and 40 and 42 mL/year for tiotropium and placebo, respectively, in 90 minutes post-study drug FEV1. No difference was observed in the frequencies of severe hospitalization either between the two treatment groups. The rates of severe exacerbation leading to hospitalization were 0.15 and 0.16 per person-year in tiotropium and placebo, respectively, with a p-value of 0.341 based on a Poisson regression model controlling over-dispersion.

Multiple endpoints on the effect of exacerbation were assessed, reflecting the frequency (also referred to as rate in this review) and duration of exacerbation. Time to the first exacerbation is also assessed to see if tiotropium delayed the onset of the first exacerbation compared with placebo. The severity of exacerbation is assessed separately with endpoints associated with the severe exacerbation leading to hospitalization. The multiple endpoints in fact provide collective views of tiotropium's effect on exacerbation. However, it worth to note that the proportion of patients experienced at least one exacerbation is not an adequate assessment as many patients dropped out from treatments prematurely over the four years of treatment. The median time to the first exacerbation was 16.7 months for tiotropium and 12.5 months for placebo with a p-value of <0.001 based on the log-rank test. Tiotropium reduced the frequencies of exacerbation episodes compared with placebo. The reduction rate was about 14% as compared with placebo with a p-value of <0.001 based on a Poisson regression model. For the severe exacerbation leading to hospitalization, tiotropium delayed the onset of the first hospitalization compared with placebo with a p-value of 0.002 based on the log-rank test. The median time to the first severe exacerbation was 35.9 months for tiotropium and 28.6 months for placebo. As mentioned earlier, there was no difference in the frequency of the severe exacerbations between the two treatment groups (p-value is 0.341). Therefore the reduction in overall exacerbations was primarily driven by mild cases of exacerbations.

The pulmonary function tests were assessed at pre- and 90 minutes post-study drugs. As expected, because the co-administration of ipratropium with study drugs and later salbutamol in both treatment groups, there was little room to show further immediate improvement by tiotropium at 90 minutes post-study drug FEV1 assessment, which was 30 minutes post-salbutamol administration. The bronchodilator effect of tiotropium was maintained on average 80 mL for trough FEV1 over the 4-year treatment period, and 40 mL for 90 minutes post-study drug FEV1.

The original proposed label revisions also included a claim in the reduction of mortality risk as a statistically significant reduction in mortality risk relative to placebo was seen in the tiotropium arm in the UPLIFT study. This claim was later removed by the sponsor during this review cycle, primarily due to the fact that additional imbalance was observed in mortality against tiotropium respimat formulation in a recently completed 1-year study. Such imbalance was also seen in two previously conducted 1-year studies in tiotropium respimat formulation. In the UPLIFT study, the sponsor reported a total of 981 deaths either during treatment or follow-up, of which, 467 from tiotropium and 514 from placebo. The average risk ratio including all events was 0.89 for tiotropium versus placebo (p-value=0.058). The cumulative mortality rates over four years were 17% for placebo and 15.6% for tiotropium. To understand the risks of mortality over time

between treatment groups, Figure 1 displays the two hazard functions over time for tiotropium and placebo. As can be seen from Figure 1, the two hazard functions are overlapping over time and there is no clear pattern of reduction in mortality risk in the tiotropium group (in red) compared with the placebo group (in black). The Kaplan-Meier curves of the two treatments with all events are displayed in Figure 2. Note that the analysis on overall survival includes deaths occurred during follow-up after withdrawal of treatments. This analysis may take care of the problem of potential informative censoring which may occur if patients were not followed after discontinuation of treatments, however, could be conservative if survival benefit indeed exists in tiotropium.

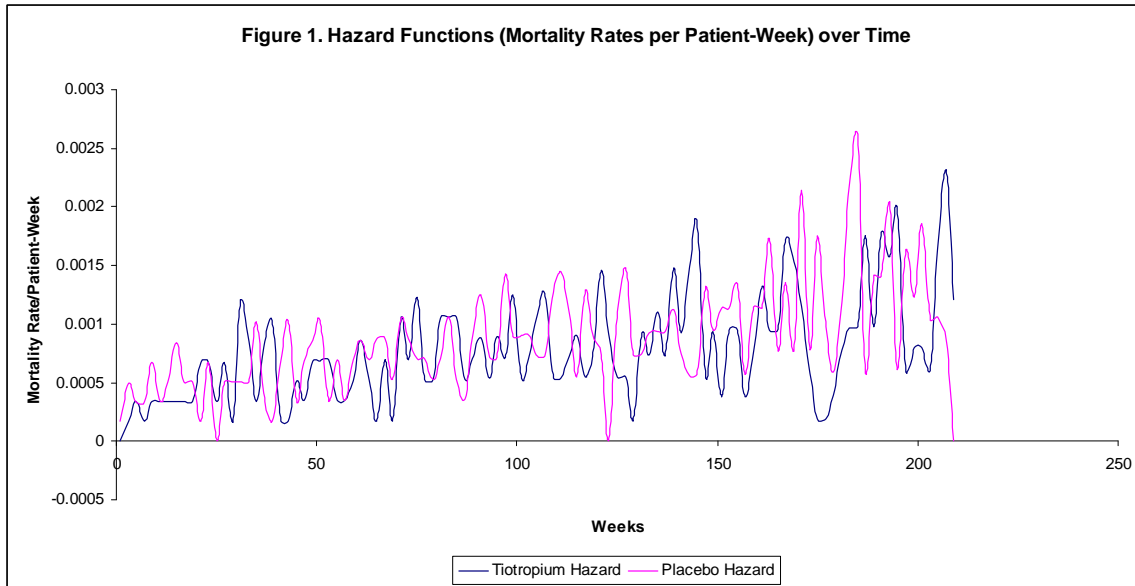
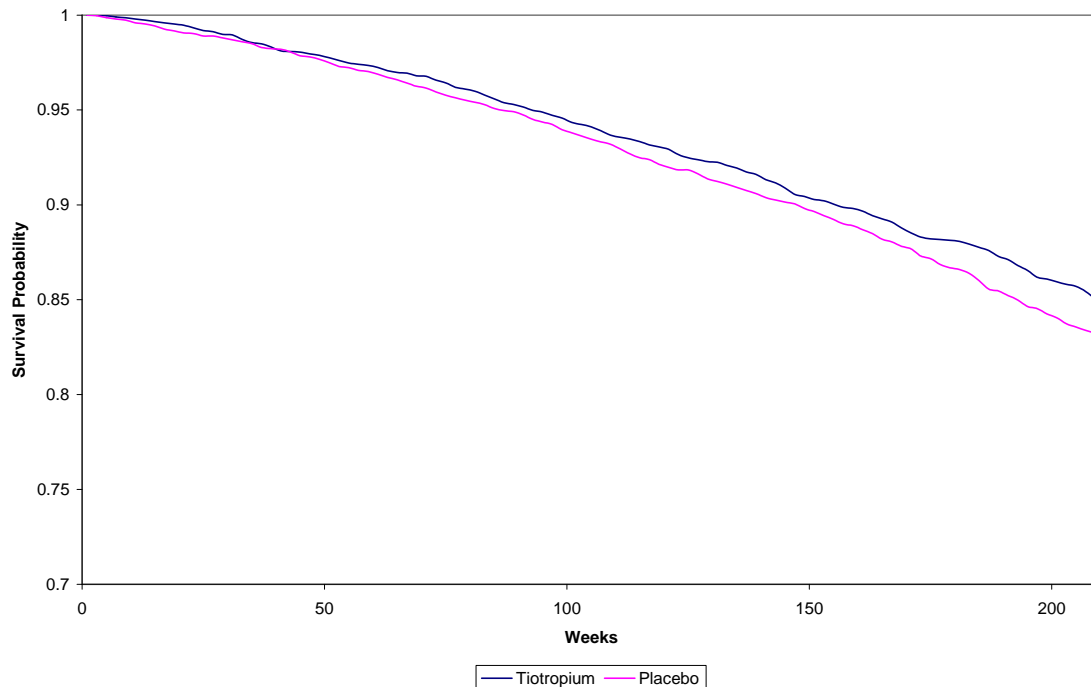


Figure 2. Kaplan-Meier Curves by Treatments



According to the study report, overall, the UPLIFT study showed less serious adverse effect in tiotropium than in placebo. The safety profile of tiotropium has been carefully evaluated by medical reviewers. The risk of respiratory failure is mentioned here as the proposed label revisions include the claim of protective effect of tiotropium on respiratory failure. A total of 198 patients reported respiratory failures, 113 in placebo and 85 in tiotropium. The risk ratio of tiotropium to placebo was 0.69 with 2-sided 95% CI [0.52, 0.92] excluding 1. While searching the reported adverse event database, it appears that a patient could experience more than one event with different severity and duration. The analyses only based on patient count may not provide complete picture of the “protective” effect. In addition, many analyses on many serious adverse events had been performed by the sponsor; the chance of observing something different can be high. Without consistent evidence from other sources to further confirm this finding, it is premature to place this claim on label.

PRE-SPECIFIED DECISION RULES VS. EVIDENCE BASED DECISION RULES

Although it is important to pre-specify in study protocols detailed experimental procedures and data analyses to ensure carefully planned studies, increased emphasis on pre-specified statistical decision rules to reduce inflation of type I error in individual clinical studies may introduce more confusion than clarity in drug evaluations. Pre-specified decision rules are particularly problematic when they are based on the expectation of study outcomes, which are often hypotheses and subject to test. The

applicability of a particular decision rule to the final outcome may be uncertain. So evaluating a drug solely based on decision rules pre-specified at the design stage, when little information is available, is not invariably a sound scientific practice.

With the case of UPLIFT, it was guessed wrong that tiotropium would slow down the decline of pulmonary function compared with placebo because of limited understanding in drug effect. As the study allowed almost all usual COPD treatments with unlimited use as concomitant therapies except the regular use of anticholinergic products, the results of no difference in decline rates of pulmonary function between the treatment groups are not a surprise.

Does this wrong decision rule imply that the data collected from the study are no longer valid? There is no reason to believe that the data collected in this study are invalid as no issue has been identified in the conduct and data collection of the UPLIFT study. In fact the conclusion of no treatment difference in rate decline of pulmonary function has to be made on valid data. The validity of information depends on the study design and conduct, rather than the expectation of the study results.

While it does not always make sense to use a pre-specified decision rule which was made when we have little information and ignores the body of new information obtained, we do need to reconcile the concern of the type I error rate inflation as it is important to control the error rate of placing spurious finding in label. This may be difficult to achieve if we have only one study, but can be an easy task if we have multiple studies. When looking for replicated and consistent evidence from the multiple studies, the error rate of false claims can be tightly controlled. An intuitive way of understanding this is that the chance for all studies to consistently show treatment effect in a drug will be very low if in truth this drug is ineffective. Mathematically, it is not difficult to calculate the probability of the error rates under the setting of collective evidence. The application of collective evidence in fact is simple and intuitive as it is illustrated below.

COLLECTIVE EVIDENCE FOR TIOTROPIUM'S EFFECT

Evidences from 6 randomized, double blind, and placebo controlled studies including UPLIFT are gathered together to collectively evaluate the effect of tiotropium in lung functions compared with placebo. Two studies, Studies 205.117 and 205.128, are one-year studies, Studies 205.130, 205.137, and 205.266 are six-month studies, and Study 205.235, the UPLIFT study, is a four-year study. Studies 205.117, 205.128, 205.130, and 205.137 were submitted in the original new drug application submission in December 2001. Study 205.266 was submitted in January 2008 and conducted in Veterans Affairs medical centers across US with less than 2% females available in this patient population. This study is also referred to as the VA study. Study 205.235 was submitted in this submission cycle. All studies allowed patients to receive certain concomitant medications. However, the VA and UPLIFT studies particularly specified in study protocols that patients were allowed to receive all usual medical care for COPD with the exception of regular use of market available anticholinergics. As mentioned before, the pulmonary function assessment in Study 235 was different from all other studies. Due to co-administration of

ipratropium and salbuterol, the effect of tiotropium on the post-study drug FEV1 is not expected to be large.

Long term effect on pulmonary function

To understand if there is sufficient evidence for the effect of tiotropium in lung function maintenance, FEV1 assessments overtime from all 6 studies are displayed in Table 1. The trough FEV1 collected in this table was the FEV1 assessed 1 hour prior the administration of study drugs and the post-dose FEV1 was collected 1 hour post study drugs for all studies with one-year duration and less except for Study 205.266. The trough FEV1 in Studies 205.235 (UPLIFT) and 205.266 (VA) was collected before the administration of study medications and the post-study drug FEV1 was collected 90 minutes post study drugs.

All pre- and post-dose FEV1 in tiotropium treatment groups are statistically significantly greater than that in the placebo groups in Table 1. Despite of the fact that the studies were designed and conducted differently and in different time period, all study results showed that tiotropium maintained better lung function in COPD patients compared with placebo measured by both pre- and post- study drug FEV1. The evidence is overwhelming within 1-year treatment duration as all of the studies except UPLIFT had treatment duration up to 1 year. Effect on lung functions longer than 1 year was only observed in the UPLIFT study.

On the surface it may appear that evidence for pulmonary function after 1 year treatment is lacking compared with what we have over the first year period. As we have concluded that tiotropium maintained better lung function over 1-year treatment period based on the collective evidence, this further validates the results of the UPLIFT study in lung function. If results in the first year of the UPLIFT study are valid, there is no reason to believe that the rest of results in lung function from the UPLIFT study are invalid. Perhaps the gradually increased dropout rate over time may be a concern in understanding the long term effect in pulmonary function. As the differential dropout rates were seen before 1 year between treatment groups in almost all studies, any bias that could be introduced may have been introduced before the first year. To understand the impact of missing data due to the discontinuation of treatment, analyses imputed with last-observation-carried-forward (LOCF) are performed by this reviewer in the UPLIFT study. The treatment differences based on LOCF approach was in fact larger than that based on the completer analyses as shown in Table 1. The analyses based on LOCF may still be considered conservative as the patients who discontinued may have even worse FEV1 than the last observation and the higher dropout rate in the placebo group compared with the tiotropium group. The sustained effect of tiotropium on lung function is therefore confirmed.

Table 1. Trough and post-dose FEV1 over time based on completer analyses.

Study	Treatment	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
Trough FEV1 (L)									
205.117	Tiotropium(n=268)	1.11	1.11						
	Placebo(n=174)	0.97	0.96						

205.128	Difference	0.14	0.16						
	Tiotropium(n=250)	1.11	1.10						
	Placebo(n=154)	0.96	0.96						
	Difference	0.15	0.15						
205.130	Tiotropium(n=202)	1.15							
	Placebo(n=179)	1.02							
	Difference	0.13							
205.137	Tiotropium(n=175)	1.17							
	Placebo(n=176)	1.05							
	Difference	0.12							
205.235	Tiotropium(n=2986)	1.20	1.20	1.18	1.17	1.16	1.16	1.14	1.14
	Placebo(n=3006)	1.11	1.10	1.10	1.08	1.08	1.07	1.08	1.07
	Difference	0.09	0.10	0.08	0.09	0.08	0.09	0.06	0.07
205.266	Tiotropium(n=904)	2.39							
	Placebo(n=908)	2.18							
	Difference	0.21							
Post dose FEV1 (L)									
205.117	Tiotropium(n=268)	1.20	1.20						
	Placebo(n=174)	0.99	0.99						
	Difference	0.21	0.21						
205.128	Tiotropium(n=250)	1.21	1.20						
	Placebo(n=154)	0.98	0.99						
	Difference	0.23	0.21						
205.130	Tiotropium(n=202)	1.29							
	Placebo(n=179)	1.07							
	Difference	0.22							
205.137	Tiotropium(n=175)	1.31							
	Placebo(n=176)	1.13							
	Difference	0.18							
205.235	Tiotropium(n=2986)	1.40	1.38	1.37	1.36	1.34	1.33	1.32	1.30
	Placebo(n=3006)	1.34	1.33	1.32	1.30	1.30	1.29	1.29	1.28
	Difference	0.06	0.05	0.05	0.06	0.04	0.04	0.03	0.02
205.266	Tiotropium(n=904)	1.24							
	Placebo(n=908)	1.07							
	Difference	0.17							

Exacerbations

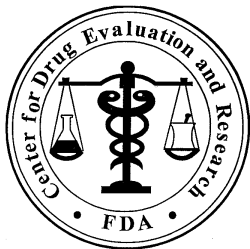
The exacerbation information was collected from the UPLIFT and VA studies. The definition of exacerbation was accepted by the medical division during the study design stage. Information from the three aspects of exacerbation including frequency, severity, and duration are summarized in Table 2. The survival analyses for the first events provided information that tiotropium delayed the first onset of exacerbation as well as the first severe events leading to hospitalization compared with placebo. Notice that the analyses for the proportions of patients who had exacerbation are not reported here as the analyses can be biased due to high rates of dropouts during the study. The cumulative incidence rates can be a better analysis as it took dropout into consideration. In the interest of understanding the reduction of exacerbation episodes, the results of Poisson regression are reported in Table 2. Looking at evidence collectively, patients treated with tiotropium experienced significantly less exacerbation episodes compared to patients treated with placebo. However, there is not consistent evidence from the two studies to show that that patients treated with tiotropium had less hospitalization episodes due to exacerbation compared to patients treated with placebo. On average there are 1 to 2 days less exacerbation days per patient-year in tiotropium compared with placebo. This difference was statistically significant in both studies. However, no difference was observed in hospitalization days due exacerbation between the two treatment groups.

Table 2. COPD Exacerbation analyses

	Study 205.235 (UPLIFT)			Study 205.266 (VA Study)		
	Tiotropium N=2986	Placebo N=3006	Ratio, (p-value)	Tiotropium N=914	Placebo N=915	Ratio, (p-value)
Exacerbation						
Median time (month)	16.7	12.5	0.86, (<0.001)	--	--	0.83, (0.034)
Total number of events	6691	7183		376	446	
Rate (number/person-year)	0.73	0.85	0.86, (<0.001)	0.71	0.88	0.81, (0.037)
Number of exacerbation days/ person-year	12.1	13.6	0.89, (0.001)	10.0	12.6	0.79, (0.056)
Exacerbation leading to hospitalization						
Median time (months)	35.9	28.6	0.86, (0.002)	--	--	0.72, (0.049)
Total number of events	1403	1379		88	124	
Rate (number/person-year)	0.15	0.16	0.94, (0.341)	0.15	0.21	0.69, (0.054)
Number of hospitalization days due to exacerbation /person-year	3.17	3.13	1.01, (0.862)	1.2	1.7	0.67, (0.249)

CONCLUSION

Based on the principle of collective evidence, it is easy to see that there is sufficient evidence to support the claim of the long term effect on pulmonary function in COPD patients treated with tiotropium. There is consistent evidence to support the exacerbation claim in tiotropium: tiotropium delayed the onset of the first exacerbation, reduced the frequency as well as duration of the exacerbation episodes as compared with placebo. However, the treatment difference was primarily driven by less severe exacerbations as the effect on the severe exacerbations leading to hospitalization was not seen in either frequency or duration. Due to the lack of effect in severe exacerbations, it is not clear if the effect on less severe exacerbation is still clinically meaningful. There is not robust evidence showing that tiotropium reduces mortality risk as the risk functions for tiotropium and placebo are almost completely overlapping. The unfavorable results on mortality imbalance observed in tiotropium respimat formulation contradict the small survival benefit observed in the UPLIFT study. There is insufficient evidence to support the claim in reduction of respiratory failure.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 02, 2009

To: Badrul A. Chowdhury
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Subject: Review of published epidemiologic literature suggesting safety concerns with tiotropium and ipratropium.

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Applicant/sponsor: Boehringer Ingelheim

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EXECUTIVE SUMMARY

Inhaled anticholinergics have been considered both effective and safe for the management of chronic obstructive pulmonary disease (COPD). Indeed, the American Thoracic Society and the Global Initiative for Chronic Obstructive Lung Disease recommend inhaled anticholinergics in the treatment of COPD [1,2].

However, a few recent publications and reports raised concerns about the safety of inhaled anticholinergics, including tiotropium bromide (TB) and ipratropium bromide (IB). These included a meta-analysis conducted by Singh and colleagues [3], which implicated anticholinergics in increasing rates of cardiovascular events; two large nested case-control studies, which suggested IB increased risk of death [4] and of certain cardiovascular events [5]; and a large cohort study by Ogale and colleagues [6], which suggested that IB and TB may increase the risk of cardiovascular events. The Office of Surveillance and Epidemiology was consulted to review these studies.

The limitations of the meta-analysis by Singh et al [3], including a biased selection of studies, lack of information on participants who discontinued trial and failure to use person-time data, and the limitations of the observational studies [4-6], of which the most important refers to their inability to adjust for important risk factors for the outcomes, may explain the reported positive associations between anticholinergics and adverse events. Additionally, these findings do not agree with the findings of previously published meta-analyses [7-10], nor do they agree with the recently published findings from a large 4-year large randomized, placebo-controlled clinical trial [11], none of which suggested an association between anticholinergics and cardiovascular events or mortality.

In conclusion, the currently available data implicating TB and IB in increasing risk of these outcomes is not compelling. While the Agency will continue to monitor the safety of these products, we do not recommend the pursuit of meta-analysis by the Agency at this time.

1 BACKGROUND/HISTORY

Tiotropium Bromide

Tiotropium bromide is a long acting anticholinergic with specificity for muscarinic receptors approved as Spiriva HandiHaler (Spiriva® Boehringer Ingelheim). This product is a dry powder capsule formulation approved on January 30, 2004 (NDA # 21-395) for the long-term, once daily management of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

On November 16 of 2007, Boehringer Ingelheim (BI) submitted a 505(b)(1) application for a novel inhalation device, the Respimat Inhalation Spray, to deliver TB for oral

inhalation. The PDUFA date for this application is September 16, 2009. During the development program, several safety issues surfaced.

On November 2005, prior to submitting the NDA, BI informed the Division of Pulmonary and Allergy Products (DPAP) about an imbalance in fatal adverse events favoring the placebo group in one of the 48-week clinical trials (study 205.255). Because the Division was concerned about the impact of this signal on the approved product Spiriva HandiHaler, the Division presented the preliminary mortality data to the Drug Safety Oversight Board (DSOB) on June of 2006. The DSOB noted the mortality signal to be weak due to the fact that (i) it was only present in one of the studies, (ii) there were no deaths in the placebo group, suggesting that the increase in mortality may have been due to the unusually low background mortality rate in that particular study, (iii) there were no specific patterns in the causes of deaths, and (iv) the safety data on HandiHaler were reassuring. The DSOB recommended that BI obtain vital status follow up data on 100% of patients who dropped out of the trials as there was substantial differential discontinuation between the placebo and TB treatment groups.

In November of 2007, BI submitted preliminary results of a routine pooled safety analysis of 29 clinical trials with Spiriva HandiHaler (n=25 studies) and Respimat (n=4 studies) (unpublished report). In this analysis, BI noted an increase in risk of stroke in patients treated with TB vs. placebo, RR and 95% CI of 1.37 (0.73, 1.56). While this analysis did not adjust for multiplicity and the association with stroke was not statistically significant, consistently with the Agency's commitment to inform the public about ongoing safety reviews, the Agency released an Early Communication on March of 2008 describing preliminary information regarding Spiriva and potential risk of stroke [12].

Additionally, the results of a recently published meta-analysis of 15* randomized clinical trials raised questions about the safety of inhaled anticholinergic agents, particularly in regards to risk of cardiovascular outcomes and premature deaths [3,13]. In this analysis, TB was associated with a borderline significant 49% increase in risk of cardiovascular outcomes [RR and 95% CI: 1.49 (0.98 - 2.26)] compared to comparator groups, which included both placebo and active controls.

Ipratropium Bromide

Ipratropium bromide is an anticholinergic agent that appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine. Atrovent HFA (®Boehringer Ingelheim) is a pressurized metered-dose aerosol unit for oral inhalation that contains a solution of IB. Atrovent HFA was approved on November of 2004 (NDA # 21-527) for maintenance treatment of bronchospasm associated with COPD.

Recently, 4 published reports raised concerns about the safety of IB. A meta-analysis of 15 randomized trials suggested a 70% increase in risk of cardiovascular events (including

* Erratum published on JAMA 301(12), 2009 which excludes data from 2 previously published trials, leaving 15 trials in the meta-analysis.

nonfatal MI, nonfatal stroke, and cardiovascular deaths) with use of IB (95% CI: 1.19 – 2.42) [3]. Additionally, a large nested case-control study including 352,631 COPD patients who utilized the Veterans Health Administration health care services, suggested that use of IB was associated with a higher risk of all-cause and cardiovascular-related deaths; OR and 95% CI were 1.11 (1.08, 1.15) and 1.34 (1.22, 1.47), respectively [4]. In another large nested case-control study of 222,272 Manitoba residents, use of IB was associated with increased risk of certain cardiovascular events (CVEs) - including supraventricular tachycardia (RR and 95% CI of 1.38 (1.10, 1.72)) and cardiac heart failure (RR and 95% CI of 1.38 (1.10, 1.72)) - although no increase in risk of myocardial infarction (MI) was observed (RR and 95% CI of 1.00 (0.85, 1.18)) [5]. Finally, a recent large cohort study suggested that anticholinergics (particularly IB) may increase risk of CVEs (RR and 95% CI of 1.29 (1.21, 1.38)) [6].

Division of Epidemiology (DEPI) Review Plan (DRP)

The Division of Epidemiology (CDER/OSE/DEPI) was consulted to review the studies/reports that recently raised concerns about the safety of inhaled anticholinergics in the management of COPD. DEPI undertook a comprehensive literature search to review the epidemiologic data concerning the association between TB/IB and various safety endpoints, including cardiac, vascular, and mortality outcomes.

The majority of previously published studies concerning the safety of inhaled anticholinergics in the management of COPD do *not* suggest that these agents may increase the risk of cardiovascular events or death (summarized in session 2.1 of this review). However, four recent publications have raised concerns regarding the cardiovascular safety of anticholinergics. This review focuses on the critical evaluation of these recently published studies, including a meta-analysis of 15 trials by Singh et al [3] (regarding the safety of both TB and IB), two large nested case-control studies by Lee et al [4] and Macie et al [5] (concerning the safety of IB regarding higher risk of death and of certain cardiovascular outcomes, respectively), and a large cohort study by Ogale et al [6], which suggested that anticholinergics may increase risk of cardiovascular events. The main objective of this review is to assess the strength and validity of these recent findings, and to discuss possible reasons for the discrepancies between these findings and the findings of previously published epidemiologic data.

Documents and databases evaluated in this review included:

- A comprehensive review of the published scientific evidence concerning the safety of inhaled anticholinergics (TB and IB)
- Report of a meta-analysis conducted by Singh et al [3],
- Report of a nested case-control study conducted by Lee et al [4],
- Report of a nested case-control study conducted by Macie et al [5],
- Report of a cohort study conducted by Ogale et al [6],
- Analyses of drug utilization patterns for TB and IB using the following databases:
 - SDI Physician Drug and Diagnosis Audit to measure indicators for use of TB and IB

- IMS Health, IMS National Sales Perspectives to determine retail and non-retail channels of distribution for TB and IB
- Wolters Kluwer Concurrent Product Analyzer to measure outpatient use of TB and IB by diagnosis code
- Wolters Kluwer SOURCE PHAST Prescription Monthly to estimate nationally projected numbers of prescriptions dispensed and unique patient counts for U.S. mail order and retail pharmacies (2005-2008)

The limitations of the meta-analysis by Singh et al [3], including a biased selection of studies, lack of information on participants who discontinued trial, and failure to use person-time data, along with the limitations of the observational studies [4-6], of which the most important refers to their inability to adjust for important risk factors for the outcomes, may explain the positive associations between anticholinergics and adverse cardiovascular events and deaths observed in these studies. Additionally, these findings do not agree with the findings of previously published meta-analyses [7-10], nor do they agree with the recent findings of a large, 4-year, randomized clinical trial [11], none of which suggest a positive association between inhaled anticholinergics and risk of serious CVEs or mortality. Therefore, the data do not provide convincing evidence to implicate use of inhaled anticholinergics in increasing risk of serious CVEs or mortality. We additionally assessed patterns of use for IB and TB between 2005 and 2008. The projected number patients (through US retail/mail order pharmacies) receiving IB prescriptions for COPD decreased steadily from 2005 to 2008 (p -trend=0.004), whereas for TB, the projected number of patients (through US retail/mail order pharmacies) receiving TB prescriptions for COPD has increased steadily from 2005 to 2008 (p -trend=0.05).

2 REVIEWER'S COMMENTS

2.1 LITERATURE REVIEW

A comprehensive literature search (in MEDLINE via PubMed, Embase, and Web of Science) was conducted to review the epidemiologic evidence concerning the association between TB / IB and various safety endpoints, including cardiac, vascular, and mortality outcomes. This review is summarized by to safety endpoint.

2.1.1 Anticholinergics and risk of stroke

In November of 2007, the sponsor submitted preliminary results of a routine safety pooled analysis of 29 clinical trials with Spiriva HandiHaler (n=25 trials) and Respimat (n=4 trials). In this analysis, the sponsor noted an increase in risk of stroke in patients treated with tiotropium vs. placebo, RR and 95% CI of 1.37 (0.73, 1.56) (unpublished report). While this analysis did not adjust for multiplicity and the association with stroke was not statistically significant, consistently with the Agency's commitment to inform the public about ongoing safety reviews, the Agency released an Early Communication on March of 2008 describing preliminary information regarding Spiriva and potential risk of stroke [12].

Recently, a large, multi-center (470 sites), multinational (37 countries) 4-year randomized, placebo-controlled double-blind trial with Spiriva HandiHaler (Understanding Potential Long-term Impacts of Function with Tiotropium - *UPLIFT*) was completed [11]. UPLIFT was conducted to assess the long-term efficacy of TB, and included 5,993 patients, males and females aged at least 40 years, who had moderate to severe COPD and a smoking history of at least 10 pack-years. Patients were randomized 1:1 to receive either 18 µg of TB or placebo once daily. In both arms, patients were allowed to take other respiratory medications, with the exception of inhaled anticholinergics. Data on vital status were systematically requested for patients who prematurely discontinued study participation 4 years after initiation of study drug. Vital status information was known for 98 and 97% of patients in the TB and placebo arms, respectively. Reports of serious and fatal adverse events were collected while patients were receiving a study drug (including the last day plus 30 days). There was no difference in the rates of stroke between the TB and the placebo groups; the RR (95% CI) was 0.95 (0.70, 1.29).

In September of 2008, BI submitted to the Agency preliminary results of a pooled analysis of 30 placebo-controlled, double blind randomized clinical trials (RCT) that also included data from UPLIFT (unpublished report). This analysis, which included 19,545 patients (10,846 on TB and 8,699 on the placebo arm) also indicated similar stroke incidence in the TB vs. placebo groups. These results were consistent with the results of the only currently published meta-analysis that examined the relation between anticholinergic and stroke risk [3], discussed in greater detail in session 2.2 of this report.

To our knowledge, there are no published observational studies that examined the relation between use of TB in the management of COPD and risk of stroke. One relatively large nested-case control in the Manitoba Population Health Research Repository reported that COPD patients who had a stroke were slightly more likely to have used IB in the year preceding the date of the event compared to COPD controls – a finding of borderline statistical significance [5]. The main limitation of this study (discussed in greater detail in session 2.4) was its inability to account for important risk factors of the outcomes, including COPD severity, smoking, BMI, and cardiac co-morbidities (beyond use of cardiac medications). Confounding by these factors may have introduced a spurious association between IB and cardiovascular events. These studies are summarized in table 1.

Table 1: Anticholinergics and risk of stroke

Ref	Design	Size	Exp	Main Results	Comments
Kesten et al 2008, <i>unpublished</i>	Meta-analysis of RCTs	30 placebo-controlled RCTs; n=19,545 patients	TB	RR: 1.03 (0.79, 1.35)	Included short and long-term BI-sponsored trials. UPLIFT alone 0.95 (0.70, 1.29) [11]
Singh et al [3]	Meta-analysis of RCTs	17 RCTs; n=13,645 patients	TB and IB	RR: 1.46 (0.81, 2.62)	10 TB RCTs, 5 IB RCTs. Placebo + active control

					trials.
Macie et al [5]	Nested case-control	4961 stroke cases/49,487 controls	IB	RR: 1.13 (1.00, 1.27)	No adjustment for important confounders

* **TB**: tiotropium bromide **IB**: ipratropium bromide

2.1.2 Anticholinergics and risk of cardiovascular events

A recently published meta-analysis by Singh et al [3] suggested that use of TB and IB is associated with increased rates of cardiovascular events (measured as a composite of nonfatal MI, nonfatal stroke, and cardiovascular death) (reviewed in detail in session 2.2 of this report). These findings do not agree with the results of two previously published meta-analyses [7,8] and of one unpublished pooled analysis that included results from UPLIFT [11].

A meta-analysis including 9 trials (n=8002 COPD patients) lasting 12+ weeks after randomization) suggested that use of TB was not related to increased rates of several cardiac events compared to placebo (n=6 trials), IB (n=2 trials) or salmeterol (n=1 trial) [8]. This meta-analysis minimized selection bias by employing pre-specified inclusion and exclusion criteria and a systematic search of both published and unpublished trials not limited to any language. All included trials used almost identical designs regarding inclusion and exclusion criteria and included patients similar in disease severity and LABA use. Bias due to selective reporting of secondary outcomes and non-intention to treat analyses was minimized by obtaining supplemental data for most studies. Summary estimates were obtained by pooling studies of similar comparator agents (*e.g.* TB vs. placebo, TB vs. IB, and TB vs. salmeterol).

A pooled analysis of 19 randomized, double-blind, placebo-controlled clinical trials of tiotropium 18 µg daily (delivered via HandiHaler), including a total of 7,819 patients and 3,821 person-years, suggested similar rates of cardiovascular events between tiotropium and placebo groups [7]. Trials were part of the pooled safety database (Boehringer Ingelheim (BI)) as of May 2004 and had similar protocols; most included patients with COPD although a limited number of trials included asthma patients. All reported safety information was collected in identical manner in the trials and the entire safety database with complete information was available for analysis, minimizing selection bias due to selective reporting of adverse events. Use of person-time analysis accounted for duration of exposure.

Finally, preliminary results of a safety pooled analysis submitted by BI on Sept of 2008, which combined the results of 30 placebo-controlled randomized clinical trials, including results from UPLIFT, suggested similar rates of cardiac and vascular events between tiotropium bromide and placebo groups (unpublished report). All included trials had similar protocols. All reported safety information was collected in identical manner in

the trials and the entire safety database with complete information was available for analysis, minimizing selection bias due to selective reporting of adverse events.

Observational data on inhaled anticholinergics and risk of cardiovascular events are scant. In a cohort study including 2862 COPD patients (470 person-years of exposure to TB and 746 person years of exposure to single-ingredient long-acting beta-agonists (LABA)) enrolled in U.K. THIN (The Health Information Network) primary care practices, no differences in cardiovascular outcomes were observed between patients taking TB against those taking LABA [14]. A recent nested case-control study [5], IB was associated with increased risk of supra-ventricular tachycardia (SVT) and heart failure (HF), but confounding may explain their findings (discussed in session 2.4 of this report). Finally, a recent cohort study [6] suggested that anticholinergics may increase risk of CVEs, but confounding may also explain these findings (discussed in greater detail in session 2.5 of this report). The main findings of these studies are summarized in table 2. Evidence for the association between cardiovascular-related mortality and anticholinergics is discussed in session 2.1.3.

Table 2: Anticholinergics and risk of cardiovascular events

Ref	Design	Size	Exp	Main Results	Comments
Singh et al [3]	Meta-analysis of RCT's	17 RCTs; 13,645 patients	TB and IB	RR of MI: 1.52 (1.04, 2.22) and CV death: 1.92 (1.23, 3.00)	12 TB RCTs, 5 IB RCTs. Placebo + active control trials.
Kesten et al [7]	Pooled analysis	19 placebo-controlled RCTs, 7,819 patients	TB	RR of various CV events compatible with 1.0; eg, RR and 95%CI of MI: 0.96 (0.46, 2.01)	Pooled safety database trials
Barr et al [8]	Meta-analysis	9 placebo-controlled RCTs, 8002 patients	TB	RR of various CV events compatible with 1.0; eg, RR and 95%CI of MI: 1.0(0.2, 3.9) and of CHF: 0.8 (0.4, 1.6)	All trials ≥12 weeks, 6 placebo-controlled trials
Kesten et al, 2008 <i>unpublished</i>	Pooled analysis	30 placebo-controlled RCTs; 19,545 patients	TB	RR of cardiac events: 0.91 (0.83, 1.01) and vascular events: 0.97 (0.87, 1.08)	Pooled safety database trials. UPLIFT alone RR of CV: 0.84 (0.73, 0.98)
Macie et al [5]	Nested case-control	11,316 cases (SVT, MI, HF)/112,920 controls	IB	RR of MI: 1.00 (0.85, 1.18), SVT: 1.38 (1.10, 1.72) and CHF: 1.47 (1.31, 1.64)	No adjustment for potentially important confounders

Jara et al [14]	Cohort	1061 TB, 1801 LABA	TB vs. LABA	RR of CV events compatible with 1.0; eg, RR and 95% CI of MI: 1.29 (0.45,3.66) and of CHF: 0.65(0.37,1.12)	UK THIN database. Matched on propensity scores. Lack of adjustment for potentially important factors
Ogale et al [6]	Cohort	82,717 newly diagnosed COPD patients	IB, TB	RR of CVEs: 1.29 (1.21, 1.38)	Lack of adjustment for potentially important risk factors

* **TB**: tiotropium bromide **IB**: ipratropium bromide; LABA: long-acting beta-agonist

2.1.3 Anticholinergics and mortality risk

A meta-analysis conducted by Singh et al [3] suggested increased rates of all-cause and cardiovascular-related mortality in anticholinergic vs. comparators (which included active control/placebo). These findings do not agree with the findings of four previously published meta-analyses [7-10] and of one recently published pooled analysis by BI which included UPLIFT (unpublished report).

A meta-analysis including 9 trials (n=8002 COPD patients) lasting 12+ weeks suggested that use of TB was not related to increased mortality compared to placebo (n=6 trials), IB (n=2 trials) or salmeterol (n=1 trial) [8]. This meta-analysis minimized selection bias by employing pre-specified inclusion and exclusion criteria and a systematic search of both published and unpublished trials not limited to any language. All included trials were of high quality, used almost identical designs regarding inclusion and exclusion criteria, and included patients similar in disease severity and LABA use. Bias due to selective reporting of secondary outcomes and non-intention to treat analyses was minimized by obtaining supplemental data for most studies.

A pooled analysis of 19 randomized, double-blind, placebo-controlled clinical trials of TB 18 µg daily (delivered via HandiHaler), including a total of 7,819 patients and 3,821 person-years, also failed to suggest an association between TB and risk of premature death (including all-cause, cardiovascular, or respiratory mortality) or serious cardiovascular outcomes [7]. Trials were part of the safety database (BI) and had similar protocols; most included patients with COPD although a limited number of trials included asthma patients. All reported safety information was collected in identical manner in the trials and the entire safety database with complete information was available for analysis, minimizing selection bias due to selective reporting of adverse events. Use of person-time analysis accounted for duration of exposure.

Salpeter and colleagues [9] published a meta-analysis of 7 placebo-controlled trials of inhaled anticholinergic agents in COPD (n=5,622 participants) which suggested a 70% decreased rates of respiratory deaths in the anticholinergics compared to placebo arms,

and similar rates of all-cause deaths between anticholinergics and placebo arms. Summary estimates of 3 randomized trials (n=1,659 participants) comparing anticholinergics vs. beta-agonists in COPD suggested a non-significant 90% decreased risk in respiratory death and 80% lower risk in all-cause mortality among those taking anticholinergics compared to those taking beta-agonists. In this meta-analysis, systematic literature search was conducted only through published studies; therefore, publication bias cannot be ruled out. Additionally, it is unclear whether information on the outcomes of interest was obtained for those who dropped out of the study so that selection bias may have influenced their results.

A meta-analysis of 9 randomized clinical trials showed similar all-cause mortality rates in anticholinergic vs. placebo groups. This analysis included COPD trials lasting 12+ weeks. Systematic literature search was conducted only through studies published in the English language; therefore, publication bias may have influenced their findings. Additionally, selection bias cannot be ruled out as information on withdrawal and follow-up was not available for some of the studies. Mortality was not the primary outcome in any of the included trials [10].

Finally, preliminary results of a report submitted by BI on Sept of 2008 (unpublished report), which combined the results of 30 placebo-controlled randomized clinical trials, including results from UPLIFT [11], suggested slightly lower mortality rates in the TB compared to placebo participants. All included trials had similar protocols. All reported safety information was collected in identical manner in the trials and the entire safety database with complete information was available for analysis, minimizing selection bias due to selective reporting of adverse events. Use of person-time analysis accounted for duration of exposure. The results of UPLIFT alone suggested a non-statistically significant decrease in mortality rates favoring the TB arm. The RR (95% CI) for all deaths was 0.89 (0.79, 1.02).

The observational data also did not provide evidence of an association between use of TB and increased risk of death. A population-based cohort study including 10,603 residents of Denmark who were of at least 40 years of age and who had been hospitalized for COPD suggested no differences in incidence of death between those who were and those who were not prescribed TB [15]. Two cohort studies compared mortality rates between TB and LABA users; one reported similar rates [14] while another suggested a modest decrease in mortality rates favoring TB users [16]. The observational data for IB and mortality are less consistent. A nested case-control study suggested that use of IB is associated with a higher risk of all-cause and cardiovascular-related deaths [4], but confounding by extraneous factors may explain the modest increase in risk (discussed in greater detail in session 2.3 of this report). A small cohort study suggested a 60% statistically significant increased risk of all-cause mortality with use of IB [17]. However, this association was largely driven by COPD and lung cancer-related deaths, and confounding by disease severity may explain this increase in risk. No association between IB use and all-cause mortality was observed in a larger cohort study [18]. The main findings of these studies are summarized in table 3.

Table 3: Anticholinergics and risk of death

Ref	Design	Size	Exp	Main Results	Comments
Singh et al [3]	Meta-analysis	17 RCTs; 13,645 patients	TB and IB	RR of all-cause: 1.29 (1.00, 1.65)	12 TB RCTs, 5 IB RCTs. Placebo + active control trials.
Kesten et al, 2008 <i>unpublished</i>	Pooled analysis	30 placebo-controlled RCTs ; 19,545 patients	TB	RR of all-cause: 0.88 (0.77, 1.00)	Included short and long-term trials in pooled safety database. UPLIFT alone : 0.86 (0.75, 0.99)
Kesten et al [7]	Pooled analysis	19 placebo-controlled RCTs, 7,819 patients	TB	RR of all-cause: 0.76 (0.50, 1.16)	Trials in pooled safety database
Barr et al [8]	Meta-analysis	9 RCTs, 8002 patients	TB	RR of all-cause: 0.91 (0.58, 1.42)	All trials ≥ 12 weeks, 6 placebo-controlled trials
Salpeter et al [9]	Meta-analysis	7 placebo-controlled RCTs, 9580 patients	TB and IB	RR of all-cause death: 0.80 (0.5, 1.2)	RR of resp death: 0.3 (0.1, 0.8)
Wilt et al [10]	Meta-analysis	9 RCTs	TB and IB	TB all cause 0.94 (0.60, 1.47), IB all-cause: 1.20 (0.81, 1.78)	5 placebo-controlled trials
Lee et al [4]	Nested case-control	32,130 cases and 320,501 participants	IB <i>vs.</i> short act beta-agonist	All cause: 1.11 (1.08, 1.15), CV deaths 1.34 (1.22, 1.47)	no adjustment for COPD severity or smoking
Sin and Tu [18]	Cohort	25,804 discharged COPD patients	IB	all-cause: 1.03 (0.98, 1.08)	population-based study, adj for multiple factors including disease severity
Ringbaek and Viskum [17]	Cohort	827 COPD patients	IB	all-cause: 1.6 (1.2, 2.1)	Association driven by COPD- and lung cancer-related deaths – No assoc with CVD-related deaths
De Luise et al [15]	Cohort	10,603 COPD participants	TB	All cause: 0.77 (0.65, 0.91), deaths r/t cardiac endpoints compatible with 1.	Danish population-based study. Lack of adjustment for potentially important confounders
Jara et al [14]	Cohort	1061 TB, 1801 LABA	TB vs. LABA	all cause: 0.93 (0.59, 1.44)	Lack of adjustment for potentially important confounders

Gershon et al [16]	Cohort	7,218 COPD participants	TB vs. LABA	all cause: 0.80 (0.70, 0.93)	Lack of adjustment for potentially important confounders
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* **TB:** tiotropium bromide **IB:** ipratropium bromide; LABA: long-acting beta-agonist

2.1.4 Summary of literature search and DEPI review plan

The preponderance of data concerning the safety of TB and IB in the management of COPD did not suggest that either agent may increase risk of cardiovascular events or death. However, four recent publications have raised concerns regarding the safety of anticholinergics [3-6]. This review focuses on the critical evaluation of these published studies, and to discuss possible reasons for the discrepancies between their findings and the findings of previously published studies.

2.2 SINGH S, LOKE YK, FURBERG CK. INHALED ANTICHOLINERGICS AND RISK OF MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PATIENTS WITH COPD – A SYSTEMATIC REVIEW AND META-ANALYSIS. JAMA 2008; 300: 1439-1450. [3]

2.2.1 Summary of Study

To examine the association between inhaled anticholinergics (TB and IB) and risk of cardiovascular outcomes, a systematic review and meta-analysis of randomized clinical trials was conducted. Two investigators - independently and in duplicate - conducted systematic literature searches of relevant randomized clinical trials of inhaled anticholinergics in patients with COPD published in English language in MEDLINE (through PubMed), the Cochrane Database of systematic reviews, regulatory authority Web sites in the United States and the United Kingdom, and manufacturers' trial registries with no date restrictions. Disagreements between these two investigators regarding relevance of articles were resolved by a third reviewer through a consensus process. The inclusion criteria for trials were (i) randomized clinical trial (RCT) with more than 30 days of follow-up, (ii) including patients with COPD of any severity, (iii) having an inhaled anticholinergic as the intervention vs. control group (active or placebo), and (iv) *reporting data* on the incidence of serious cardiovascular adverse events, including MI, stroke, or cardiovascular death.

The primary outcome measure was specified *a priori* as a composite of nonfatal MI, nonfatal stroke (including transient ischemic attack), and cardiovascular death (including sudden death). The secondary outcome measure was specified as all-cause mortality. Two reviewers independently and separately extracted data on MI, stroke, cardiovascular death, and all-cause mortality among trial reporting of serious adverse events. A third reviewer adjudicated in the event of discrepancy between the two reviewers.

Pooled relative risks (RR) and 95% confidence intervals (CI) for the outcomes were estimated using fixed-effect models when substantial statistical heterogeneity across

studies was not present. Statistical heterogeneity was assessed using the I^2 statistic [19]. The Rosenberg method [20] was used to assess the impact of unpublished studies in the pooled analysis. The number needed to harm (NNH) – or the number of patients with COPD who need to be treated with inhaled anticholinergics vs. comparators for one additional case of cardiovascular event – was estimated by applying the RR and estimates in a large population-based study.

A total of 703 potentially relevant citations were identified, of which 103 (n=66 tiotropium bromide, n=37 ipratropium bromide) were considered for inclusion. Of these, 86 were excluded because these were not randomized trials of anticholinergics with greater than 30 days of follow-up (n=15), did not report cardiovascular adverse events (n=69), or had no events in both study groups (n=2), leaving 17 studies (n=12 tiotropium bromide, n=5 ipratropium bromide) for the pooled analysis. Two of these studies were later excluded due to double counting of trials [21]. The trials included a total of 13,645 participants, 6,984 receiving anticholinergics and 6,661 receiving active control or placebo. Eight trials evaluated inhaled anticholinergics vs. placebo while the remaining trials evaluated anticholinergics vs. active comparators, including salmeterol, a combination of salmeterol and fluticasone, or albuterol. Of the included trials, 5 studies were of duration longer than 48 weeks (range 48 weeks to 5 years). Although trial quality was assessed, it is not clear whether and how this information was used in the pooled analysis.

Inhaled anticholinergics were found to significantly increase the risk of cardiovascular outcomes, the RR and 95% CI for anticholinergics vs. active control/placebo were 1.60 (1.22, 2.10). Among the individual components of the cardiovascular outcomes, anticholinergics increased risk of MI (RR and 95% CI for anticholinergics vs. active control/placebo in 13 trials were 1.52 (1.04, 2.22) and cardiovascular deaths; the RR and 95% CI for anticholinergics vs. vs. active control/placebo in 12 trials was 1.92 (1.23, 3.00). Anticholinergics were not significantly associated with risk of stroke; the RR and 95% CI for anticholinergics vs. vs. active control/placebo in 7 trials were 1.46 (0.81, 2.62). Tests for heterogeneity by study were not significant for primary endpoints. Anticholinergics were not associated with a significant increase in all-cause mortality (secondary outcome), the RR and 95% CI for anticholinergics vs. vs. active control/placebo in 15 trials were 1.29 (1.00, 1.65). Analyses based on random-effect models yielded results similar in magnitude and direction.

The NNH was also estimated assuming a baseline MI event rate of 10.9/1000 person-years and a baseline cardiovascular mortality event rate of 31.9/1000 person-years. The NNH for MI and cardiovascular death with inhaled anticholinergics was 174 per year (75 - 1835 per year) and 40 per year (18 – 185 per year).

Finally, the fail-safe number was estimated to assess the impact of unpublished studies in the pooled results. Sixteen non-significant long-term trials, each with a sample size of 1450, would be required to reverse the increase in risk of cardiovascular outcomes observed in the 5 long-term trials.

2.2.2 OSE Comments on Study Objectives

None

2.2.3 OSE Comments on Study Design

In the study by Singh et al, the differences/heterogeneity across the individual trials makes the summary estimates difficult to interpret, despite non-significant statistical tests for heterogeneity. Because tests for heterogeneity are customarily limited in statistical power, it is essential that investigators additionally use expert judgment to determine when and whether summary estimates are appropriate. There are several potentially important differences in the trials included in the meta-analysis by Singh et al. First, the included trials utilize different comparator groups; it is unclear whether estimates of studies comparing anticholinergic vs. placebo are comparable to estimates of studies comparing anticholinergics vs. active drugs (e.g. salmeterol, ipratropium). Further, the length of follow-up varies substantially across studies (6 weeks to 5 years). Because risk of cardiovascular outcome/mortality may differ according to length of drug exposure, pooling of studies of varying duration of follow up is not advisable. Finally, while TB and IB belong to the same class and may share many of the same side effects, the short-versus long-acting nature of the drugs can have significant implications for systemic effects such as cardiovascular events. Therefore, pooled estimates for TB and IB are difficult to interpret.

2.2.4 OSE Comments on Informed Consent (if any)

None

2.2.5 OSE Comments on Data Sources

Literature search was conducted through both published and unpublished trials independently by two reviewers (disagreements resolved by a third reviewer), which is likely to minimize the impact of publication bias and also to some extent, of selection bias. However, studies were restricted to the English language, which could have introduced publication/selection bias to the extent that ‘positive’ findings are more likely to be both published in English and to be included in the meta-analysis. There are also some important concerns regarding the inclusion criteria used to select studies that may have resulted in selection bias. These are discussed in session 2.2.7.

2.2.6 OSE Comments on Study Time Period(s)

Because cardiovascular risk associated with anticholinergics may vary according to length of drug exposure, the pooling of estimates across studies of long and shorter follow up may not be appropriate.

2.2.7 OSE Comments on Study Population

Arguably, the major limitation of the meta-analysis by Singh et al lies on their method of study inclusion, which was based on the availability of reported data on adverse events. Because none of the trials was designed to prospectively examine safety endpoints, trials

with an imbalance of events between study arms may be both more likely to report on adverse events and to be included in the meta-analysis. Indeed, despite the seriousness of the adverse events considered by Singh et al, 69 studies were not included due to failure to report on cardiovascular adverse events (study figure 1, appendix 1). According to the fail-safe number method by Rosenberg, inclusion of 16 negative trials with an average sample size of 1450 participants would render the results of Singh et al non-significant.

Selection bias from differential loss to follow up is also likely to have influenced the findings of Singh et al. Withdrawal/discontinuation proportions varied across the included trials (6.1 to 41.9% for those on anticholinergic arm, 6.6 to 28% among those on placebo arm and 11.0 – 35.2% among those in the active comparator arm); in most studies, the discontinuation proportions were 4.9 to 16% higher in placebo vs. anticholinergic groups (study table 2, appendix 1). Most of the included COPD randomized trials stopped patient follow-up at the time they discontinued the study drug therapy so that adverse effect information was unavailable after patients were withdrawn. This is particularly problematic in trials comparing anticholinergics against an inferior compound (e.g. placebo), as patients receiving no relief from their symptoms may be more likely to drop out of the study. Differential discontinuation rates are likely to result in a biased study population because those who decide to continue on the placebo arm may be, on average, healthier than those receiving the superior treatment. This bias is likely to introduce a spurious association between anticholinergics and the outcomes of interest.

2.2.8 OSE Comments on Measurement of Exposure

Duration of study drug exposure varied across included studies (short term trials ranged from 6 to 26 weeks; long term trials ranged from 46 weeks to 5 years). Because it is likely that risk differs with length of exposure, pooled estimates of studies of long and short duration are difficult to interpret.

Also, while treatment dose is uniform across most trials (e.g. daily 18 µg of TB via Handihaler), one small study randomized participants to substantially lower doses of TB [22]. Because risk of adverse events is likely to differ with drug dosage, sensitivity analysis excluding this particular trial would be informative.

Additionally, while TB and IB belong to the same class and may share many of the same side effects, the short- versus long-acting nature of the drugs can have significant implications for systemic effects such as cardiovascular events. Therefore, pooled estimates for TB and IB are difficult to interpret.

2.2.9 OSE Comments on Disease Outcome of Interest

Most of the trials included in the meta-analysis were conducted to examine the effectiveness of anticholinergics in the management of COPD; none of the trials was prospectively designed to uniformly assess cardiovascular outcomes associated with anticholinergic use. Instead, cardiovascular outcomes were ascertained through routine serious adverse event reporting within each trial. These outcomes were not adjudicated

and may not have been defined in a uniform fashion across the trials. Therefore, misclassification of outcome is a concern both for the meta-analysis as a whole, which may include different definitions of outcome, and for the individual studies included in the meta-analysis. Within each individual study, misclassification of the disease (measurement error) in the randomized, double-blind setting is likely to be non-differential, which may attenuate the associations. However, due to the seriousness of the outcomes under study, misclassification may not have played a major role in the study findings.

2.2.10 OSE Comments on Sample Size

Despite the relatively large number of participants included in this meta-analysis, the number of events in each individual trial was small, with 40% of the trials with 0 events in the placebo arm. Of note, the results of the largest study included in this meta-analysis [23] has been questioned as the increase in risk of cardiovascular events was restricted to participants who did not use IB [24].

2.2.11 OSE Comments the Analysis / Results

There are several important issues regarding the analysis of Singh et al. First, there appears to be a discrepancy in the number of serious cardiovascular events reported in one of the studies [25] (34 and 23 in the tiotropium and placebo groups, respectively) and those included in the analysis by Singh et al (23 and 13 in the tiotropium and placebo groups). This discrepancy may have biased the association away from the null value. Additionally, there were double-counting of participants, as some studies report on the same study populations (i.e. Brusasco et al [26] reported findings already reported by Donohue et al [27]; Casaburi et al [28] reported findings already reported by Casaburi et al [29]). However, this issue has been recently addressed by investigators of the meta-analysis; corrected findings did not differ substantially from the previously reported results.

Moreover, the largest trial driving the association between IB and cardiovascular events is the Lung Health Study [23]. *Post-hoc* analysis of this trial questioned their results as the increase in cardiovascular mortality was restricted to patients who failed to comply with the study drug [24].

Another issue includes the difficulty in interpreting estimates pooled across TB and IB studies. While these two compounds belong to the same class and may share many of the same side effects, the short- versus long-acting nature of the drugs can have significant implications for systemic effects such as cardiovascular events. Similarly, studies comparing TB vs. placebo and those comparing TB vs. an active comparator are pooled together in the analysis by Singh et al. The nature and design of these two types of trials are fundamentally different, and the active controls may have side effects of their own. Therefore, these pooled estimates are difficult to interpret. Pooling estimates across trials of different duration of follow-up are also difficult to interpret.

Further, the analysis by Singh et al failed to account for person-time data. Therefore, participants who discontinued treatment early in the trial – who were both less exposed to the treatment and had less time to develop the outcomes of interest –and those who completed the study follow-up contributed equal weight to the analysis. As most included trials had higher discontinuation rates among placebo, failure to use person-time data is likely to bias the results in favor of the placebo.

2.2.12 OSE Comments on strength of evidence

The strengths of this meta-analysis include the fact that the literature search included both published and unpublished trials and that it was conducted independently by two reviewers.

Limitations of this study are also noted. These are discussed according to their ability to bias the results (i) towards the null value (i.e. attenuate the findings), (ii) away from the null value (i.e. strengthen or introduce a spurious association), or (iii) in a direction which is difficult to predict.

i. Limitations that may bias results towards the null value

Misclassification of outcome: None of the included trials was prospectively designed to examine risk of death, cardiovascular outcomes or stroke; thus, these outcomes were not adjudicated in most trials, which may have resulted in misclassification of the outcome (likely to be non-differential between the study groups). However, due to the seriousness of the outcomes under study, it is possible that misclassification did not play a major role in the study findings.

ii. Limitations that may bias results away from the null value

Inclusion criteria resulting in biased selection of studies: This is particularly important as none of the included trials was designed to evaluate risk of cardiovascular adverse events. Therefore, studies with an imbalance in the number of adverse events are both more likely to provide information on adverse events as well as to be included in the meta-analysis. It would be important to obtain information on adverse events for the studies not included in the analysis, particularly as a substantial number of studies were excluded due to failure to report on the adverse events of interest (n=69).

Lack of information for participants who discontinued the study: Most of the included COPD randomized trials stopped patient follow-up at the time they discontinued the study drug therapy so that adverse effect information was unavailable after patients were withdrawn. Because of this, an authentic intent-to-treat analysis of safety endpoints is not possible for these trials. The discontinuation rates vary in each of the COPD trials, and these drop outs tend to occur early in the trial. Analyses based on data censored at discontinuation are likely to introduce biases that are difficult to disentangle. This is particularly problematic in trials comparing anticholinergics against an inferior compound (e.g. placebo), as patients receiving no relief from their symptoms may be more likely to drop out of the study. Differential discontinuation rates are likely to result

in bias in these instances because those who decide to continue on the placebo arm may be, on average, healthier than those receiving the superior treatment. Indeed, Kesten et al [30] reported that the incidence of adverse events – including deaths – tends to be higher during the discontinued period compared to the period during which participants were on the assigned study treatment. In the meta-analysis by Singh et al, withdrawal/discontinuation proportions varied across studies (6.1 to 41.9% for those on anticholinergic arm, 6.6 to 28% among those on placebo arm and 11.0 – 35.2% among those in the active comparator arm); in most studies, the discontinuation proportions were 4.9 to 16% higher in placebo vs. anticholinergic groups. It would be informative to compare the baseline distribution of risk factors for cardiovascular outcomes (e.g. smoking, diabetes, hypertension, use of cardioprotective agents) for those who withdrew vs. those who remained in each of the study arms; however, most trials lacked this information.

Failure to account for person-time data: Therefore, participants who discontinued treatment early in the trial – who were both less exposed to the treatment and had less time to develop the outcomes of interest – and those who completed the study follow-up contributed equal weight to the analysis. As most included trials had higher discontinuation rates among placebo, failure to use person-time data is likely to bias the results in favor of the placebo.

Inclusion of trial with different exposure dose: While treatment dose is uniform across most trials (e.g. daily 18 ug of tiotropium via Handihaler), one study randomized participants to substantially smaller doses of tiotropium [22]. This was a small trial that suggested a non-significant increase in risk of cardiovascular events with tiotropium.

Inclusion of trial with anomaly in results: The largest trial driving the association between ipratropium and cardiovascular events is the Lung Health Study [23]. Post hoc analysis of this trial questioned their results as the increase in risk was restricted to patients who failed to comply with the study drug [24].

iii. Limitations that may bias results either away or towards the null value

Combining data for TB and IB trials: While these two compounds belong to the same class and may share many of the same side effects, the short- vs. long-acting nature of the drugs can have significant implications for systemic effects such as cardiovascular events. Therefore, pooled estimates for TB and IB are difficult to interpret.

Combining data from placebo and active controlled trials: The nature and design of these two types of trials are fundamentally different, and the active controls may have side effects of their own. Estimates pooled across studies that compared study drugs vs. placebo and those comparing study drug vs. active comparator are difficult to interpret.

Considering the limitations of this meta-analysis, the study of Singh et al is not particularly helpful in determining the potential cardiovascular risks associated with

inhaled anticholinergics used in the management of COPD. All previously published meta-analyses of randomized trials failed to show an increase in cardiovascular events with the use of anticholinergics [7,8]. Moreover, the results of UPLIFT [11], a large 4-year randomized clinical trial, do not replicate the findings of Singh et al. Unlike in most trials included in Singh et al, vital status were systematically requested for patients who prematurely discontinued participation in UPLIFT 4 years after initiation of study drug. Also, the use person time data may more appropriately have accounted for patients who discontinued the trial prematurely. Finally, the size of UPLIFT (n=5993) is comparable with that of Singh et al (n=7084 across TB trials).

2.3 LEE TA, PICKARD AS, AU DH, BARTLE B, AND WEISS KB. RISK FOR DEATH ASSOCIATED WITH MEDICATIONS FOR RECENTLY DIAGNOSED COPD. ANN OF INT MED 2008; 149: 380-391 [4]

2.3.1 Summary of Study

This is a report of a case-control study nested within the U.S. Veterans Health Administration health care system to examine the relation between respiratory medications and risk of death (all-cause, respiratory, cardiovascular). The full cohort comprised of patients newly diagnosed with COPD, who were at least 45 years of age, used the Veterans Health Administration health care services for at least 1 year prior to their COPD diagnosis, and had received respiratory medications. Cases were identified from all deaths occurring during follow-up (10/1999 – Sept 2003) using the Veterans Affairs Vital Status database. Cause of death was ascertained through the National Health Index Plus (National Center for Health Statistics) for a random sample of 40% of the death cases. Four groups of case patients were defined, including respiratory, cardiovascular, respiratory or cardiovascular and all-cause deaths. Control participants were randomly selected at an approximately 10:1 ratio among eligible participants who were alive at the time of the case diagnosis. Controls were matched to case patients individually on sex, age (45-54, 55-64, 65-75, 75-84, and ≥ 84 years categories), and year of diagnosis. This study was approved by the Hines Veterans Affairs Hospital, Hines, Illinois Institutional Review Board.

Exposure was defined according to medication prescribed 180 days preceding each participant's index date (National Veterans Affairs pharmacy database). Any exposure to corticosteroid, IB, long-acting beta-agonists, theophylline, and short acting beta-agonists 180 days prior to index date was identified as primary exposure to study drug. Mutually exclusive medication regimens were also created by investigators based on medication exposure (note: it is *not* clear how this was operationalized).

Covariates identified during the year preceding diagnosis until the index date were considered for the analysis. These variables included medication use (e.g. systemic steroids, anti-hypertensives, lipid lowering medications, anti-arrhythmics, and diabetes medications), co-morbid conditions, number of hospitalizations, number of COPD exacerbations, and number of outpatient physician visits. Information on COPD severity and smoking were not available for the analysis.

Conditional logistic regression models were used to estimate odds ratios and 95% confidence intervals separately for respiratory-specific, cardiovascular-specific, and all-cause mortality. Adjusted OR represent the risk of events for patients receiving medication compared to those who had not received inhaled corticosteroids, IB, long-acting beta-agonists, or theophylline in the previous 6 months. Several sensitivity analyses were conducted, included restricting the comparison group to patients who were actively treated with a short-acting beta-agonist, (ii) restricting analyses to patients 65 or older (who are less likely to use health services outside of the VA system), (iii) excluding patients who received a combination of IB and short-acting beta-agonists in a single inhaler, and (iv) matching on history of chronic heart failure. Additionally, (v) dose-response was examined by classifying exposure in quartiles of average daily dose usage. Moreover, investigators used an array approach to estimate the effect of unmeasured confounding.

A total of 145,020 patients were identified, of whom 32,130 died. Cause of death was determined for 11,897 of these patients; of whom 2405 died from respiratory-related deaths and 3,159 died from cardiovascular-related deaths. Compared to matched controls, participants who died of cardiovascular-related deaths had higher rates of cardiovascular conditions, including hypertension, ischemic heart disease, diabetes and chronic heart failure.

In multivariable analysis, inhaled corticosteroids and long-acting beta-agonists were with moderate decreases in risk of all-cause mortality, corticosteroids were also associated with lower risk of respiratory and cardiovascular-related deaths. Ipratropium was associated with a moderate increase in risk of death (all-cause mortality, respiratory and cardiovascular-related deaths). Theophylline was associated with increased rates of respiratory-related deaths.

There was evidence of a dose-response relationship with increased dose of medications, but specific results are not available in the manuscript. Sensitivity analysis using external information on disease severity and smoking attenuated with ORs for IB and mortality from 1.15 to 1.02 and from 1.15 to 1.08, respectively (no information on confidence interval was given).

2.3.2 OSE Comments on Study Objectives

None

2.3.3 OSE Comments on Study Design

None

2.3.4 OSE Comments on Informed Consent (if any)

None

2.3.5 OSE Comments on Data Sources

A limitation of the National Veterans Affairs databases is that they do not capture outpatient care provided to veterans outside of the Veterans Affairs health system – which may include the private sector. However, this may have been in part remedied by supplementing the study with information from the Centers for Medicare and Medicaid Services and by sensitivity analysis restricted to participants who were 65 years or older. Another important limitation of this data source is the fact that they lack important clinical details that cannot be determined from ICD coding. Some important information not available includes smoking history, BMI, and severity of COPD (e.g. GOLD). All these are important risk factors for mortality and potentially important confounders of the association between respiratory medications and mortality.

2.3.6 OSE Comments on Study Time Period(s)

None

2.3.7 OSE Comments on Study Population

There are notable differences between cases and controls which may indicate differences in disease severity among study groups. Respiratory death cases were less likely than controls to have co-morbid conditions including hypertension, ischemic heart disease, and cancer, although they were more likely to have chronic heart failure. Cardiovascular death cases were more likely than controls to have co-morbid conditions and to use medications including cardiac medications, diuretics, hypoglycemic agents, and non-steroidal anti-inflammatory drugs. All cases (respiratory, cardiovascular, and all cause deaths) had substantially higher number of overall and recent (in the previous 6 months) COPD exacerbations and were more likely to be hospitalized compared to their controls (study table 1, appendix 2). Cases were generally more likely to use respiratory medications compared to controls (study table 2, appendix 2).

Taken together, the differences may indicate more severe respiratory disease among cases compared to their matched controls. As patients on respiratory medications are more likely to have more severe disease than those who were not receiving inhaled corticosteroids, IB, long acting beta-agonists, or theophylline (comparison group), confounding by disease severity may explain, at least in part, the association between IB and mortality (although it would not explain the protective effects of ICS). Information on COPD severity (e.g. GOLD stages) was not available in this study. Adjustment for markers of disease severity is likely to result in residual confounding by disease severity.

Finally, the study population is largely composed of males. Therefore, results of this study may not be generalizable to female patients with COPD.

2.3.8 OSE Comments on Measurement of Exposure

Misclassification of exposure is likely in this study. Drug prescription was used as surrogate for drug exposure, which requires the assumption that participants used the drugs as prescribed. Additionally, exposure is defined as any exposure to the respiratory medication 180 days prior to index date. Therefore, changes in medication

regimen within 6 months of index date are not captured in this study. This type of misclassification, however, is unlikely to differ between cases and controls (exposure information obtained from the National Veterans Affairs pharmacy database). Non differential misclassification may have attenuated their findings.

2.3.9 OSE Comments on Disease Outcome of Interest

Underlying cause of death was determined through the National Health Index Plus for a randomly selected sample of cases. It is not clear how adjudicated deaths correlate with cause of deaths defined in National Death Index Plus data. Determining cause of death for persons with COPD is particularly problematic as these individuals tend to have several co-morbidities. Deaths of patients with more severe COPD may be more likely to be classified as COPD deaths. If cases were more likely to have more severe disease than controls and therefore be more likely to have their deaths classified as COPD-related deaths, this bias would have attenuated the association between IB and non-COPD mortality.

2.3.10 OSE Comments on Sample Size

Sample size was sufficient to detect moderate effects (reported by authors).

2.3.11 OSE Comments on Study Analysis / Results

This study failed to control for important risk factors of the outcomes of interest, including – but not limited to - smoking history, BMI, and COPD severity. COPD patients have an increased risk of death from cardiovascular diseases due to their smoking history and reduced lung function [31]. Patients with more severe COPD are more likely to be prescribed respiratory medications. Therefore, when unaccounted for, these factors are likely to bias the association between respiratory medications and mortality away from the null value (i.e. introducing a spurious association or artificially strengthen the association). In smoking-adjusted analysis using external data, all-cause mortality estimates were indeed attenuated from 1.15 to 1.08; COPD-severity adjusted analysis (using external data) attenuated estimates from 1.15 to 1.02 (confidence intervals were not provided; thus it is unknown whether adjusted estimates remained significant). It would be informative to present results of analyses adjusted for *both* smoking and COPD severity; these multivariate analyses would tend to further attenuate the estimates towards the null value.

2.3.12 OSE Comments on Strength of Evidence

This study has a few strengths. Its large sample size allowed for the detection of small to moderate estimates of effects. Also, its prospective nature minimized possibility of recall bias.

Limitations of this study are also noted. These are discussed according to their ability to bias the results (i) towards the null value (i.e. attenuate the findings) or (ii) away from the null value (i.e. strengthen or introduce a spurious association).

i. Limitations that may bias results towards the null value

Misclassification of exposure due to hospitalization: It is unclear whether prescriptions during hospitalizations were captured in this study. If those who died were also more likely to be hospitalized within 6 months of death, the resulting bias may attenuate the association between respiratory drug use and risk of death.

Misclassification of exposure due to switching of drug: Exposure is defined as any exposure to the respiratory medication 180 days prior to index date. Therefore, changes in medication regimen within 6 months of index date are not captured in this study. This type of misclassification may bias the estimates, but the direction of the resulting bias is difficult to predict as several different exposures are being considered in this study.

Misclassification of outcome: Cause of death, which was not adjudicated in this study, tends to be problematic particularly for COPD patients, who generally have co-morbidities. Deaths of patients with more severe COPD may be more likely to be classified as COPD deaths. Cases prescribed IB may both tend to have more severe COPD than controls as well as to be more likely to have their deaths classified as COPD deaths, therefore attenuating the association between IB use and non-COPD related deaths. This misclassification may also explain why theophylline, known to have cardiac side effects, was associated with increased respiratory mortality but not with cardiovascular mortality, as theophylline users may tend to have more severe COPD.

ii. Limitations that may bias results away from the null value

Failure to account for important potential confounders: The most important limitation of this study includes failure to control for important risk factors of the outcomes of interest, including – but not limited to - smoking history, BMI, and COPD severity. COPD patients have an increased risk of death from cardiovascular diseases due to their smoking history and reduced lung function (Sin and Mann 2003; Sin et al 2005). Indeed, baseline differences point to greater disease severity among cases compared to controls. Additionally, patients with more severe COPD are more likely to be prescribed respiratory medications. Therefore, when unaccounted for, these factors are likely to bias the association between respiratory medications and mortality away from the null value (*i.e.* introducing a spurious association or artificially strengthen the association). In smoking-adjusted sensitivity analysis (using external data), all-cause mortality estimates were indeed attenuated from 1.15 to 1.08. Sensitivity analyses adjusting for COPD severity based on information from NHANES (National Health and Nutrition Examination Surveys) also attenuated ipratropium estimates from 1.15 to 1.02. It would be informative to present results of analyses adjusted for *both* smoking and COPD severity (using information on these from external populations), likely to further attenuate the estimates towards the null value.

Therefore, despite its large size, the study by Lee et al may not be particularly helpful in determining risk of mortality associated with use of IB bromide due to its limitations.

The most important limitation included the inability to properly account for important risk factors of the outcome including COPD severity and smoking. Sensitivity analyses adjusting for these factors using external data suggest substantial attenuation of the association between IB and mortality risk. Therefore, confounding by these factors is likely to explain the small increase in mortality risk associated with IB use.

2.4 MACIE C, WOOLDRAGE K, MANFREDA J, ANTHONISEN N. CARDIOVASCULAR MORBIDITY AND THE USE OF INHALED BRONCHODILATORS. INT J OF COPD 2008; 1: 163-169 [5]

2.4.1 Summary of Study

This is a case-control study nested within a cohort comprised of all permanent residents of the Province of Manitoba, 35 years or older, who had a physician visit between January of 1996 and December of 2000 for bronchitis, COPD, or asthma. The Manitoba Population Health Research Repository integrates anonymous records of all inpatient and outpatient physician contacts, vital statistics, and prescription records. Physicians are remunerated on basis of claims for payment describing services provided and diagnosis. The Drug Programs Information Network (DPIN) database is created by provincial retail pharmacies entering prescriptions in real time.

This study was approved by the Ethics Board of University of Manitoba and the health Information Privacy Committee of Manitoba Health.

Cases were those with a hospitalization for selected cardiovascular events (CVEs). CVEs included supra-ventricular tachycardia (ICD-9 427.0, 427.31, 427.32, 427.61), myocardial infarction (ICD-9 410), heart failure (ICD-9 428), and stroke (ICD-9 430-438). Controls were selected among those who did not have a hospitalization for a CVE before or at the index date of the case. Controls were matched to cases on sex, age, and duration of insurance coverage.

Exposure to respiratory drug was defined according to receipt of a beta-agonist, ipratropium bromide, or inhaled steroids 60 or 365 days prior to index date (those exposed within 365 days included those exposed within 60 days). Three groups of respiratory medications were examined, including inhaled beta agonists (BA), inhaled ipratropium bromide (IB), and inhaled corticosteroids (ICS).

Conditional logistic regression was used to obtain odds ratios and 95% confidence intervals. Multivariate models considered use of other respiratory drugs, respiratory diagnostic group, number of physician visits for respiratory diagnoses, non-cardiac co-morbidities and cardiac drugs. Non-cardiac co-morbidities included diabetes, renal failure, liver disease, peptic ulcer, malignancy, collagen vascular disease, and dementia. Cardiac drugs included anti-arrhythmics, nitrates, furosemide, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other anti-hypertensives and cholesterol lowering agents.

A total of 222,272 Manitoba residents with a respiratory diagnosis were identified within the 5 years ending on December 2000. A total of 2,054 cases of SVT were identified

and matched to 20,501 controls on sex, age, and duration of insurance coverage. Similarly, 3,855 cases of MI, 5,407 cases of CHF, and 4,961 cases of stroke were identified and matched to 38,490; 53,929; and 49,487 controls on sex, age, and duration of insurance coverage, respectively.

Compared to controls, cases were substantially more likely to take cardiac medications, suggesting that cases were more likely to have cardiovascular co-morbidities at index date. Use of IB 60 days prior to index date was associated with a 38% increase in risk of SVT and with a 47% increase in risk of CHF. Use of IB one year prior to index date was associated with a 27% increase in risk of SVT, a 55% increase in risk of cardiac heart failure, and with a borderline significant increase in risk of stroke of 13%. IB was unassociated with risk of MI. Other respiratory medications were also analyzed in this study, including beta agonists and corticosteroids. Beta agonists were also associated with increased risk of SVT, CHF, and stroke. Inhaled corticosteroids were associated with a small decrease in risk of CHF and stroke.

2.4.2 OSE Comments on Study Objectives

None

2.4.3 OSE Comments on Study Design

None

2.4.4 OSE Comments on Informed Consent (if any)

None

2.4.5 OSE Comments on Data Sources

The databases utilized provided a rich source of record-linked information on exposure, outcome, and medical services utilized (including inpatient and patient physician contacts).

2.4.6 OSE Comments on Study Time Period(s)

Controls were matched to cases on several factors including length of insurance coverage, which may help ensure that controls had duration of follow-up at least as long as the time to the event for the corresponding case.

2.4.7 OSE Comments on Study Population

This study included patients with a diagnosis of asthma, COPD and bronchitis. Because COPD is a risk factor for cardiac outcomes, it would be appropriate to restrict the study to COPD patients. Indeed, cases are generally more likely to have COPD than their matched controls (study table 1, appendix 3). Confounding by COPD could explain, at least in part, the association between respiratory medications and cardiovascular outcomes.

2.4.8 OSE Comments on Measurement of Exposure

Prescription dispensed served as surrogate for exposure, a metric that is generally used in pharmacoepidemiology studies. Non-prescription medications, such as use of aspirin in cardioprophylaxis, would not be captured in this study. However, prevalence of misclassification is likely to be non-differential between medication and non medication groups, which bias the results towards the null value (attenuate the results). Additionally, dietary and lifestyle factors, which could confound the relation between respiratory medication use and cardiac events, are not available in this study.

Further, although this study considered first hospitalization due to cardiac outcomes, it did not seem to have taken into account hospitalization due to respiratory co-morbidities. If cases were more likely to be hospitalized than controls, this type of bias would tend to attenuate the association between respiratory medication and cardiac outcome as medications dispensed during hospitalization may not be captured in the database [32].

2.4.9 OSE Comments on Disease Outcome of Interest

Outcome definition was based in ICD coding only. Therefore, misclassification of outcome is possible although it is unlikely to vary differentially between cases and controls.

2.4.10 OSE Comments on Sample Size

None

2.4.11 OSE Comments on Analyses and/or Study Results

This study suggested that IB (as well as beta agonists) may increase risk of certain cardiovascular events including SVT and HF (but not of MI). However, because this study was not restricted to COPD patients, it is likely that greater prevalence of COPD among cases may explain the positive association between ipratropium and cardiac events (as COPD is generally associated with both increased likelihood of use of respiratory medications as well as with cardiac co-morbidities). Indeed, the difference in COPD prevalence between heart failure cases and their matched controls is substantial (41.7 vs. 29.9%, respectively); while comparatively small between MI cases and their matched controls (29.5 vs. 25.6%, respectively). Therefore, differences in COPD prevalence could explain the positive association between ipratropium and risk of HF and the lack of association between these agents and MI.

Additionally, COPD severity, which is also associated with both use of respiratory medications and with cardiac comorbidities, was not accounted for in this study and may also have confounded their results. Further, multivariate analysis did not adjust for cardiac co-morbidities beyond cardiac medications. Laboratory data was also not available in this dataset. Therefore, residual confounding by cardiac co-morbidity is likely to have influenced their results. Other important risk factors of cardiac outcomes, including smoking and BMI were also not accounted for in the analyses and are likely to have confounded their results. Due to the small to moderate size of their reported effect estimates, it is possible that confounding by COPD, severity of COPD cardiac co-

morbidities, smoking, and BMI would explain the increase in risk associated with use of ipratropium bromide.

2.4.12 OSE Comments on Strength of Evidence

This study has a few strengths. Its large sample size allowed for the detection of small to moderate differences in risk of cardiovascular events between users and non users of respiratory medications. The databases utilized provided a rich source of record-linked information on exposure, outcome, and medical services utilized (including inpatient and patient physician contacts).

Limitations of this study are also noted. These are discussed according to their ability to bias the results (i) towards the null value (i.e. attenuate the findings) or (ii) away from the null value (i.e. strengthen or introduce a spurious association).

i. Limitations that may bias results towards the null value

Exposure misclassification due to hospitalizations: Although this study considered first hospitalization due to cardiac outcomes, it did not consider other hospitalizations (e.g. due to respiratory co-morbidities). Because medications dispensed during hospitalization may not be captured in the study, this type of bias would tend to attenuate the association between respiratory medication and cardiac outcome.

Misclassification of exposure: Prescription dispensed served as surrogate for exposure, although this metric is generally used in pharmacoepidemiology studies. Non prescription medications, such as use of aspirin for cardioprophylaxis, would not be captured in this study. This type of misclassification is likely to be non-differential with respect with case-control status, which may attenuate the study findings.

ii. Limitations that may bias results away from the null value

Confounding by presence of COPD: As shown in study table 1 (appendix 3), cases were generally more likely to have COPD compared to their matched controls. Long term use of anticholinergics may be more likely among COPD patients than among asthma or bronchitis patients. Therefore, confounding by COPD may have confounded the association between ipratropium bromide and cardiovascular events.

Confounding by important risk factors of the outcomes: This study failed to account for important risk factors for the outcomes. These factors include severity of COPD, history of smoking, and BMI, all likely to be associated with both use of respiratory medications and with cardiac comorbidities and to confound the association between respiratory medications and cardiac outcomes. Additionally, dietary and lifestyle factors, which could confound the relation between respiratory medication use and cardiac events, are not available in this study.

Therefore, despite its relatively large size, the study by Macie et al may not be particularly helpful in determining risk of cardiovascular events associated with use of IB bromide due to its limitations. The most important limitations included their failure to restrict the study to COPD patients and their inability to properly account for important risk factors of the outcome including COPD severity and smoking. Therefore, confounding by COPD and by important risk factors of the outcomes are likely to explain the moderate increase in the risk of cardiovascular events associated with IB use reported in this study.

2.5 OGALE SS, LEE TA, AU DH, BOUDREAU DM, SULLIVAN SD. CARDIOVASCULAR EVENTS ASSOCIATED WITH IPRATROPIUM BROMIDE IN COPD. CHEST 2009 (EPUB AHEAD OF PRINT) [6]

2.5.1 Summary of Study

This was a cohort study conducted within the Veteran's Health Administration healthcare databases (inpatient and outpatient data, pharmacy data and vital status information). This study consisted of newly diagnosed COPD patients who had at least one inpatient primary diagnosis or two outpatient primary or secondary diagnosis of COPD (ICD-9 CM 490-492.8, 496) within a twelve month period between October 1998 and September 2002. Patients with a diagnosis of asthma as well as those who had been dispensed asthma medications not approved for COPD were excluded. Cohort entry was marked by the date of the second outpatient encounter or the date of discharge for the first hospitalization. Participants were followed until their first hospitalization for CVE, death, or end of study follow-up period. This study was approved by the Hines VA Hospital and University of Washington Institutional Review Boards.

The primary endpoint was a composite measure of cardiovascular events (CVEs), including a first hospitalization of a primary diagnosis of acute coronary syndrome (ICD-9-CM 410-411.89), heart failure (ICD-9-CM 425-425.4, 425.7-425.9, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.9) or cardiac dysrrhythmia (ICD-9-CM 427-428.93, 785.0).

The main exposure was *any* exposure to inhaled anticholinergics, which included 60 µg of ipratropium bromide by MDI or 0.5 mg by nebulizer four times a day, OR 18 µg of tiotropium daily for 30 days. Exposure was defined as any exposure to anticholinergics over the past year, number of months since last exposure to anticholinergics (recency of exposure), and number of 30-day equivalents of inhaled anticholinergics over the past year (cumulative exposure). These were time-dependent covariates in that at each event, exposure within the past year was recalculated for patients experiencing the event/s and for those who had been in the cohort for the same amount of time but had not experienced the event/s.

Baseline covariates included age, sex, race, year at cohort entry, distance to nearest VA hospital, cardiovascular risk factors based on both diagnosis and mediations, including prior cardiovascular disease, hypertension, hyperlipidemia, and diabetes during the year

preceding cohort entry. Site of initial diagnosis of COPD (inpatient vs. outpatient) was used as a proxy for COPD severity at diagnosis.

Time dependent-covariates included number of inpatient and outpatient COPD exacerbations, number of canisters of SABA dispensed within the past year, and other respiratory medications including long acting beta-agonists, inhaled corticosteroids, theophylline, supplemental oxygen, oral or nebulized beta agonists, *nebulized anticholinergics*, and other anticholinergics within the past year.

Multivariate Cox proportional hazards were used to determine the association between exposure to anticholinergics and risk of cardiovascular events, after adjusting for all non time dependent and time dependent covariates. All exposure characteristics (any use, recently, and cumulative) were included in the models. Likelihood ratio tests were used to assess whether effect estimates varied by use of ICS within the past year and prior CVD.

A total of 82,717 patients (and 274,025 patient-years) newly diagnosed with COPD were included in this study. During follow-up, 6,234 CVDs were identified. The majority (44%) of these events referred to heart failure.

Exposure to anticholinergics compared to no exposure within the past year was associated with 29% increased risk of CVDs in multivariate models. Remote exposure (>6 months) was not associated with risk of CVDs. There was no evidence of dose response; among those last exposed in the previous 6 months or less, patients dispensed 4 or less 30-day equivalent of anticholinergics had a 40% increase in risk of CVDs, while those who were dispensed more than 4 30-day equivalents had a 23% increase in risk. Additionally, estimates varied significantly according to presence of CVD at baseline; use of anticholinergics was associated with higher risk of cardiovascular events among those without history of cardiovascular disease.

2.5.2 OSE Comments on Study Objectives

None

2.5.3 OSE Comments on Study Design

Investigators did not exclude participants with cardiovascular disease at baseline. Therefore, *prevalent* cardiovascular disease cases may be also included in this study. This is not ideal as the risk profile for prevalent is likely to differ from that of incident cases. However, analyses stratified by baseline history of CVD may have partially addressed this issue (it would be helpful to know the number of patients/person-moments included in these analyses; this information is not provided).

2.5.4 OSE Comments on Informed Consent (if any)

None

2.5.5 OSE Comments on Data Sources

A limitation of the National Veterans databases is that they do not capture outpatient care provided to veterans outside of the Veterans Affairs health system. Another important limitation of this data source is the fact that they lack important clinical details that cannot be determined from ICD coding. Some important information not available includes smoking history, BMI, and severity of COPD (e.g. GOLD). All these are important risk factors for mortality and potentially important confounders of the association between respiratory medications and mortality. Finally, information on cause of death is not available from this data source. Therefore, cardiovascular-related deaths, including sudden deaths, are not included as cases.

2.5.6 OSE Comments on Study Time Period(s)

None

2.5.7 OSE Comments on Study Population

Information on baseline characteristics of participants *according exposure status* is not provided in this study report. Therefore, it is difficult to assess whether the exposed and non-exposed groups are comparable and whether there are important covariates that need to be taken into consideration. It is likely that patients prescribed respiratory medications have more severe COPD and perhaps more co-morbidities, which could explain, at least in part, the association between anticholinergics and CVEs.

2.5.8 OSE Comments on Measurement of Exposure

The main exposure is any exposure to inhaled anticholinergics, which includes 60 µg of ipratropium bromide by MDI or 0.5 mg by nebulizer four times a day, OR 18 µg of tiotropium daily for 30 days. The manuscript does not specify which device used for the delivery of tiotropium. Misclassification of exposure is likely in this study, as drug prescription was used as surrogate for drug exposure, which requires the assumption that participants used the drugs as prescribed. However, this misclassification is unlikely to differ between those who subsequently developed CVEs and those who did not.

Also, the prevalence of tiotropium use is extremely low (n=78 of 329,255 prescriptions dispensed). It would be helpful to analyze the data restricted to ipratropium users.

2.5.9 OSE Comments on Disease Outcome of Interest

Incomplete ascertainment of outcome is an important issue in this study, as hospitalizations for cardiovascular events that occurred outside of the VA system were not captured in this study. Also, information on cause of death was not available for over 50% of the cohort; thus, cases of cardiovascular-related death or sudden cardiac death were not captured as “cardiovascular event” cases in this study.

Additionally, misclassification of outcome is likely to play a role in the findings of this study. The primary endpoint was a composite measure of several cardiac endpoints, including acute coronary syndrome, heart failure, and cardiac dysrhythmia. The

reliability of identifying heart failure and cardiac arrhythmia based on ICD codes is questionable. Additionally, because payment for services is linked to diagnosis-related groups, over-reporting of cardiovascular diagnosis is possible. However, it is unlikely that misclassification of outcome differed between those who were prescribed anticholinergics and those who were not prescribed anticholinergics; therefore, this misclassification may have attenuated the findings.

Finally, investigators did not analyze the association between anticholinergics and risk of cardiovascular events individually (e.g. myocardial infarction). Therefore, it is not possible to know whether/which particular event drove the reported association.

2.5.10 OSE Comments on Sample Size

None.

2.5.11 OSE Comments on Analyses / Study Results

A few unexpected findings are noted. As shown in study figure 1 (appendix 4), theophylline was associated with a borderline significant 19% *decrease* in risk of CVEs. As the cardiac side effects for theophylline are well known, this unusual finding may point to the effect of channeling bias, as patients with greater susceptibility to cardiac events may be prescribed other medications, including IB. This type of bias could explain, at least in part, the positive association between IB and risk of CVEs (as well as the inverse association between theophylline and CVEs).

Also, it is unexpected that nebulizer anticholinergics were unassociated with risk of CVEs (RR=1.03) (study figure 1, appendix 4), while the exposure of interest, which included anticholinergics delivered either via nebulizer or MDI was significantly associated with increased risk of CVEs. Additionally, the decrease in risk for CVEs with increase cumulative exposure to anticholinergics (40% and 23% increase in risk with lower and higher cumulative exposure, respectively) is difficult to explain (study table 2, appendix 4). It would be helpful to have information on numbers/percentages of patients in each exposure category to assess the robustness of these findings (not provided in the manuscript).

Data on important risk factors of cardiovascular disease including smoking, BMI, laboratory measures of hyperlipidemia, is another fundamental limitation of this study. Presence of these factors may have influenced prescription of IB as physicians may be more likely to prescribe IB for patients with cardiovascular disease history. Confounding by these factors is likely to bias estimates away from the null. Similarly, failure to adjust for COPD severity, which is likely to be closely associated with cardiac comorbidities, is also likely to bias the estimates away from the null value. Attempt to adjust for COPD severity by considering inpatient vs. outpatient COPD diagnosis, which is unlikely to represent COPD severity, is not reassuring. Given the magnitude of the increase in risk reported in this study (RR=1.29), it is possible and likely the RR for CVEs would approximate 1.0 after proper adjustment for relevant confounders.

2.5.12 OSE Comments on Strength of Evidence

The main strengths of this study include its relatively large size and its prospective nature.

Several important limitations are also noted. These are discussed according to their ability to (i) bias the results towards the null, (ii) away from the null value, or (iii) in a direction that is difficult to predict.

i. Limitations that may bias the findings towards the null value

Misclassification of exposure: Drug prescription was used as surrogate for drug exposure, which requires the assumption that participants used the drugs as prescribed. However, this misclassification is unlikely to differ between those who developed CVEs and those who did not and may have attenuated the study findings.

Misclassification of outcome: The primary endpoint was a composite measure of several cardiac endpoints based on ICD coding, including acute coronary syndrome, heart failure, and cardiac dysrhythmia. The reliability of identifying heart failure and cardiac arrhythmia based on ICD codes is questionable. Additionally, because payment for services is linked to diagnosis-related groups, over-reporting of cardiovascular diagnosis is possible. However, it is unlikely that misclassification of outcome differed between those who were prescribed anticholinergics and those who were not prescribed anticholinergics; therefore, this misclassification may have attenuated the findings.

Incomplete case ascertainment: Ascertainment of outcome was probably incomplete. Hospitalizations for cardiovascular events that occurred outside of the VA system were not captured in this study. Also, information on cause of death was not available for over 50% of the cohort; thus, cases of cardiovascular-related death or sudden cardiac death were not captured as “cardiovascular event” cases in this study.

ii. Limitations that may bias the findings away from the null value

Confounding: Lack of data on important risk factors of cardiovascular disease including smoking, BMI, laboratory measures of hyperlipidemia, is a fundamental limitation of this study. Presence of these factors may have influenced prescription of ipratropium as physicians may be more likely to prescribe anticholinergics for patients with no cardiovascular risk factors. Confounding by these factors is likely to bias estimates away from the null. Similarly, failure to adjust for COPD severity, which is likely to be closely associated with cardiac co-morbidities, is also likely to bias the estimates away from the null value. Attempts made by the investigators to adjust for COPD severity by considering inpatient vs. outpatient COPD diagnosis, which is unlikely to represent COPD severity, is not reassuring. Given the magnitude of the increase in risk reported in this study (RR=1.29), it is possible - and likely – that the RR for CVEs would approximate 1.0 after proper adjustment for relevant confounders.

iii. Limitations that may introduce bias in a direction that is difficult to predict

Failure to exclude TB users: While IB and TB belong to the same drug class and may share many of the same side effects, the short- versus long-acting nature of the drugs can have significant implications for systemic effects such as cardiovascular events. Therefore, pooling of these two exposures is not recommended. Because the number of TB prescriptions is very small, it would have been appropriate to restrict the study to IB users vs. non users.

Due to its several limitations, of which lack of ability to properly account for important confounders is the most concerning – this study may not be helpful in determining risk of cardiovascular events with use of ipratropium/anticholinergics.

3 DRUG UTILIZATION

3.1 DETERMINING SETTINGS OF USE

The IMS Health, IMS National Sales Perspectives™ was used to determine the retail and non-retail channels of distribution for ipratropium and tiotropium oral inhalation products in terms packages of product sold (boxes, canisters, etc). During the years 2004 through 2008, U.S. retail and mail order pharmacies accounted for the majority of the wholesale sales for ipratropium and tiotropium. Retail and mail order pharmacies combined accounted for 53-66% of the annual wholesale distribution of ipratropium products and 77-82% of the distribution for tiotropium products. Since the majority of distribution was into the outpatient pharmacy setting pharmacies, we examined outpatient dispensing patterns to evaluate the use of ipratropium, ipratropium with albuterol combination, and tiotropium products.

3.2 DATA SOURCES AND METHODS

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

Outpatient use of ipratropium and tiotropium products by diagnosis code was measured using data obtained from Wolters Kluwer Health's Concurrent Product Analyzer (CPA). From this data source, we obtained nationally projected counts of the number of patients who had received a prescription for ipratropium and/or tiotropium through U.S. mail order and retail pharmacies, stratified by the most recent respiratory diagnosis occurring within a one year look back period, as well as patient age and sex information. Diagnoses associated with the use of ipratropium and tiotropium were imputed from a subset of the patients by looking back 6 months from each prescription claim for the most recently billed medical claim for a respiratory diagnosis. Respiratory diagnoses were group into 4 categories: asthma, chronic obstructive pulmonary disease, chronic bronchitis, and emphysema. CPA data is provided for the calendar years 2005 through 2008.

Indications for use were also obtained using the SDI, Physician Drug and Diagnosis Audit (PDDA). PDDA is a survey of 3,100 U.S. office based physicians. Data are provided from years 2005 through 2008.

Nationally projected number of prescriptions dispensed and unique patient counts for U.S. mail order and retail pharmacies were obtained from the Wolters Kluwer SOURCE PHAST database . These data are provided for the years 2005 through 2008.

Complete descriptions of the databases are provided in Appendix 2.

3.3 RESULTS

Wolters Kluwer estimates that the nationally projected number of patients who received ipratropium containing products (including ipratropium/albuterol products) through U.S. mail order and retail pharmacies decreased by 16% between the years 2005 through 2008, falling from 3.6 million patients in year 2005 to 3.0 million during year 2008 (Appendix 1, Table 1). Wolters Kluwer estimates that during year 2008 asthma patients accounted for approximately 15% of the use (~458,617 patients), chronic obstructive pulmonary disease patients for nearly 16% of the use (~473,052 patients) and chronic bronchitis for nearly 3% of the use (~78,409 patients). There were nearly 2 million patients with other diagnoses (both respiratory and non-respiratory) which accounted for about 66% of the year 2008 projected patient count. The relative proportions for the previous years were similar.

The retail and mail order projected patient count for tiotropium increased from ~1.01 million patients during year 2005 to ~1.95 million patients during 2008, a 93% relative increase. Using the most currently billed respiratory diagnosis, Wolters Kluwer estimates COPD patients accounted for approximately 22% (~438,559 patients) of the total number of tiotropium patients during year 2008, and asthma patients accounted for nearly 14% (~269,967 patients). Approximately 60% of patients (~1.2 million patients) did not have a billed respiratory diagnosis during the 6 months prior to their tiotropium prescription.

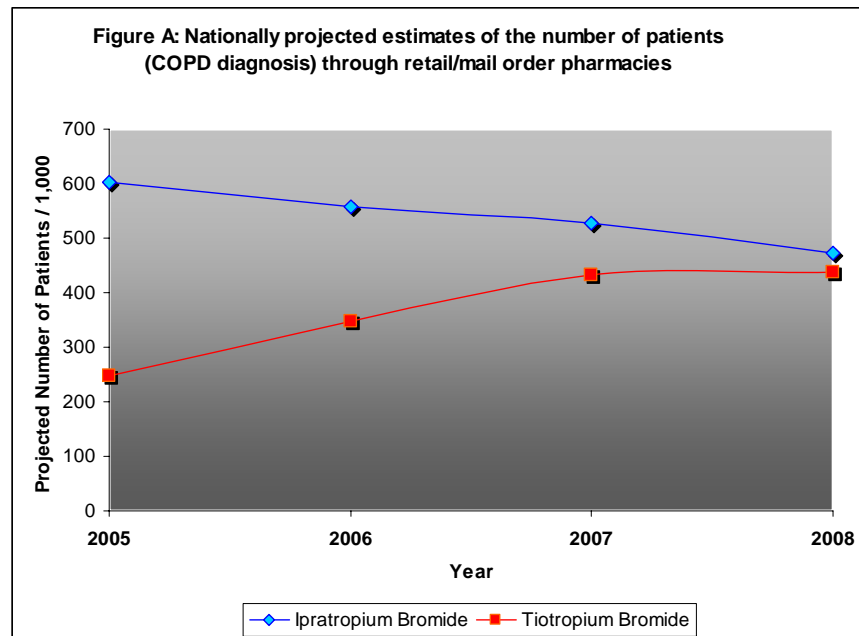
Female patients accounted for approximately 57% of the total number of patients who received a retail or mail order ipratropium prescription during each year from years 2005 through 2008, and roughly 55% of patients who received a tiotropium prescription (Appendix 1, Table 2). Patients under 65 years of age accounted for approximately 49% of ipratropium prescription patients and between 40% and 42% of tiotropium patients during each year of this analysis (Appendix 1, Table 3).

To provide a count of the total number of retail and mail order prescriptions dispensed for orally inhaled ipratropium and tiotropium, we obtained nationally projected estimates of prescription dispensing from Wolter Kluwer's PHAST (Appendix 1, Table 4). For all ipratropium products combined, the number of prescriptions dispensed decreased from 10.2 million prescriptions in year 2005 to 8.4 million prescriptions during year 2008, an 18% decrease. The declines seen with the single agent products were much greater than the decline seen with the albuterol combination product (25% and 15%, respectively). Prescriptions for tiotropium increased during each year from year 2005 through year 2008 from 3.3 million prescriptions to 7.5 million prescriptions.

Finally, we examined the intended indications for the use of ipratropium and tiotropium products from the SDI, PDDA, a survey of approximately 3,100 office based physicians

(Appendix 1, Table 5). For all orally inhaled ipratropium products combined, the most frequently mentioned diagnosis associated with a mention of these products was chronic airway obstruction, which accounted for between 40% and 46% of the mentions during the years between 2005 through 2008. Asthma was the second most frequently mentioned diagnosis, accounting for between 17% and 22% of diagnosis mentions. For tiotropium, chronic airway obstruction was also the most frequently mentioned diagnosis, accounting for 66% of mentions during year 2007 and 73% of mentions during year 2008. The number of tiotropium mentions prior to year 2007 were too low to evaluate.

Figure A (below) displays the nationally projected estimates of the number of patients using TB and IB for chronic obstructive disease via US retail and mail order pharmacies (based on Wolters Kluwer estimates presented in table 1, appendix 5). Prescriptions for IB decreased steadily from 2005 to 2008, while for TB, prescriptions increased steadily from 2005 to 2008. The estimated p-trend for IB and TB was 0.04 and 0.05, respectively.



3.4 DRUG UTILIZATION DISCUSSION

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that ipratropium and tiotropium products are distributed primarily to retail and mail order pharmacy settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

The Wolters Kluwer data which provides projected patient counts in relation to the billed medical claims diagnosis is subject to a number of limitations. First, respiratory diagnoses were not captured for a substantial number of patients during the study period.

This is likely due to possibility that chronic patients were not billed for a respiratory specific claim during the 6 month look back period rather than the use of the product for non-respiratory conditions. Secondly, since the medical claims represents a subset of all patients in the database, the projected estimates may not be as reliable.

Indications for use were obtained using SDI's PDDA, a monthly survey of 3,100 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. Low estimates may be seen in the first two years of tiotropium data and the data should not be trended during this period. In general, PDDA data are best used to identify the typical uses for the products in clinical practice.

4 SUMMARY OF REVIEW AND RECOMMENDATIONS

The limitations of the meta-analysis by Singh et al [3], including a biased selection of studies, lack of information on participants who discontinued trial and failure to use person-time data, and the limitations of the observational studies [4-6], of which the most important refers to their inability to properly account for important risk factors of the outcomes (*e.g.* smoking, BMI, COPD severity, cardiac co-morbidities), may explain the reported positive associations between anticholinergics and serious CVEs and mortality. Additionally, these findings do not agree with the findings of previously published meta-analyses [7-10], nor do they agree with the findings of a large 4-year randomized clinical trial on TB vs. placebo [11], none of which suggest an association between anticholinergics and increasing risk of cardiovascular events or mortality. Taken together, these data are not convincing in implicating use of inhaled anticholinergics in increasing risk of cardiovascular events or mortality. Assessment of drug utilization patterns suggest a decrease in use/prescriptions of ipratropium products coupled with an increase in use/prescriptions of tiotropium products from 2005 to 2008. In summary, the current available evidence implicating TB and IB in increasing risk of these outcomes is not compelling. Therefore, we do not recommend the pursuit of a meta-analysis by the Agency at this time.

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6 APPENDICES

APPENDIX 1 – SINGH *ET AL*, MAIN TABLES AND FIGURES

Figure 1

Figure 1. Study Selection

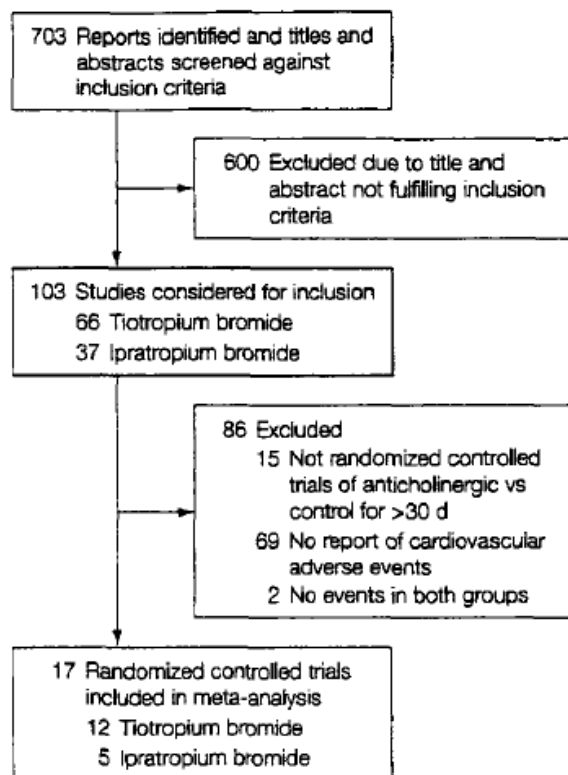


Table 2

Table 2. Quality Assessment of Included Trials				
Source	Allocation Concealment	Adverse Event Monitoring	Withdrawal Rates, %	Loss to Follow-up, %
Anthonisen et al, ⁴ 2002	Adequate	Cardiovascular deaths reviewed and participants followed up every 3 mo	23.1	0.03
Placebo			21.5	0.02
Casaburi et al, ¹⁹ 2002	Unclear	Adverse events detected at regular intervals (first d, first wk, Q3 wk up to 13 wks; Q6 wks until study end)	18.7	NA
Placebo			27.8	NA
Wedzicha et al, ²⁰ 2008	Adequate	Serious adverse events recorded up to 30 d poststudy	41.9	1.9
Placebo			35.2	2.2
Powrie et al, ²¹ 2007	Unclear	Adverse event, vital signs, laboratory results, and examination recorded during the study at 4, 16, 32 and 52 wk and 30 d poststudy	30.4	NA
Placebo			28.8	NA
Chan et al, ²² 2007	Unclear	Adverse events monitored throughout treatment period	22.2	NA
Placebo			27.5	NA
Casaburi et al, ²³ 2000	Adequate	Adverse events recorded every 3 wk	6.1	NA
Placebo			11	NA
Brusasco et al, ²⁴ 2003	Unclear	Adverse events tracked through baseline and 24 wk	15.4	NA
Placebo			18.8	NA
Placebo			25.7	NA
Donohue et al, ²⁵ 2002	Unclear	Adverse events tracked through 24 wk	12	NA
Placebo			17	NA
Placebo			28	NA
Covelli et al, ²⁶ 2005	Unclear	Electrocardiography and Holter performed at entry and 12 wk	10	NA
Placebo			17.7	NA
Niewoehner et al, ²⁷ 2005	Adequate	Serious adverse events included if occurred within 30 d of study medication	16	0.07
Placebo			27	0.04
Bateman et al, ²⁸ 2008	Unclear	Adverse events and vital signs, physical examination at each visit	NA	NA
Placebo			NA	NA
Moita et al, ²⁹ 2008	Unclear	Adverse events and vital signs, physical examination at each visit	7.5	3.4
Placebo			6.7	2.4
Voshaar et al, ^{29,30} 2008	Unclear	Adverse event, vital signs, 12-lead electrocardiographic routine laboratories, and physical examination	8.8	NA
Placebo			10	NA
Placebo			17.4	NA
Placebo			12.1	NA
Combivent Inhalation Aerosol Study Group, ³¹ 1994	Unclear	Adverse events monitored every 2 wk	13.2	2.7
Placebo			12.7	2.3
Placebo			14.5	3.4

Source	Allocation Concealment	Adverse Event Monitoring	Withdrawal Rates, %	Loss to Follow-up, %
GlaxoSmithKline study SMS40315, ³² 2005	Unclear	NA	12	NA
Salmeterol and ipratropium				
Salmeterol			16	NA
Ipratropium			17	NA
Placebo			16	NA
GlaxoSmithKline study SMS40314, ³³ 2005	Unclear	NA	15	NA
Salmeterol and ipratropium				
Salmeterol			11	NA
Ipratropium			11	NA
Placebo			19	NA
Mahler et al, ³⁴ 1999	Unclear	Adverse events and vital signs at 2 wk, laboratory examinations, and physical examination at beginning and end of treatment; electrocardiography at regular intervals	13.5	1.5
Ipratropium				
Salmeterol			6.6	0
Placebo			16	1.3

Abbreviation: NA, data not available.

APPENDIX 2: LEE *ET AL*, MAIN STUDY TABLES

Table 1

<i>Table 1. Participant Characteristics</i>						
Characteristic	Respiratory Death		Cardiovascular Death		All-Cause Mortality	
	Case Patients (n = 2405)	Control Participants (n = 23 907)	Case Patients (n = 3159)	Control Participants (n = 31 534)	Case Patients (n = 32 130)	Control Participants (n = 320 501)
Men, %	98.2	98.5	99.2	99.3	98.7	98.8
Age, %						
45–54 y	4.7	4.7	6.8	6.9	7.1	7.1
55–64 y	12.9	12.9	13.9	13.9	15.4	15.4
65–74 y	35.3	35.5	35.6	35.6	35.9	35.9
75–84 y	40.8	41.0	38.7	38.8	37.3	37.4
≥85 y	6.4	6.0	5.0	4.9	4.3	4.2
Race, %						
White	85.4	84.0	84.2	83.8	83.0	83.7
Black	8.7	10.1	10.7	10.6	11.2	10.1
Hispanic	2.3	2.4	1.9	2.1	2.3	2.3
Other	0.6	0.9	0.5	0.8	0.6	0.9
Unknown	3.0	2.5	2.7	2.7	3.0	3.1
Comorbid conditions, %						
Hypertension	53.1	62.0	67.9	61.8	61.6	62.3
Ischemic heart disease	33.6	36.0	56.7	36.2	40.7	36.3
Diabetes	19.1	20.5	32.2	20.8	26.7	22.0
Osteoarthritis	18.9	24.3	20.3	23.6	19.5	23.0
Depression	11.2	10.5	12.2	11.5	12.3	11.7
Cancer	18.4	20.1	18.0	20.0	25.6	20.2
Chronic heart failure	22.9	13.4	38.1	13.0	24.3	13.8
Medications, %						
Hydrochlorothiazide	13.9	16.8	19.8	16.3	17.4	18.3
Loop diuretic	46.5	29.2	63.3	28.0	49.0	30.9
Potassium-sparing diuretic	10.6	9.5	19.3	9.5	15.1	10.4
β-Blocker	25.2	31.4	44.5	30.9	38.2	34.5
Calcium-channel blocker	32.2	33.9	36.1	34.0	35.3	34.8
ACE inhibitor	40.6	42.3	59.0	41.1	47.7	44.4
Angiotensin-receptor blocker	3.7	4.8	6.2	4.7	5.7	5.7
Antiarrhythmic	4.6	3.3	9.0	3.3	6.3	3.6
Digoxin	22.3	13.2	38.5	12.8	24.5	13.6
Lipid-lowering medication	24.7	40.9	42.7	40.6	36.6	44.4
Insulin	7.8	6.1	14.2	6.1	11.7	7.3
Oral hypoglycemic agent	13.4	15.8	22.7	15.9	19.4	17.6
Nonsteroidal anti-inflammatory drugs	24.7	33.4	26.3	33.5	28.8	34.4
Annual health care utilization						
Mean primary care visits (SD), n	3.6 (3.7)	4.1 (3.4)	4.5 (4.1)	4.0 (3.3)	4.2 (3.8)	4.0 (3.4)
Mean hospitalizations (SD), n	0.4 (0.7)	0.2 (0.6)	0.6 (1.1)	0.2 (0.6)	0.5 (1.0)	0.3 (0.7)
Cumulative COPD exacerbations, %						
0	9.4	43.1	15.3	44.6	14.7	40.5
1	18.8	28.5	23.4	28.4	22.3	27.7
2	19.7	13.4	19.8	13.0	20.2	14.1
≥3	52.2	15.0	41.6	14.0	42.8	17.8
Exacerbation in previous 6 mo, %	70.2	13.6	64.4	22.2	62.1	22.3

ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease.

Table 2

<i>Table 2. Medication Use Related to Chronic Obstructive Pulmonary Disease</i>								
Regimen	Respiratory Death, %		Cardiovascular Death, %		Respiratory or Cardiovascular Death, %		All-Cause Mortality, %	
	Case Patients (n = 2405)	Control Participants (n = 23 907)	Case Patients (n = 3159)	Control Participants (n = 31 534)	Case Patients (n = 5564)	Control Participants (n = 55 441)	Case Patients (n = 32 130)	Control Participants (n = 320 501)
Medication use within 6 mo of Index date								
Short-acting β -agonists	71.2	61.9	70.0	62.3	70.5	61.8	65.9	61.2
Inhaled corticosteroids	31.0	24.8	24.7	24.9	27.4	24.8	24.2	24.7
Ipratropium	65.8	52.4	65.3	52.4	65.5	52.1	60.8	52.5
Long-acting β -agonists	16.0	10.7	11.0	10.2	13.1	10.5	12.9	12.2
Theophylline	12.8	6.4	7.3	6.3	9.7	6.3	7.0	6.0
Medication regimen use within 6 mo of Index date								
None or short-acting β -agonists only	24.5	37.2	26.4	37.0	25.6	37.3	31.1	37.2
Inhaled corticosteroids	3.7	4.9	3.6	5.0	3.6	5.0	3.3	4.5
Ipratropium	31.6	30.1	40.0	30.4	36.4	30.1	35.6	30.0
Long-acting β -agonists	1.3	1.4	1.1	1.4	1.2	1.4	1.3	1.6
Theophylline	2.4	1.8	1.9	1.9	2.1	1.9	1.6	1.6
Inhaled corticosteroids plus ipratropium	14.3	12.0	13.2	12.1	13.7	11.8	11.7	11.4
Inhaled corticosteroids plus long-acting β -agonists plus ipratropium	6.0	3.8	4.2	3.6	5.0	3.9	5.1	4.6
Long-acting β -agonists plus ipratropium	4.3	2.6	3.2	2.5	3.7	2.6	3.6	2.9
Inhaled corticosteroids plus long-acting β -agonists	1.4	1.7	1.1	1.6	1.2	1.6	1.4	1.9
Ipratropium plus theophylline	4.0	1.7	2.3	1.6	3.0	1.6	2.2	1.5
Inhaled corticosteroids plus ipratropium plus theophylline	3.2	1.4	1.4	1.4	2.2	1.4	1.5	1.2
Other	3.3	1.6	1.7	1.5	2.4	1.5	1.8	1.6

APPENDIX 3: MACIE *ET AL*, MAIN TABLES

Table 1

Table 1 Characteristics of cases (at first hospitalization) and controls

	SVT cases	Controls	MI cases	Controls	HF cases	Controls	Stroke cases	Controls
Number of subjects	2054	20501	3855	38490	5407	53929	4961	49487
Gender Males	48.2		61.7		49.8		49.8	
Age mean	71.2		69.1		76.0		73.4	
25th, 75th percentile	64, 80		61, 79		70, 84		67, 82	
Respiratory Co-morbidity								
Asthma	10.1	10.9	9.6	11.0	7.1	9.1	8.0	10.0
COPD	27.1	26.3	29.5	25.6	41.7	28.9	31.5	27.9
Asthma and COPD	10.5	9.1	10.8	9.5	13.3	10.1	9.4	10.0
Bronchitis	52.3	53.7	50.1	53.9	37.9	52.1	51.1	52.2
Any Non-cardiac Co-morbidity	39.5	34.0	44.4	32.9	51.7	35.8	46.2	34.9
Drug dispensed within								
IB 60 Days	7.8	4.8	6.6	4.7	14.9	5.4	5.6	5.0
1 Year	11.2	7.6	10.3	7.5	20.4	8.4	10.1	7.9
BA 60 Days	13.2	9.3	13.1	9.4	24.4	10.1	10.5	9.8
1 Year	22.4	17.2	21.1	16.8	34.3	17.6	19.3	17.4
ICS 60 Days	7.2	6.4	7.9	6.2	12.0	6.9	6.1	6.7
1 Year	13.5	11.3	14.0	11.6	18.7	12.0	11.6	11.7
Cardiac Drugs								
Antiarrhythmics	36.8	9.2	11.8	7.9	34.6	9.8	16.8	9.6
Nitrates	31.0	16.1	30.1	13.7	40.7	16.6	25.0	16.4
Antihypertensives	37.5	27.6	32.4	25.7	42.0	28.8	37.8	28.1
Furosemide	33.9	17.3	23.8	14.5	65.0	18.8	27.8	18.2
Betablockers	29.4	14.1	20.1	12.8	20.7	13.8	20.4	13.8
Calcium Channel Blockers	16.5	7.6	12.4	6.6	15.2	7.7	11.3	7.4
ACEI	37.1	21.9	30.2	20.5	52.4	21.6	34.9	21.9
Anticholesterol	13.0	10.5	15.1	10.2	12.1	9.2	13.8	9.4
Any	81.2	55.3	67.4	51.6	88.9	58.6	73.2	56.7

APPENDIX 4: OGALE ET AL, MAIN TABLES AND FIGURES

Figure 1

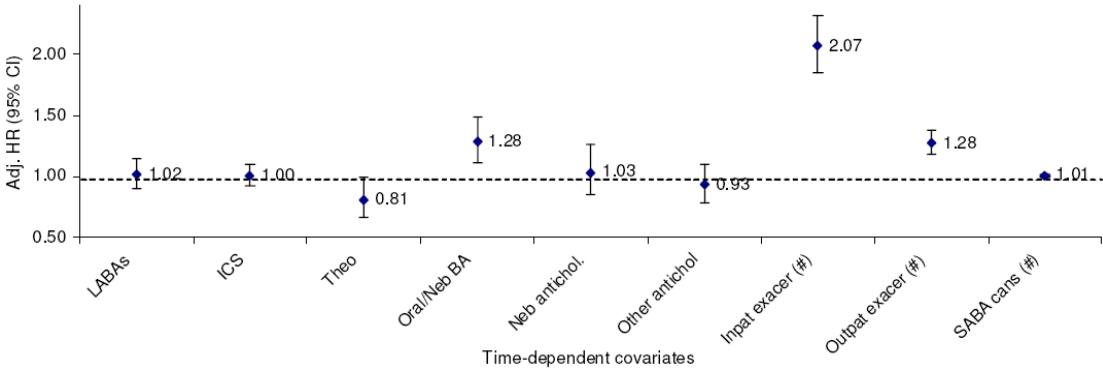


Table 2

Table 2. Crude and Adjusted RRs for CVEs				
	Crude	Baseline Adj.^a	Final Adj. Model^b	
	HR	HR	HR (95% CI)	p-value
Unexposed to Anticholinergics	1.00	1.00	1.00	-
Exposed to Anticholinergics	1.48 (1.40-1.56)	1.47 (1.39-1.55)	1.29 (1.21-1.38)	0.00
Recency of exposure: Past 6 months				
Anticholinergic equivalents (≤ 4)	1.55 (1.44-1.66)	1.51 (1.41-1.62)	1.40 (1.30-1.51)	0.00
Anticholinergic equivalents (> 4)	1.49 (1.39-1.60)	1.52 (1.42-1.63)	1.23 (1.12-1.35)	0.00
Recency of exposure: > 6 months				
Anticholinergic equivalents (≤ 4)	1.17 (1.02-1.35)	1.13 (0.98-1.29)	1.08 (0.94-1.24)	0.27
Anticholinergic equivalents (> 4)	1.13 (0.96-1.33)	1.14 (0.97-1.34)	0.95 (0.80-1.12)	0.57

^a Adjusted for all baseline variables from table 1 and fiscal year of cohort entry

^b Adjusted for all baseline variables from table 1, fiscal year of cohort entry, and all time-dependent variables from figure 1.

APPENDIX 5. DRUG UTILIZATION DATA TABLES

Table 1. Nationally projected estimates of the number of patients receiving ipratropium or tiotropium oral inhalation through U.S. retail and mail order pharmacies, stratified by recent diagnosis code, for years 2005 - 2008

	2005		2006		2007		2008	
	Projected Patients	Share %	Projected Patients	Share %	Projected Patients	Share %	Projected Patients	Share %
Ipratropium	3,579,872	100.0%	3,277,848	100.0%	3,112,357	100.0%	2,998,596	100.0%
Asthma	531,490	14.8%	503,765	15.4%	487,650	15.7%	458,617	15.3%
Ipratropium	178,745	33.6%	166,492	33.0%	162,987	33.4%	151,717	33.1%
Ipratropium/albuterol	352,745	66.4%	337,273	67.0%	324,663	66.6%	306,900	66.9%
Chronic Bronchitis	93,020	2.6%	84,444	2.6%	80,485	2.6%	78,409	2.6%
Ipratropium	27,556	5.2%	24,224	4.8%	23,897	4.9%	22,828	5.0%
Ipratropium/albuterol	65,465	12.3%	60,220	12.0%	56,589	11.6%	55,580	12.1%
COPD	602,451	16.8%	558,570	17.0%	526,286	16.9%	473,052	15.8%
Ipratropium	178,297	33.5%	160,983	32.0%	152,822	31.3%	132,706	28.9%
Ipratropium/albuterol	424,155	79.8%	397,587	78.9%	373,464	76.6%	340,346	74.2%
Emphysema	23,937	0.7%	22,399	0.7%	21,285	0.7%	20,140	0.7%
Ipratropium	6,747	1.3%	6,374	1.3%	5,982	1.2%	5,746	1.3%
Ipratropium/albuterol	17,190	3.2%	16,026	3.2%	15,303	3.1%	14,394	3.1%
Other	2,328,974	65.1%	2,108,670	64.3%	1,996,650	64.2%	1,968,379	65.6%
Ipratropium	668,145	125.7%	591,502	117.4%	564,779	115.8%	547,146	119.3%
Ipratropium/albuterol	1,660,829	312.5%	1,517,168	301.2%	1,431,870	293.6%	1,421,233	309.9%
Tiotropium	1,010,359	100.0%	1,464,634	100.0%	1,833,577	100.0%	1,954,702	100.0%
Asthma	146,804	14.5%	210,570	14.4%	262,236	14.3%	269,967	13.8%
Chronic Bronchitis	32,869	3.3%	46,711	3.2%	57,434	3.1%	60,824	3.1%
COPD	246,381	24.4%	348,452	23.8%	433,157	23.6%	438,559	22.4%
Emphysema	10,098	1.0%	14,576	1.0%	19,280	1.1%	21,073	1.1%
Other	574,206	56.8%	844,324	57.6%	1,061,469	57.9%	1,164,279	59.6%

Source: Wolters Kluwer Source Lx: Concurrent Product Analyzer, Data extracted 6/2009,
File: WK CPA 2009-312 Ipratropium market by diagnosis.xls

Table 2. Nationally projected estimates of the number of patients receiving ipratropium or tiotropium oral inhalation through U.S. retail and mail order pharmacies, stratified by recent diagnosis code, for years 2005 - 2008

	2005		2006		2007		2008	
	Projected Patients	Share %	Projected Patients	Share %	Projected Patients	Share %	Projected Patients	Share %
Ipratropium	3,579,872	100.0%	3,277,848	100.0%	3,112,357	100.0%	2,998,596	100.0%
Female	2,042,657	57.1%	1,875,011	57.2%	1,774,090	57.0%	1,714,163	57.2%
Ipratropium	622,258	30.5%	557,860	29.8%	534,108	30.1%	507,589	29.6%
Ipratropium / albuterol	1,420,399	69.5%	1,317,151	70.2%	1,239,982	69.9%	1,206,573	70.4%
Male	1,447,471	40.4%	1,332,939	40.7%	1,281,005	41.2%	1,230,290	41.0%
Ipratropium	409,571	20.1%	369,273	19.7%	357,831	20.2%	335,479	19.6%
Ipratropium / albuterol	1,037,900	50.8%	963,666	51.4%	923,175	52.0%	894,811	52.2%
Unspecified	89,744	2.5%	69,899	2.1%	57,262	1.8%	54,143	1.8%
Ipratropium	27,661	1.4%	22,442	1.2%	18,529	1.0%	17,074	1.0%
Ipratropium / albuterol	62,083	3.0%	47,457	2.5%	38,732	2.2%	37,069	2.2%
Tiotropium	1,010,359	100.0%	1,464,634	100.0%	1,833,577	100.0%	1,954,702	100.0%
Female	547,726	54.2%	808,609	55.2%	1,010,719	55.1%	1,078,520	55.2%
Male	439,054	43.5%	629,509	43.0%	794,839	43.3%	846,087	43.3%
Unspecified	23,579	2.3%	26,516	1.8%	28,019	1.5%	30,094	1.5%

Source: Wolters Kluwer Source Lx: Concurrent Product Analyzer, Data extracted 6/2009,
File: WK CPA 2009-312 Ipratropium market by gender.xls

Table 3. Nationally projected estimates of the number of patients receiving ipratropium or tiotropium oral inhalation through U.S. retail and mail order pharmacies, stratified by patient sex, for years 2005 - 2008

	2005		2006		2007		2008	
	Projected Patients	Share %	Projected Patients	Share %	Projected Patients	Share %	Projected Patients	Share %
Ipratropium	3,579,872	100%	3,277,848	100%	3,112,357	100%	2,998,596	100%
0-64	1,791,361	50%	1,613,035	49%	1,528,121	49%	1,481,243	49%
Ipratropium	524,157	29%	464,163	29%	449,617	29%	432,462	29%
Ipratropium / albuterol	1,267,204	71%	1,148,872	71%	1,078,504	71%	1,048,781	71%
65+	1,729,793	48%	1,610,939	49%	1,536,211	49%	1,468,497	49%
Ipratropium	517,528	30%	468,345	29%	445,259	29%	412,325	28%
Ipratropium / albuterol	1,212,265	70%	1,142,594	71%	1,090,953	71%	1,056,172	72%
Unknown	58,718	2%	53,874	2%	48,025	2%	48,856	2%
Tiotropium	1,010,359	100%	1,464,634	100%	1,833,577	100%	1,954,702	100%
0-64	423,952	42%	595,036	41%	734,689	40%	798,705	41%
65+	569,858	56%	848,026	58%	1,074,215	59%	1,128,679	58%
Unknown	16,549	2%	21,572	1%	24,673	1%	27,318	1%

Source: Wolters Kluwer Source Lx: Concurrent Product Analyzer, Data extracted 6/2009,
File: WK CPA 2009-312 Ipratropium market by age.xls

Table 4. Nationally projected number of prescriptions dispensed for ipratropium and tiotropium by U.S. retail and mail-order pharmacies, Years 2005 through 2008

	2005		2006		2007		2008	
	TRx (000)	%	TRx (000)	%	TRx (000)	%	TRx (000)	%
Total	13,593	100.0%	14,262	100.0%	15,460	100.0%	15,906	100.0%
Ipratropium Combined	10,250	75.4%	9,147	64.1%	8,724	56.4%	8,440	53.1%
Ipratropium	2,904	28.3%	2,437	26.6%	2,328	26.7%	2,174	25.8%
Atrovent	1,446	0.0%	99	0.0%	7	0.0%	1	0.0%
Atrovent HFA	63	0.0%	1,053	0.0%	1,035	0.0%	944	0.0%
Ipratropium Bromide	1,395	0.0%	1,284	0.1%	1,285	0.1%	1,229	0.1%
Ipratropium-albuterol	7,346	0.1%	6,710	0.1%	6,397	0.1%	6,266	0.1%
Combivent	6,192	0.1%	5,550	0.1%	5,203	0.1%	4,864	0.1%
Duoneb	1,154	0.0%	1,160	0.0%	787	0.0%	95	0.0%
Ipratropium-Albuterol	0	0.0%	0	0.0%	407	0.0%	1,307	0.0%
Tiotropium	3,343	0.0%	5,115	0.0%	6,736	0.0%	7,466	0.0%

Source: *Wolters Kluwer SOURCE PHAST Prescription Monthly™*, Extracted 6-18-2009, File: WK PHAST 2009-312 Ipratropium.xls

Table 5. Nationally projected indications for use of ipratropium and tiotropium by U.S. office based physicians, by top 4 diagnosis groups, for years 2005 through 2008.

	2005		2006		2007		2008	
	Uses (000)	Share %	Uses (000)	Share %	Uses (000)	Share %	Uses (000)	Share %
Ipratropium Combined	6,967	100.0%	6,031	100.0%	5,265	100.0%	4,868	100.0%
496 Chr Airway Obstruct Nec	3,027	43.4%	2,789	46.2%	2,080	39.5%	1,965	40.4%
493 Asthma	1,503	21.6%	1,106	18.3%	913	17.3%	876	18.0%
491 Chronic Bronchitis	746	10.7%	649	10.8%	897	17.0%	734	15.1%
486 Pneumonia, Organism Nos	255	3.7%	181	3.0%	309	5.9%	270	5.5%
All Others	1,436	20.6%	1,306	21.7%	1,065	20.2%	1,024	21.0%
Tiotropium Bromide	19	100.0%	6	100.0%	2,500	100.0%	2,720	100.0%
496 Chr Airway Obstruct Nec	1	4.1%	--	--	1,652	66.1%	1,974	72.6%
491 Chronic Bronchitis	--	--	--	--	168	6.7%	201	7.4%
493 Asthma	13	67.5%	1	13.9%	228	9.1%	199	7.3%
492 Emphysema	--	--	5	86.1%	56	2.3%	115	4.2%
All Others	5	28.4%	--	--	396	15.9%	230	8.5%

Source: SDI Physician Drug and Diagnosis Audit, Extracted 6=2--5, File:PDDA 2009-312 ipratropium 6-09

SDI Physician Drug & Diagnosis Audit (PDDA)

SDI's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based

physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Wolters Kluwer Concurrent Product Analyzer (CPA)

Data used in CPA are derived from Wolters Kluwer prescription and medical claims databases. CPA integrates activity from a variety of sources, including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups, physician offices, and outpatient treatment centers. Wolters Kluwer receives over 1.4 billion prescription claims annually, 292 Million medical claims, representing over 128.9 million unique patients. Approximately 18.9 million patients have both medical and prescription activity in the database.

CPA allows users to measure and evaluate concurrent drug therapy usage in unique patients during a selected time period. The data are projected to a national level.

Wolters Kluwer SOURCE PHAST Prescription Monthly™

The Wolters Kluwer Source PHAST Prescription Monthly is a syndicated view of U.S. retail and mail order pharmacy prescription activity, updated on a monthly basis. Source PHAST Prescription Monthly covers over 40,000 retail pharmacies in the sample including mail order and specialty pharmacies. The dispensed prescriptions in the sample represent approximately 80% of all U.S. retail prescriptions (cash, Medicaid, 3rd party) as well as 60% of all U.S. mail order prescriptions. The retail and mail order prescriptions are projected to the national level.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 19, 2009

To: Badrul A. Chowdhury
Director, Division of Pulmonary and Allergy Products
Office of New Drugs

Through: Solomon Iyasu, MD, MPH
Director, Division of Epidemiology

Office of Surveillance and Epidemiology

From: Simone P. Pinheiro, ScD MSc
Epidemiologist
Office of Surveillance and Epidemiology

Subject: Review of ERASMUS observational study on safety of
tiotropium bromide

Drug Name(s): Tiotropium bromide (marketed as Spiriva)

Submission Number: S029

Application Type/Number: NDA # 021-395

Applicant/sponsor: Boehringer Ingelheim

OSE RCM #: 2009-1598

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EXECUTIVE SUMMARY

Inhaled anticholinergics have been considered both effective and safe for the management of chronic obstructive pulmonary disease (COPD). However, a few recent publications and reports raised concerns about the safety of inhaled anticholinergics, including tiotropium bromide (TB) and ipratropium bromide (IB). These reports were recently reviewed by the Office of Surveillance and Epidemiology (OSE) (DARRTS Communication PK # 2663713, Communication Date 08/04/2009). In this review, the OSE concluded that the data implicating inhaled anticholinergics in increasing risk of cardiovascular outcomes and death was not compelling due to substantial limitations of these studies. Additionally, the findings of these reports did not agree with the findings of previously published meta-analyses of randomized clinical trials, nor do they agree with the findings of a large 4-year placebo-controlled randomized clinical trial (UPLIFT), none of which suggested an association between anticholinergics and increased risk of cardiovascular events or mortality.

An epidemiology study report concerning the safety of tiotropium bromide, conducted by Erasmus Medical Center (Rotterdam, The Netherlands), was recently submitted by Boehringer Ingelheim. The Division of Pulmonary and Allergy Products (DPAP) within the Office of New Drugs consulted the Division of Epidemiology (DEPI) within the Office of Surveillance and Epidemiology (OSE) to review the methodology and results of this study.

In summary, the study conducted by Erasmus Medical Center is a population-based case-control study nested within a cohort of COPD patients over the age of 40 years, participating in the IPCI - a longitudinal observational database that contains data from computer-based patient records of a selected group of GPs in The Netherlands. The primary objective of this study was to evaluate the safety profile of tiotropium compared to both non-users of anticholinergics drugs as well as to users of LABA. The main limitation of this study is the potentially inadequate statistical power to detect associations between safety outcomes including cardiovascular adverse events and mortality between tiotropium users vs. non users or LABA users. However, confidence limits were relatively narrow, and the upper bound confidence interval for cardiovascular/cerebrovascular events of current users vs. non users of anticholinergics (95% CI of 0.64 -1.27) and for current user of tiotropium vs. LABA [(95% CI (0.50, 1.41)] were lower than the increase in risk reported in the only meta-analysis of randomized trials that suggested an increase in risk in cardiovascular events [RR (tiotropium vs. controls) =1.49, 95% CI (0.98, 2.26); RR (anticholinergics vs. controls) = 1.60 (1.22, 2.10)] [3, correction in JAMA 2009]. The results of this study, in combination with most of the epidemiologic evidence noted in the OSE's previous review (DARRTS communication PK # 2663713, Communication Date 08/04/2009) failed to provide evidence for an association between tiotropium and increased risk of cardiovascular events, mortality or stroke.

1 BACKGROUND/HISTORY

Tiotropium bromide is a long acting anticholinergic with specificity for muscarinic receptors approved as Spiriva HandiHaler (Spiriva® Boehringer Ingelheim). This product is a dry powder capsule formulation approved on January 30, 2004 (NDA # 21-395) for the long-term, once daily management of bronchospasm associated with chronic obstructive pulmonary disease (COPD).

On November 16 of 2007, Boehringer Ingelheim (BI) submitted an NDA (NDA # 021-936) application for a novel inhalation device, the Respimat Inhalation Spray, to deliver tiotropium bromide (TB) for oral inhalation. During the development program, several safety issues surfaced.

On November 2005, prior to submitting the NDA, BI informed the Division of Pulmonary and Allergy Products (DPAP) about an imbalance in fatal adverse events favoring the placebo group in two of the Respimat 1-year clinical trials. Because DPAP was concerned about the impact of this signal on the approved product Spiriva HandiHaler, DPAP presented the preliminary mortality data to the Drug Safety Oversight Board (DSOB) on June of 2006. The DSOB noted the mortality signal to be weak. However, the DSOB recommended that BI obtain vital status follow up data on 100% of patients who dropped out of the trials as there was substantial differential discontinuation between the placebo and TB treatment groups. The mortality issue was reviewed again in an internal Regulatory Briefing meeting held on July 18, 2008 once complete follow-up data for the above mentioned trials were submitted as part of the NDA 21-936. The committee concluded that while a portion of the mortality signal could be explained by differential follow-up, additional data are required to determine if the potential signal represents a true safety issue.

In November of 2007, BI submitted preliminary results of a routine pooled safety analysis of 29 clinical trials with Spiriva HandiHaler (n=25 studies) and Respimat (n=4 studies) (unpublished report). In this analysis, BI noted an increase in risk of stroke in patients treated with TB vs. placebo [RR and 95% CI of 1.37 (0.73, 1.56)]. While this analysis did not adjust for multiplicity and the association between TB and stroke was not statistically significant, the Agency released an Early Communication on March of 2008 describing potential risk of stroke associated with tiotropium [12].

The results of a recently published meta-analysis of 17 randomized clinical trials raised questions about the safety of inhaled anticholinergic agents, particularly in regards to the risk of cardiovascular outcomes [3,13]. In this analysis, TB was associated with a non-significant 49% increase in risk of cardiovascular outcomes [RR and 95% CI: 1.49 (0.98 - 2.26)] compared to comparator groups, which included both placebo and active controls. Moreover, a few other recent observational studies raised concerns about the safety of ipratropium bromide (IB), another inhaled anticholinergic agent. These studies included two large nested case-control studies, which suggested that IB increased the risk of death [4] and of certain cardiovascular events [5]; and a large cohort study by Ogale and colleagues [6], which suggested that IB may increase the risk of cardiovascular events.

These reports were recently reviewed by the Office of Surveillance and Epidemiology (OSE) (DARRTS Communication PK # 2663713, Communication Date 08/04/2009). In this review, OSE concluded that, due to the limitations of these studies, including biased selection of studies, lack of information on participants who discontinued trial, failure to use person-time data [3], and failure to adjust for important confounders [4-6], these studies did not provide substantial and convincing data to implicate inhaled anticholinergics in increasing risk of cardiovascular outcomes. Furthermore, the findings of these reports did not agree with findings of previously published meta-analyses [7-10], nor did they agree with the recently published findings from a 4-year large randomized, placebo-controlled clinical trial [11], none of which suggested an association between anticholinergics and cardiovascular events or mortality. Based on the currently available data, while the Agency will continue to monitor the safety of anticholinergics, OSE did not recommend the pursuit of further studies by the Agency or by the sponsor to assess the safety of inhaled anticholinergics.

An epidemiology study report concerning the safety of TB, conducted by Erasmus Medical Center (Rotterdam, The Netherlands), was submitted by the BI (by Erasmus Medical Center, report dated 20 May 2009). The Division of Pulmonary and Allergy Products (DPAP) within the Office of New Drugs consulted the Division of Epidemiology (DEPI) within OSE to review the methodology and results of this study. The review focuses on the results related to the safety of tiotropium bromide.

2 REVIEW METHODS AND MATERIALS

2.1 MATERIALS REVIEWED

- Epidemiology Study Report entitled “Cardiovascular, cerebrovascular, and respiratory events in association with long-acting bronchodilators: a comparative study in persons with COPD.” (by Erasmus Medical Center, report dated 20 May 2009).

3 RESULTS OF REVIEW

3.1 PROPOSED OBJECTIVES/ACTUAL OBJECTIVES

3.1.1 Actual Objective

This study had several objectives. These are described below.

Objective 1: To describe use of tiotropium bromide in the source population and to assess indication of first use of tiotropium in the source population.

Objectives 2:

To explore the safety of tiotropium bromide in comparison to a long acting β_2 agonist (i.e. salmeterol or formoterol) on several safety endpoints (e.g. cardiovascular and cerebrovascular endpoints, mortality, diabetes mellitus (DM), renal failure) and on a few effectiveness endpoints (e.g. COPD-related hospitalization and exacerbation rates).

Objective 3: To assess event rates in the cohort of incident COPD patients

Objective 4: To describe and compare the baseline characteristics of persons starting with different respiratory drugs in incident COPD patients.

3.1.2 OSE Comments on Actual Objectives

We concur with the objectives of this study. Objective # 2 is the most relevant objective to evaluate the safety of tiotropium bromide.

3.2 ACTUAL DESIGN

3.2.1 Actual Design

The study designs differed according to each study objective and they are outlined below:

Objective 1

Retrospective cohort study

Objective 2

Several case-control studies nested in a cohort

Objective 3

Retrospective cohort study

Objective 4

Cross-sectional study

3.2.2 OSE Comments on Actual Design

The study designs were appropriate to evaluate the objectives of this study.

3.3 INFORMED CONSENT

3.3.1 Proposed/Actual Informed Consent

Patient identification information, notes, prescriptions, physician linked indications for therapy, physical findings, and laboratory values are entered into the database directly by the GPs. This information was anonymized by the database gatekeeper.

3.3.2 OSE Comments on Actual Informed Consent

Not applicable

3.4 DATA SOURCE

3.4.1 Data Source

The IPCI is a longitudinal observational database that contains data from computer based patients records of a selected group of general practitioners (GPs) throughout the Netherlands, who voluntarily chose to supply data to the database. GPs receive a minimal reimbursement for their data and completely control usage of their data through

the Steering Committee and through the possibility to withdraw data for specific studies. Collaborating practices are spread throughout the Netherlands and collaborating GPs are comparable to other GPs regarding age and gender. As of Sept of 2007, there were more than 400 GP practices that have provided data to the database. The IPCI database contains information on more than 1 million patients (including any patient who was ever registered). Turnover occurs as patients move and transfer to new practices. The database contains identification information (age, sex, patient identification, GP registration information), notes, prescriptions, physician-linked indications for therapy, physical findings, and laboratory values, all directly entered by the GPs.

3.4.2 OSE Comments on Actual Data Sources

Data comparing IPCI participants against residents of the Netherlands (*e.g.* distribution of age, gender, region) would be helpful to assess whether source population is representative of the general country population. Additionally, it would be also helpful to have information on participating practices (*e.g.* location/region, rural/urban, number of patients, type of practice).

The turnover and the mean length of follow-up time in the database are not described. In the IPCI, patients exit the database if they transfer to a new practice. Therefore, case ascertainment is likely to be incomplete if patients who develop certain outcomes seek new practices.

3.5 STUDY TIME PERIOD(S)

3.5.1 Study Time Period(s)

Objective 1

Patients entered the study on January 1st of 2000 or after one year of valid history (whichever came latest) and were followed up until death, latest availability of data or end of study (1st of July 2007).

Objective 2

Patients entered the study on January 1st of 2000, after one year of valid history, or at diagnosis of COPD (whichever came latest) and were followed up until the earliest of the following events: death, latest availability of data, transfer to nursing home, occurrence of outcome, or end of study (1st of July 2007).

Objective 3

Patients entered the study upon diagnosis of incident COPD and were followed up until the earliest of the following events: death, latest availability of data, transfer out of GP practice, occurrence of outcome, or end of study (1st of July 2007).

Objective 4

Patients entered the study upon diagnosis of incident COPD. Only baseline characteristics were assessed for this objective; therefore, patients were not followed up over time.

3.5.2 OSE Comments on Actual Study Time Period(s)

Length of study time period seems appropriate to allow for the occurrence of the safety outcomes of interest (e.g. cardiovascular and cerebrovascular outcomes, death, DM, renal failure) among COPD patients as well as for the occurrence of effectiveness outcomes of interest after exposure to respiratory medications.

3.6 POPULATION

3.6.1 Population

Objective 1

A total of 185,325 patients in the IPCI-PHARMO GP database, all of whom had 365 days of history available in the database and were at least 40 years of age at start of follow-up.

Objective 2

Incident cases of diseases and matched control-moments nested in a cohort of patients in the IPCI-PHARMO GP database (01/01/2000-07/01/2007) who had at least 365 days of history available in the database, who were diagnosed with COPD (prevalent and incident COPD) and who were at least 40 years of age at study entry were selected.

For each endpoint, a separate case-control study including incident cases of the particular disease and a maximum number of control moments matched to cases on *index date*, *gender*, and *year of birth* was created. These ten case-control studies include:

- Myocardial Infarction Case-Control Study included 155 cases of MI and 6,799 matched control moments
- Ventricular Arrhythmia Case-Control Study included 17 cases and 833 matched control moments
- Cardiac Heart Failure Case-Control Study included 466 cases and 16,039 matched control moments
- Stroke/Transient Ischemic Attack Case-Control Study included 357 cases and 13,909 matched control moments
- Cardiovascular/Cerebrovascular events Case-Control Study included 784 cases and 25,899 matched control moments
- Mortality Case-Control Study included 1032 cases and 40,615 matched control moments
- Diabetes Mellitus Case-Control Study included 295 cases and 10,428 matched control moments
- Renal failure Case-Control Study included 83 cases and 3,975 matched control moments
- COPD-related hospitalization Case-Control Study included 357 cases and 13,909 matched control moments
- COPD exacerbation Case-Control Study included 3,439 cases and 88,724 matched control moments

Objective 3

Retrospective cohort study including all patients in the IPCI-PHARMO GP database (from 1st of January 2000 to 1st of July 2007) who had at least 365 days of history available in the database and who had a diagnosis of COPD dated after cohort entry (*incident* COPD)

Objective 4

Cross-sectional study describing baseline characteristics of all patients in the IPCI-PHARMO GP database (from 1st of January 2000 to 1st of July 2007) who had at least 365 days of history available in the database and who had a diagnosis of COPD dated after cohort entry (*incident* COPD).

In *objectives 2* through *4* (described in session 3.1.1 of this report), patients with either *definite* or *probable* COPD diagnosis were included in the analyses. Diagnosis of COPD was assessed via review of medical files searching on ICPC codes ICPC-R95, ICPD_R91, as well as spirometry and free text searching including “COPD” or “chronic bronchitis” or “emphysema” or “exacerbation.” Diagnosis of *definite* COPD was made based on *either* records of COPD diagnosis, confirmed by a specialist *or* COPD diagnosed by a GP only and confirmed by spirometry (a single record was sufficient). A diagnosis of *probable* COPD was made based on COPD diagnosis by a GP only and a subsequent at least 2 records of COPD (free text, ICPC coding or prescription of bronchodilator drugs) within 1 year of first record of COPD.

3.6.2 OSE Comments on Actual Population

The definition of *control-moments* is not clearly stated in the study report for Objective #2. OSE reviewer assumed control moments referred to person-years.

3.7 EXPOSURE

3.7.1 Exposure

Information on usage of drugs given for treatment of COPD was retrieved from the prescription records of both cases and controls. The National Database of drugs, maintained by the Royal Dutch Association for Advancement of Pharmacy, enables coding of prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO.

In the case-control studies (*objective 2*), treatment exposure was categorized by type of drug, timing and dose. Drug exposure was defined as, *current* (last prescription covered the index date or ended less than 30 days prior to the index date), *recent* (last prescription ended 30 days < 6 months prior to index date), *distant* (last prescription ended > 6 months prior to index date), or *none*. Some analyses used *none* use of the study drug as the reference categories while other analyses used *use of another class of drug* as the reference category. Tiotropium was the main exposure of interest. Other drugs considered in this study included short acting anticholinergic agents, single-ingredient LABA, single-ingredient SABA, inhaled corticosteroids, theophyllines, fixed combination therapies (e.g. LABA + inhaled corticosteroids, anticholinergic agents +

SABA), oral β_2 -agonists, leukotriene receptor antagonists. In the main analyses of objective 2 (nested case-control studies), tiotropium was compared to *no anticholinergics*, *LABA* and *SABA*.

In some analyses, mutually exclusive categorization of current use of bronchodilators was created (*i.e.* only tiotropium, only other short acting anticholinergics, only LABA, only SABA, only xanthines). Patients who used multiple products were classified as multiple drug combinations. ICS was not used for categorization but instead adjusted for. In analyses of class effects of drugs, short and long-acting anticholinergics (called *anticholinergics*), short and long-acting β_2 -agonists (called *beta-agonists*), and xanthines were combined.

For current users of the primary study drugs (*i.e.* short acting anticholinergics drugs and tiotropium), the dose effect was assessed with daily dose in daily recommended average dosage (DDD) and categorized as *low*, *medium*, or *high*. Recency of starting (first 2 weeks of index date), route of administration (nebulizer, aerosol, power) and cumulative effect of duration were assessed.

To assess drug specific event rates, exposure cohorts were created based on the actual exposure at each day. Patients contributed person-time to a specific exposure category during current use of that drug without carry-over (objective 3). In objective 4, exposure cohorts were defined according to first drug use of the various respiratory medications. Patients were classified as exposed to a particular drug at the moment they used one of the drugs for the first time. Therefore, one person was allowed to contribute to multiple cohorts upon switching of therapy.

3.7.2 OSE Comments on Actual Exposure

Medication prescription was used as surrogate for drug exposure, which requires the assumption that participants used the drugs as prescribed. This type of misclassification, however, is unlikely to have differed between those who subsequently developed the outcomes of interest and those who did not. This non-differential misclassification would tend to make the comparison groups more similar to one another in respect to the exposure of interest, ultimately attenuating the association between tiotropium use and risk of the outcomes of interest.

3.8 DISEASE OUTCOME OF INTEREST

3.8.1 Disease Outcome of Interest

The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnosis; these can be mapped to ICD-9 codes. Additionally, diagnoses and complaints can be entered as free text. Safety endpoints were searched in the database and reviewed by 2 medical doctors blinded to patients' exposure status as described below for each outcome.

Safety endpoints

Mortality : Deaths were reviewed by a broad search in the database on ICPC code A96 (death), a free text search on death related terms, and death as reason for end of follow-up. For patients who died, the complete electronic record file, including referral and discharge letters, were reviewed and deaths were classified according to respiratory, cardiovascular or other reasons. The cause of death was adjudicated by the Physician reviewers. A sample of the adjudicated deaths was sent for GPs for validation. The positive predictive value was 90%.

Stroke (overall and hemorrhagic/ischemic, fatal and non-fatal stroke) and transient ischemic attack (TIA): Cases of stroke and TIA were searched in the database according to ICPC codes and free text search. The medical records of all potential stroke/TIA cases were manually reviewed by 2 medical doctors blinded to the patients' exposure status. A patient was considered a case if a CT scan was done or a neurologist diagnosis or discharge letter was available. For those not hospitalized, a GP diagnosis was required and the clinical symptoms needed to be consistent. All doubtful cases and a sample of the definite cases were reviewed by an expert neurologist. Stroke and TIA were combined as endpoints in primary analyses.

Myocardial Infarction (fatal and non-fatal): MI cases were identified via automatic search on ICPC codes for myocardial infarction as well as through search of free text, ECG and cardiac enzyme results. All potential cases of MI were manually reviewed by 2 medical doctors blinded to the patients' exposure status. Only MI confirmed by a specialist (via discharge letters) or MI diagnosed by the GP in the presence of typical symptoms in combination with ECG findings and/or elevation of cardiac enzymes were considered valid.

Heart failure: Cases of CHF were identified via search on ICPC codes for heart failure as well as via searches in the free text and medication codes from prescription dataset in IPCI. All potential cases of CHF were manually reviewed by 2 medical doctors blinded to the patients' exposure status. Cases were classified as *definite* or *possible* heart failure. *Definite* cases were patients with heart failure confirmed by a specialist by means of an echocardiography. *Possible* cases were patients diagnosed by a GP as having symptoms of heart failure and receiving cardiovascular treatment with heart failure as indication.

Ventricular arrhythmia: Cases of ventricular arrhythmia were identified via search on ICPC codes as well as via searches in the free text. All potential cases of Ventricular arrhythmias were manually reviewed by 2 medical doctors blinded to the patients' exposure status. Only VA cases confirmed by a cardiologist or on ECG were considered as cases.

Renal failure: Cases of renal failure were identified via search on ICPC codes as well as via searches in the free text. Chronic renal failure was defined as patients requiring dialysis or those indicating renal failure based on age adjusted clearance formulas for at least 3 months apart. All potential cases of renal failure were manually reviewed by 2 medical doctors blinded to the patients' exposure status.

Diabetes mellitus: Cases of diabetes mellitus were identified via search on ICPC codes as well as via searches in the free text and glucose levels. A patient was considered as having DM upon specialist diagnosis (hospital discharge letter) or upon diagnosis by the GP (ICPC code/free text) in combination with an increased blood glucose or need to anti-diabetic drug. All potential cases of DM were manually reviewed by 2 medical doctors blinded to the patients' exposure status

Combined cardiovascular endpoint (including MI, stroke, heart failure, and ventricular arrhythmias): Identification and validation of these events as described above.

Effectiveness endpoint

COPD exacerbations (hospitalized and non hospitalized): defined as hospitalizations due to COPD (identified via manual search through free text of discharge summaries and referral letters from GPs) or short course (i.e. < 4 weeks) of oral corticosteroids/antibiotics for COPD exacerbations.

3.8.2 OSE Comments on Actual Disease Outcome of Interest

In the IPCI, patients exit the database if they transfer to a new practice. Therefore, case ascertainment is likely to be incomplete if patients who develop certain outcomes seek new practices. This type of misclassification/under-ascertainment is unlikely to differ between those exposed and not exposed to tiotropium. In the case-control studies (objective 2), this is unlikely to play important role as cases and controls were matched on index dates.

3.8.3 Sample Size

The source population consisted of 185,325 persons. Prevalence of tiotropium at baseline was 0/1000 person-years (product marketed in 2002 in The Netherlands) and peaked in 2006, reported as 17 users/1,000 person-years (please refer to report figure 5.1.1. below). The sample size for each case-control is as follows:

- Myocardial Infarction Case-Control Study included 155 cases of MI and 6,799 matched control moments
- Ventricular Arrhythmia Case-Control Study included 17 cases and 833 matched control moments
- Cardiac Heart Failure Case-Control Study included 466 cases and 16,039 matched control moments
- Stroke/Transient Ischemic Attack Case-Control Study included 357 cases and 13,909 matched control moments
- Cardiovascular/Cerebrovascular events Case-Control Study included 784 cases and 25,899 matched control moments
- Mortality Case-Control Study included 1032 cases and 40,615 matched control moments
- Diabetes Mellitus Case-Control Study included 295 cases and 10,428 matched control moments

- Renal failure Case-Control Study included 83 cases and 3,975 matched control moments
- COPD-related hospitalization Case-Control Study included 357 cases and 13,909 matched control moments
- COPD exacerbation Case-Control Study included 3,439 cases and 88,724 matched control moments

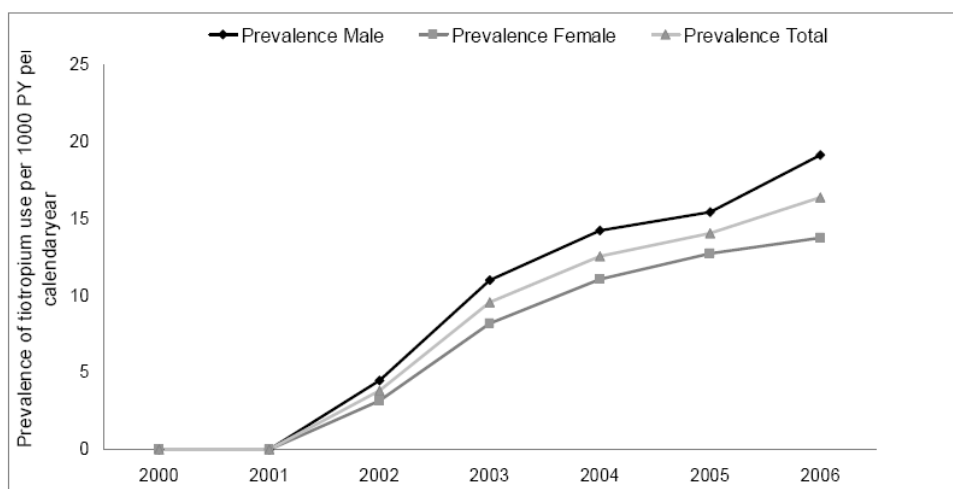


Figure 5.1.1 prevalence of tiotropium use in the population by calendar year

3.8.4 OSE Comments on Actual Sample Size

Because tiotropium was only marketed in the Netherlands in 2002, there would be no cases and controls exposed to tiotropium before 2002. This time period represents 25% of the study follow-up period, which could translate in substantial decrease in statistical power to detect an association between tiotropium and adverse events. Information on the number of cases and controls identified during this time period (not provided in the current report) would be informative.

Additionally, due to the limited number of cases in some of the case-control studies, this study had limited power to detect differences in incidence of ventricular arrhythmia (n=17 cases) and renal failure (n=83 cases) associated with use of tiotropium. Additionally, analyses restricted to incident COPD patients as well as analyses of effect modification by various variables were limited in statistical power due to low number of cases.

3.9 ANALYSES AND/OR STUDY RESULTS

3.9.1 Analyses and Study Results

Analyses

Use of tiotropium in the source population was described as the number of users and number of prescriptions over time. To study channeling in prescribing behavior, the cardiovascular risk profile at the time of first prescription of LABA *vs.* tiotropium was compared.

Within the incident cohort, event rates associated with each exposure (alone) were calculated. Use of multiple drugs during the same duration of time was classified as 'combination of drugs' in these analyses.

Within the COPD cohort (incident and prevalent), conditional logistic regression analysis was used to assess the matched unadjusted and adjusted risk estimates for the association between tiotropium and the different outcomes. Several covariates were considered in these analyses. COPD severity was assessed longitudinally on the basis of available spirometry data and severity classification schemes according to the GOLD criteria (if spirometry was available). In cases where spirometry was not available, COPD severity was categorized using data from GP or health care databases, which include a combination of recency of diagnosis, treatment with bronchodilators, xanthines or combination therapy, COPD-related hospitalization with antibiotic for treatment of respiratory infections, systemic corticosteroids for the treatment of COPD exacerbations, and/or diagnosis of pneumonia, and use of oxygen therapy. Other covariates were also assessed, including smoking history, drug use, (central nervous system drugs, anticholinergic drugs, drugs affecting cerebrovascular and cardiovascular disease, other respiratory drugs), use of resources (i.e. number of GP office visits and home visits in the year preceding the index date), and co-morbidities (e.g. myocardial infarction, angina pectoris, other fatal and non-fatal ischemic heart diseases, stroke or TIA, peripheral arterial disease, heart failure, arrhythmia, hypertension, lipid disorder, diabetes, renal insufficiency, migraine, other diseases, malignancies). In adjusted analyses, all covariates which were individually associated with the outcome ($p < 0.10$) were included in the models. Risk factors that changed the estimates by more than 5% were included in models. COPD severity (primary analyses adjusted for severity as measured one year prior to index date), duration and smoking were always included in the models.

Effect modification by several factors (i.e. gender, calendar year, smoking status, and severity of COPD, incident/prevalent COPD at baseline) was examined through stratified analyses as well as through the inclusion of interaction terms in logistic regression models. Presence of effect modification was determined if interaction terms between the potential effect modifier and tiotropium were statistically significant at the 0.05 level.

Results

The source population consisted of 185,325 persons, 48% of them were male. The mean age for males and females were 55.4 and 57.7 years, respectively. Prevalence of tiotropium peaked in 2006 and it was reported as 17 users per 1000 person years. Incidence of tiotropium peaked in 2003-2004 at the rate of 6 new users per 1000 person years and decreasing from 2005 onwards. The main indication for tiotropium use is COPD, followed by asthma.

Among patients newly diagnosed with COPD, new users of tiotropium were more likely to have *moderate* COPD while new users of LABA were more likely to have *mild* COPD. LABA users were more likely to have a history of asthma, stroke or TIA, and pneumonia, while less likely to have lipid disorders compared to tiotropium users. The prevalence of other co-morbidities (*e.g.* history of MI, peripheral arterial disease, heart failure, hypertension, diabetes, malignancy, depressive disorders) were similar between new users of tiotropium and LABA.

Of the 6,788 COPD patients, 5,230 (77%) were prevalent COPD. Compared to prevalent COPD patients, incident COPD patients were slightly younger, more likely to be *past* or *current* smokers (and more likely to have a non missing smoking history), more likely to have *mild* COPD, while slightly less likely to have a history of heart failure.

Unadjusted event rates associated with various respiratory medications (in mutually exclusive categories) were estimated among patients newly diagnosed with COPD. No cases of MI occurred among tiotropium users. Unadjusted incident rates (IR) of MI for ipratropium vs. LABA users were 15.9 vs. 10.1 cases/1,000 p-years, respectively. IR of heart failure for tiotropium, ipratropium, and LABA users were 19.0, 41.6, and 19.5 cases per 1,000 person-years, respectively. The IR of stroke/TIA for tiotropium, ipratropium and LABA users were 34.3, 28.1, and 10.2 per 1,000 p-years, respectively. For all cardiovascular and cerebrovascular events combined, the IR associated with tiotropium, ipratropium and LABA were 38.9, 66.9, and 35.5 cases per 1,000 p-years, respectively. The IR of death for tiotropium, ipratropium and LABA users were 33.8, 39.0, and 32.1 per 1,000 p-years, respectively. The IR of diabetes mellitus for tiotropium, ipratropium and LABA users were 27.3, 13.3, and 21.7 per 1,000 p-years, respectively. The IR of renal failure for ipratropium was 4.1 per 1,000 p-years, respectively. No new cases of renal failure were observed among exclusive users of tiotropium or LABA among incident COPD users. The IR of hospital admissions for tiotropium, ipratropium and LABA users were 23.1, 35.9, and 18.5 per 1,000 p-years and those associated with COPD exacerbation were 249.7, 329.9, and 215.6 per 1,000 p-years, respectively.

Within the COPD cohort (incident and prevalent COPD), 784 new cases of combined cardiovascular and cerebrovascular events (which included new cases of MI, heart failure, ventricular arrhythmias, stroke and TIA) and 25,899 matched control moments were identified. Patients with a history of heart failure were excluded from these analyses. Current use of tiotropium or ipratropium was not associated with increased risk of cardiovascular and cerebrovascular events when compared to non users of anticholinergics (multivariate OR and 95% CI were 0.90 (0.64, 1.27) and 1.19 (0.99, 1.45), respectively). Multivariate models accounted for age, gender, index date, COPD severity 1 year prior to index date, duration of COPD, and smoking. Current use of either product independent of ICS and SABA were unchanged. Compared to non-use of anticholinergics, use of tiotropium of duration ≥ 365 days was associated with a decrease in risk of combined endpoints (multivariate OR and 95% CI was 0.43 (0.20, 0.93), although these estimates were based on only 7 exposed cases. Compared to non use of anticholinergics, ipratropium use at doses ≤ 0.5 DDD, as well as recent start, aerosol

formulation, and duration of use >30 days were associated with increased risk of cardiovascular and cerebrovascular events (multivariate OR and 95% CI were 1.50 (1.12, 2.01), 3.59 (1.74, 7.43), 1.49 (1.19, 1.87), and 2.46 (1.33, 4.57), respectively). The risk of cardiovascular and cerebrovascular events did not differ between current users of tiotropium *vs.* LABA, tiotropium *vs.* SABA, or ipratropium *vs.* LABA (independently of ICS).

Association between respiratory drugs and individual cardiovascular and cerebrovascular events were also examined. In a case-control including 155 new cases of MI and 6,799 matched control moments, no significant associations were observed between use, dose, duration and recency of use of tiotropium or ipratropium and risk of MI. Risk of MI associated with current use of either of these agents independently of ICS use did not differ from that associated with current use of LABA (multivariate OR and 95% CI for current use of tiotropium *vs.* LABA and ipratropium *vs.* LABA were 0.82 (0.55, 1.23) and 1.30 (0.79, 2.14), respectively). Due to the limited number of participants in the ventricular arrhythmia case-control (N=17 cases and 883 matched control moments), the association between respiratory drug use (including tiotropium and ipratropium) and risk of ventricular arrhythmias were not obtained in this study. In a case-control including 446 new cases of heart failure and 16,039 matched controls, current and recent use of anticholinergics were associated with an increase in risk of heart failure compared to non-use of anticholinergics (multivariate OR and 95% CI were 1.35 (1.05, 1.72) and 1.39 (1.00, 1.93), respectively). Tiotropium use, recency of first use, and duration were unassociated with risk of heart failure compared to non users of anticholinergics (multivariate OR and 95% CI were 1.26 (0.81, 1.95), 1.28 (0.82, 2.00), and 0.46 (0.14, 1.50) for use, non-recent first use, and duration length of ≥ 365 days, respectively). However, ipratropium use was associated with an increase in risk (multivariate OR and 95% CI was 1.33 (1.03, 1.72)). Low doses (≤ 0.5 DDD), recent first use, aerosol formulation, and short duration of use (< 30 days) of ipratropium were also associated with increased risk of heart failure compared to non use (multivariate OR and 95% CI were 5.18 (2.40, 11.2), 1.74 (1.29, 2.35), and 2.95 (1.41, 6.15), respectively). RR of heart failure independently from ICS use were similar for current use of tiotropium *vs.* LABA (multivariate OR and 95% CI 1.06 (0.53, 2.10)) as well as for current use of ipratropium *vs.* LABA (multivariate OR and 95% CI 1.22 (0.85, 1.74)). Finally, no significant associations were observed between use of tiotropium and risk of stroke in a case-control including 357 new cases of stroke/TIA and matched 13,909 control moments except for an increase in risk among recent starters of ipratropium (multivariate OR and 95% CI 1.61 (1.08, 2.39)). Risk of stroke/TIA (independently of ICS use) was similar between current users of tiotropium *vs.* LABA (multivariate OR and 95% CI 0.89 (0.45, 1.76)) and between current users of ipratropium *vs.* LABA (multivariate OR and 95% CI 1.07 (0.73, 1.55)).

Compared to non users of anticholinergics, current use of tiotropium or ipratropium was not associated with an increase in risk of death in a case-control study including 1032 new cases of death and 40,615 matched control moments (multivariate OR and 95% CI were 0.89 (0.65, 1.21) and 1.09 (0.90, 1.32), respectively). However, recent past use of tiotropium and both recent and distant past use of ipratropium were associated with an

increase in risk of death (multivariate OR and 95% CI were 1.69 (1.17, 2.44), 1.32 (1.05, 1.67) and 1.23 (1.02, 1.49), respectively). Risk of death was similar between current use of tiotropium vs. LABA (multivariate OR and 95% CI 0.79 (0.49, 1.28)), tiotropium vs. SABA multivariate OR and 95% CI 0.67 (0.38, 1.18)), and (between current use of ipratropium vs. LABA (multivariate OR and 95% CI 1.17 (0.91, 1.49)).

Risk of diabetes mellitus and renal failure were also examined in this study. In a case-control of 295 new DM cases and matched 10,428 control moments, neither tiotropium nor ipratropium were associated with risk of diabetes. Patients with a history of DM prior to cohort entry were excluded from these analyses. The risk of DM also did not differ between current use of tiotropium vs. LABA (multivariate OR and 95% CI 0.71 (0.31, 1.61)), between current use of tiotropium vs. SABA (multivariate OR and 95% CI 0.92 (0.35, 2.40)), or between current use of ipratropium vs. LABA (multivariate OR and 95% CI 0.92 (0.59, 1.41)), independently of ICS use. Similarly, these respiratory medications were also unassociated with risk of renal failure. In a case-control study including 83 new cases of renal failure and 3,975 matched control moments, tiotropium and ipratropium were not associated with risk of renal failure. Patients with a history of renal failure prior to cohort entry were excluded from these analyses. Risk also did not differ between current users of ipratropium vs. LABA (multivariate OR and 95% CI 1.18 (0.39, 3.56); estimates comparing current user of tiotropium vs. LABA or SABA were not provided due to limited number of cases available in these analyses.

Additionally, two case-control studies were constructed to examine effectiveness endpoints. In a case-control study including 619 new COPD-related hospital admissions and 24,820 matched controls, current use of tiotropium and of ipratropium was unassociated with increased risk of COPD-related hospitalization compared to users of LABA (multivariate OR and 95% were 0.51 (0.24, 1.06) and 1.17 (0.85, 1.61) for tiotropium vs. LABA and ipratropium vs. LABA, respectively). The association between these drugs and COPD exacerbation requiring oral steroids or antibiotics was also examined. In a case-control study including 3,439 new COPD exacerbations and 88,725 controls, rate of exacerbation was similar between current users of tiotropium and current users of LABA (multivariate OR and 95% was 0.93 (0.70, 1.23). Current use of ipratropium was associated with an increased risk of exacerbations compared to current use of LABA (multivariate OR and 95% was 1.26 (1.10, 1.44)).

No compelling evidence for effect modification by factors including gender, calendar time, incident vs. prevalent COPD, certainty of COPD diagnosis, COPD severity and smoking were provided.

3.9.2 OSE Comments on Proposed/Actual Analyses and/or Study Results

The results of this study do not provide evidence for an association between tiotropium and increased risk of cardiovascular events, mortality, or stroke. The current study also fails to suggest an association between tiotropium and increased risk of renal failure and of diabetes mellitus.

Objective 1

Indication for tiotropium use was missing in large proportions of new users of tiotropium, ranging from 23.4% (in 2003) and 50% (in 2007). Additionally, the date of data extraction for some of the practices fell before 2006. Thus, analyses on indication of use are based on information on a relatively small number of participants (i.e. N=268 in 2002, N=535 in 2003, N=482 in 2004, N=322 in 2005, N=105 in 2006, and N=3 in 2007) and may not appropriately represent the utilization in the source population.

Objective 2:

The large majority of COPD patients (77%) were diagnosed prior to cohort entry (prevalent COPD). These patients are therefore likely to have used respiratory medications prior to cohort entry. Inclusion of prevalent drug users in observational studies makes adjustment for certain covariates challenging because these variables may be affected by use of study drug itself (intermediate variables). For instance, adjustment for COPD severity among prevalent users of tiotropium may not be appropriate as COPD symptoms/severity may be affected by use of respiratory medications. Adjustment for variables affected by drug exposure typically attenuate the association between tiotropium and outcomes of interest. This problem may have been alleviated as COPD severity as measured 1 year prior to index date was used in primary analyses. It would be helpful to compare new vs. prevalent drug users in this study particularly in relation to age, COPD severity, and co-morbidities. Additionally, it would be helpful to restrict case-control analyses to incident COPD patients, although these analyses would probably lack statistical power due to the small number of incident COPD patients in the dataset.

Information on smoking is missing for approximately 46% of the patients (32% and 50% of incident and prevalent COPD patients, respectively). Therefore, residual confounding by smoking is likely in this study. However, this type of confounding would tend to over-estimate the association between tiotropium and study outcome; and, is therefore unlikely to explain the null associations observed in this study.

Additionally, information on spirometry values is missing for 69% of COPD patients. For these patients, COPD severity was classified according to data from GP or health care databases, which included a combination of recency of diagnosis, treatment with bronchodilators, xanthines or combination therapy, COPD-related hospitalization with antibiotic for treatment of respiratory infections, systemic corticosteroids for the treatment of COPD exacerbations, and/or diagnosis of pneumonia, and use of oxygen therapy. Thus, residual confounding by COPD severity cannot be ruled out this study. If tiotropium users tend to have more severe COPD (and more co-morbidities), confounding by COPD severity would attend to over-estimate the association between tiotropium and the outcomes of interest, and, is therefore unlikely to explain the null associations observed in this study.

Moreover, in many of the nested case-control studies, the final models did not adjust for several factors associated with the outcome, probably because these may not have been associated with the outcome at the $p<0.10$. For instance, previous history of diabetes, hyperlipidemia, and arrhythmia (among other factors) increased risk of cardiovascular

and cerebrovascular events (matched OR and 95% CI were 2.71 (1.99, 3.69), 1.20 (1.03, 1.41, and 1.69 (1.36, 2.09), respectively)) but were not included in the final models. Therefore, it may be advisable to adjust for factors associated with the outcome at the $p < 0.05$ level. Confounding by these factors would likely to lead to an over-estimation of the RR and is therefore unlikely to explain the lack of association between TB and cardiovascular and cerebral events observed in this study.

While current use of tiotropium was not associated with increased risk of cardiovascular or cerebrovascular events; low doses, recent use, short duration and aerosol formulation of ipratropium were associated with a moderate increase in risk of cardiovascular or cerebrovascular events when compared to non users of anticholinergics. These findings were mostly driven by cases of heart failure. Due to the early symptoms of heart failure, which may include coughing and dyspnea, these patients may have been prescribed ipratropium for relief of COPD exacerbation (*i.e.* protopathic bias), explaining the association with low dose, recent use and short duration of ipratropium and risk of heart failure.

While current use of tiotropium was not associated with an increased risk of death, an increase in risk was suggested with recent past use of anticholinergics (*i.e.* prescriptions ending >30 days and < 6 months prior to index) [RR (95% CI) = 1.31 (1.03, 1.66)] and with distant past use of anticholinergics (*i.e.* prescriptions ending 6+ months prior to index) [RR (95% CI) = 1.21 (0.98, 1.48)]. However, this increase in risk among recent past users may reflect worsening of COPD and/or potential switching of medications as patients near death (*i.e.* confounding by disease severity). Similarly, the not statistically significant increase in risk with distant past use is also difficult to interpret as these patients may have been using other respiratory medications (*i.e.* confounding by medication use).

Objective 3:

Analyses yielding unadjusted event rates per respiratory medication may not be informative in determining the safety profile of tiotropium because (i) they are based on small number of cases (only incident COPD included) and because (ii) they are likely to be confounded by several factors, including age, gender, smoking, COPD severity, among other important risk factors for the outcomes of interest.

4 SUMMARY AND RECOMMENDATIONS

This is a review of the results of a population-based case-control study nested within a cohort of COPD patients over the age of 40 years conducted by Erasmus Medical Center by the Sponsor. This review focuses on the results related to the safety of tiotropium bromide.

This study has several strengths, including its population-based nature and the large amount of information, including identification information (age, sex, patient identification, GP registration information), notes, prescriptions, physician-linked indications for therapy, physical findings, laboratory values (all directly entered by the

GPs), in addition to medication prescription information, including use, dose, duration and timing of drug exposure is also available.

Limitations were also noted. Limitations that could potentially bias the results towards the null value (i.e. attenuate the associations) and explain the results of this study are described below.

Misclassification of exposure: Medication prescription was used as surrogate for drug exposure, which requires the assumption that participants used the drugs as prescribed. This type of misclassification, however, is unlikely to have differed between those who subsequently developed the outcomes of interest and those who did not. This non-differential misclassification would tend to make the comparison groups more similar to one another in respect to the exposure of interest and may attenuate the association between tiotropium use and risk of the outcomes of interest.

Inclusion of prevalent drug users: the large majority of COPD patients (77%) were diagnosed prior to cohort entry (prevalent COPD). These patients are therefore likely to have used respiratory medications prior to cohort entry. Inclusion of prevalent drug users in observational studies makes adjustment for covariates that may be affected by drug use very difficult. For instance, adjustment for COPD severity among prevalent users of tiotropium may not be appropriate as COPD symptoms/severity may be affected by use of respiratory medications. Adjustment for variables affected by drug exposure may attenuate the association between tiotropium and outcomes of interest. This problem may have been alleviated as COPD severity as measured 1 year prior to index date was used in primary analyses.

Low statistical power: Tiotropium was only marketed in the Netherlands in 2002; therefore, cases and controls exposed to tiotropium before 2002 (potentially 25% of the total number of cases and controls) are necessarily unexposed. Information on the number of cases and controls identified during this time period (not provided in the current report) would be informative. Additionally, this study may not have had sufficient statistical power to examine the association between TB use and certain outcomes including renal failure and ventricular arrhythmias. Additionally, this study lacked statistical power to examine risk of mortality according to cause of death. Finally, this study had limited statistical power to examine effect modification by various factors.

In summary, this is a population-based case-control study nested within a cohort of COPD patients over the age of 40 years, participating in the IPCI - a longitudinal observational database that contains data from computer-based patient records of a selected group of GPs in The Netherlands. The primary objective of this study was to evaluate the safety profile of tiotropium compared to both non-users of anticholinergics drugs as well as to users of LABA. The main limitation of this study is potentially inadequate statistical power to detect associations between safety outcomes including cardiovascular events and mortality between tiotropium users vs. non users or LABA users due to the fact that a proportion of cases and controls could not contribute exposed person-time before 2002 (when tiotropium was marketed in the Netherlands).

Nonetheless, it is worth noting that confidence limits were relatively narrow; the upper bound confidence interval for cardiovascular/cerebravascular events of current tiotropium users vs. non users of anticholinergics (95% CI of 0.64 -1.27) and for current user of tiotropium vs. LABA [(95% CI (0.50, 1.41)] is lower than the increase in risk reported by the only meta-analysis of randomized trials [3] which suggested an increase in risk in cardiovascular events [RR (tiotropium vs. controls) =1.49, 95% CI (0.98, 2.26); RR (anticholinergics vs. controls) = 1.60 (1.22, 2.10)] [3]. The results of this study, in combination with most of the epidemiologic evidence noted in the OSE's previous review (DARRTS communication PK # 2663713, Communication Date 08/04/2009) failed to provide evidence for an association between tiotropium and increased risk of cardiovascular events, mortality or stroke.

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Do Not Swallow Spiriva Capsules

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DESCRIPTION

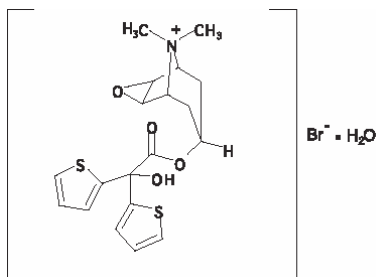
SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) consists of a capsule dosage form containing a dry powder formulation of tiotropium intended for oral inhalation only with the HandiHaler device.

Each light green, hard gelatin SPIRIVA capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate as the carrier.

The dry powder formulation within the SPIRIVA capsule is intended for oral inhalation only.

The active component of SPIRIVA HandiHaler is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1 α , 2 β , 4 β , 5 α , 7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

The structural formula is:



Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of $\text{C}_{19}\text{H}_{22}\text{NO}_4\text{S}_2\text{Br} \cdot \text{H}_2\text{O}$.

The HandiHaler device is an inhalation device used to inhale the dry powder contained in the SPIRIVA capsule. The dry powder is delivered from the HandiHaler device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HandiHaler device delivers a mean of 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2L total). In a study of 26 adult patients with chronic obstructive pulmonary disease (COPD) and severely compromised lung function [mean FEV₁ 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16%–65%)], the median peak inspiratory flow (PIF) through the HandiHaler device was 30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HandiHaler device, which may vary from patient to patient, and may vary with the exposure time of the SPIRIVA capsule outside the blister pack.

For administration of SPIRIVA HandiHaler, a SPIRIVA capsule is placed into the center chamber of the HandiHaler device. The SPIRIVA capsule is pierced by pressing and releasing the green piercing button on the side of the HandiHaler device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece (see **Patient's Instructions for Use**).

CLINICAL PHARMACOLOGY

Mechanism of Action

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M₁ to M₅. In the airways, it exhibits pharmacological effects through inhibition of M₃-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects were dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

Pharmacokinetics

Tiotropium is administered by dry powder inhalation. In common with other inhaled drugs, the majority of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in the lung, the intended organ. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract. Food is not expected to influence the absorption of tiotropium for the same reason. Oral solutions of tiotropium have an absolute bioavailability of 2–3%. Maximum tiotropium plasma concentrations were observed five minutes after inhalation.

Distribution

Tiotropium shows a volume of distribution of 32 L/kg, indicating that the drug binds extensively to tissues. The drug is bound by 72% to plasma proteins. At steady state, peak tiotropium plasma levels in COPD patients were 17–19 pg/mL when measured 5 minutes after dry powder inhalation of an 18 mcg dose and decreased rapidly in a multi-compartmental manner. Steady-state trough plasma concentrations were 3–4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Biotransformation

The extent of biotransformation appears to be small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol *N*-methyscopine and dithienylglycolic acid, neither of which bind to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination

The terminal elimination half-life of tiotropium is between 5 and 6 days following inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers with an inter-individual variability of 22%. Intravenously administered tiotropium is mainly excreted unchanged in urine (74%). After dry powder inhalation, urinary excretion is 14% of the dose, the remainder being mainly non-absorbed drug in the gut which is eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating active secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2–3 weeks with no accumulation thereafter.

Drug Interactions

An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once daily was conducted.

Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC_{0-4h} , a 28% decrease in the renal clearance of tiotropium and no significant change in the C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium. Therefore, no clinically significant interaction occurred between tiotropium and cimetidine or ranitidine.

Electrophysiology

In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30–60 msec was higher in the SPIRIVA HandiHaler group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with SPIRIVA HandiHaler did not detect an effect of the drug on QTc intervals. The effect of Spiriva HandiHaler on QT interval was also evaluated in a randomized, placebo and positive controlled crossover study in 53 healthy volunteers. Subjects received Spiriva HandiHaler 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for SPIRIVA HandiHaler 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥ 60 msec.

Special Populations

Elderly Patients

As expected for drugs predominantly excreted renally, advanced age was associated with a decrease of tiotropium renal clearance (326 mL/min in COPD patients <58 years to 163 mL/min in COPD patients >70 years), which may be explained by decreased renal function. Tiotropium excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased with advancing age within COPD patients (43% increase in AUC_{0-4} after dry powder inhalation), which was not significant when considered in relation to inter- and intra-individual variability (see **DOSAGE AND ADMINISTRATION**).

Hepatically-impaired Patients

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied. However, hepatic insufficiency is not expected to have relevant influence on tiotropium pharmacokinetics. Tiotropium is predominantly cleared by renal elimination (74% in young healthy volunteers) and by simple non-enzymatic ester cleavage to products that do not bind to muscarinic receptors (see **DOSAGE AND ADMINISTRATION**).

Renally-impaired Patients

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 ($CrCl$ 50–80 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 ($\text{CrCl} < 50 \text{ mL/min}$), 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 (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS**).

CLINICAL STUDIES

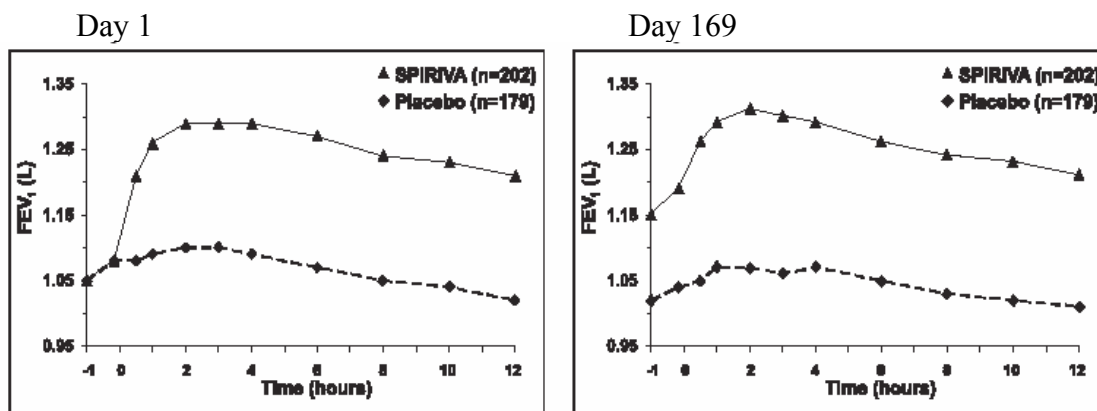
The SPIRIVA HandiHaler (tiotropium bromide inhalation powder) clinical development program consisted of six Phase 3 studies in 2,663 patients with COPD (1,308 receiving SPIRIVA HandiHaler): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had an FEV_1 less than or equal to 60% or 65% of predicted, and a ratio of FEV_1/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (forced expiratory volume in one second, FEV_1), with peak effect occurring within 3 hours following the first dose.

In the 1-year, placebo-controlled trials, the mean improvement in FEV_1 at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to baseline after the first dose (Day 1). Further improvements in FEV_1 and FVC were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV_1 , relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV_1 values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV_1) with SPIRIVA HandiHaler, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

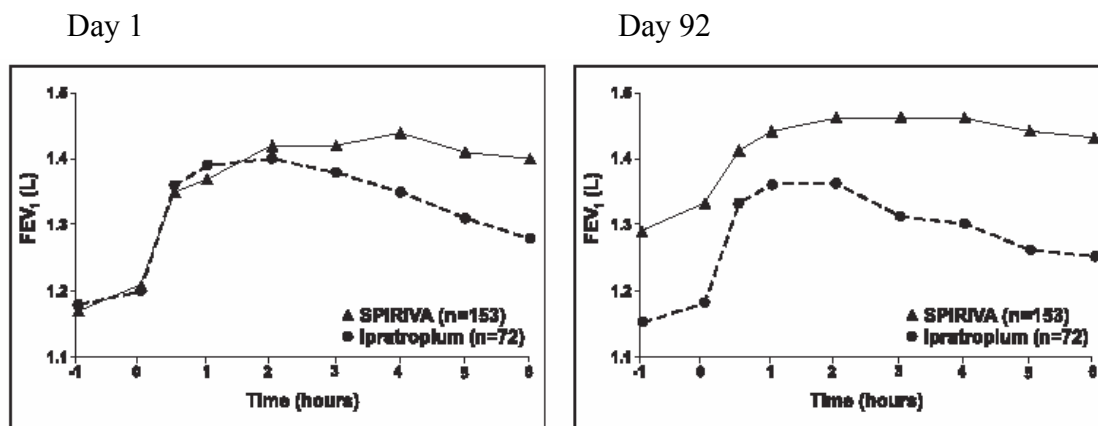
Figure 1 Mean FEV₁ Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*



* Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HandiHaler and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

Results of each of the one-year ipratropium-controlled trials were similar to the results of the one-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV₁ Over Time (0 to 6 hours post-dose) on Days 1 and 92, respectively for one of the two Ipratropium-Controlled Studies*



* Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HandiHaler and ipratropium groups, respectively, completed through three months of observation. The data for the remaining patients were imputed using last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HandiHaler was administered in the morning or in the evening.

Throughout each week of the one-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HandiHaler had a reduced requirement for the use of rescue short-acting beta₂-agonists. Reduction in the use of rescue short-acting beta₂-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

INDICATIONS AND USAGE

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

CONTRAINDICATIONS

SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder) is contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, including ipratropium, or to any component of this product.

WARNINGS

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm, i.e., rescue therapy.

Immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue or throat), itching, and rash may occur after administration of SPIRIVA HandiHaler. If such a reaction occurs, therapy with SPIRIVA HandiHaler should be stopped at once and alternative treatments should be considered.

Inhaled medicines, including SPIRIVA HandiHaler, may cause paradoxical bronchospasm. If this occurs, treatment with SPIRIVA HandiHaler should be stopped and other treatments considered.

PRECAUTIONS

General

As an anticholinergic drug, SPIRIVA HandiHaler (tiotropium bromide inhalation powder) may potentially 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 (creatinine clearance of ≤ 50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Renally-impaired Patients**).

Information for Patients

It is important for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler device (see **Patient's Instructions for Use**). SPIRIVA capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications. **The contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed.**

SPIRIVA capsules should always be stored in sealed blisters. Remove only one SPIRIVA capsule immediately before use, or its effectiveness may be reduced. Additional SPIRIVA capsules that are exposed to air (i.e., not intended for immediate use) should be discarded.

Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Should any of these signs and symptoms develop, consult a physician immediately. Miotic eye drops alone are not considered to be effective treatment.

Care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

SPIRIVA HandiHaler is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems, i.e., as a rescue medication.

Drug Interactions

SPIRIVA HandiHaler has been used concomitantly with other drugs commonly used in COPD without increases in adverse drug reactions. These include short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and inhaled steroids. However, the co-administration of SPIRIVA HandiHaler with other anticholinergic-containing drugs (e.g., ipratropium) has not been studied and is therefore not recommended.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to 25, 35, and 0.5 times the Recommended Human Daily Dose (RHDD) on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDD on a mg/m² basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the RHDD on a mg/m² basis). The fertility index, however, was not affected at inhalation doses

up to 1.689 mg/kg/day (approximately 760 times the RHDD on a mg/m² basis). These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Pregnancy

Pregnancy Category C.

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the recommended human daily dose (RHDD) on a mg/m² basis. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of ≥ 0.078 mg/kg (approximately 35 times the RHDD on a mg/m² basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDD on a mg/m² basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDD on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA HandiHaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Labor and Delivery

The safety and effectiveness of SPIRIVA HandiHaler has not been studied during labor and delivery.

Nursing Mothers

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA HandiHaler is administered to a nursing woman.

Pediatric Use

SPIRIVA HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. This disease does not normally occur in children. The safety and effectiveness of SPIRIVA HandiHaler in pediatric patients have not been established.

Geriatric Use

Of the total number of patients who received SPIRIVA HandiHaler in the 1-year clinical trials, 426 were <65 years, 375 were 65–74 years and 105 were ≥ 75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA HandiHaler and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA HandiHaler group (differences from placebo were 9.0%, 17.1%, and 16.2% in

the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA HandiHaler group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were – 0.6%, 4.6% and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of SPIRIVA HandiHaler dosage in geriatric patients is warranted.

ADVERSE REACTIONS

Of the 2,663 patients in the four 1-year and two 6-month controlled clinical trials, 1,308 were treated with SPIRIVA HandiHaler (tiotropium bromide inhalation powder) at the recommended dose of 18 mcg once a day. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, increased heart rate, blurred vision, glaucoma (new onset or worsening), urinary difficulty, and urinary retention.

Four multicenter, 1-year, controlled studies evaluated SPIRIVA HandiHaler in patients with COPD. Table 1 shows all adverse events that occurred with a frequency of $\geq 3\%$ in the SPIRIVA HandiHaler group in the 1-year placebo-controlled trials where the rates in the SPIRIVA HandiHaler group exceeded placebo by $\geq 1\%$. The frequency of corresponding events in the ipratropium-controlled trials is included for comparison.

Table 1 Adverse Experience Incidence (% Patients) in One-Year-COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA [n = 550]	Placebo [n = 371]	SPIRIVA [n = 356]	Ipratropium [n = 179]
Body as a Whole				
Accidents	13	11	5	8
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (upper)				
Epistaxis	4	2	1	1
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Sinusitis	11	9	3	2
Upper Respiratory Tract Infection	41	37	43	35
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of $\geq 3\%$ in the SPIRIVA HandiHaler treatment group, but were $< 1\%$ in excess of the placebo group.

Other events that occurred in the SPIRIVA HandiHaler group at a frequency of 1–3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole*: allergic reaction, leg pain; *Central and Peripheral Nervous System*: dysphonia, paresthesia; *Gastrointestinal System Disorders*: gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders*: hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders*: skeletal pain; *Cardiac Events*: angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder*: depression; *Infections*: herpes zoster; *Respiratory System Disorder (Upper)*: laryngitis; *Vision Disorder*: cataract. In addition, among the adverse events observed in the clinical trials with an incidence of $< 1\%$ were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age (see **PRECAUTIONS, Geriatric Use**).

Two multicenter, 6-month, controlled studies evaluated SPIRIVA HandiHaler in patients with COPD. The adverse events and the incidence rates were similar to those seen in the 1-year controlled trials.

The following adverse reactions have been identified during worldwide post-approval use of SPIRIVA HandiHaler: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, epistaxis, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

OVERDOSAGE

High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium.

Accidental Ingestion

Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since it is not well-absorbed systemically.

A case of overdose has been reported from post-marketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, SPIRIVA HandiHaler (tiotropium bromide inhalation powder) was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day.

No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7 mg/kg in rats, and 0.6 mg/kg in dogs. These doses correspond to 7,300, 120,000, and 850 times the recommended human daily dose on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

DOSAGE AND ADMINISTRATION

SPIRIVA capsules must not be swallowed as the intended effects on the lungs will not be obtained. The contents of the SPIRIVA capsules are only for oral inhalation and should only be used with the HandiHaler device (see OVERDOSAGE section).

The recommended dosage of SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is the inhalation of the contents of one SPIRIVA capsule, once-daily, with the HandiHaler device (see “**Patient Information**” and “**Patient’s Instructions for Use**”).

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given SPIRIVA HandiHaler should be monitored closely (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations** and **PRECAUTIONS**).

HOW SUPPLIED

SPIRIVA HandiHaler consists of SPIRIVA capsules and the HandiHaler device. SPIRIVA capsules contain 18 mcg of tiotropium and are light green, with the Boehringer Ingelheim

company logo on the SPIRIVA capsule cap and TI 01 on the SPIRIVA capsule body, or vice versa.

The HandiHaler device is gray colored with a green piercing button. It is imprinted with SPIRIVA HandiHaler (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo, and the Pfizer company logo. It is also imprinted to indicate that SPIRIVA capsules should not be stored in the HandiHaler device and that the HandiHaler device is only to be used with SPIRIVA capsules.

SPIRIVA capsules are packaged in an aluminum/aluminum blister card and joined along a perforated-cut line. SPIRIVA capsules should always be stored in the blister and only removed immediately before use. The drug should be used immediately after the packaging over an individual SPIRIVA capsule is opened.

The following packages are available:

- carton containing 5 SPIRIVA capsules (1 unit-dose blister card) and 1 HandiHaler device (NDC 0597-0075-75)
- carton containing 30 SPIRIVA capsules (3 unit-dose blister cards) and 1 HandiHaler device (NDC 0597-0075-41)
- carton containing 90 SPIRIVA capsules (9 unit-dose blister cards) and 1 HandiHaler device (NDC 0597-0075-47)

Storage

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].

The SPIRIVA capsules should not be exposed to extreme temperature or moisture. Do not store SPIRIVA capsules in the HandiHaler device.

Distributed by:

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

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SPIRIVA® (tiotropium bromide inhalation powder) is covered by U.S. Patent Nos. RE38,912, RE39,820, 5,478,578, 6,777,423, 6,908,928, 7,070,800, and 7,309,707 with other patents pending. The HandiHaler® inhalation device is covered by U.S. Design Patent No. D355,029 with other patents pending.

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Patient Information

SPIRIVA® (speh REE vah) HandiHaler®
(tiotropium bromide inhalation powder)

Important Information: Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HandiHaler device. SPIRIVA HandiHaler should only be inhaled by mouth (oral inhalation).

Read the information that comes with your SPIRIVA HandiHaler before you start using it and each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is SPIRIVA HandiHaler?

SPIRIVA HandiHaler is a prescription medicine that you use one time every day (a maintenance medicine) to control symptoms of chronic obstructive pulmonary disease (COPD). SPIRIVA HandiHaler helps make your lungs work better for 24 hours. SPIRIVA HandiHaler relaxes your airways and helps keep them open. You may start to feel like it is easier to breathe on the first day, but it may take longer for you to feel the full effects of the medicine. SPIRIVA HandiHaler works best and may help make it easier to breathe when you use it every day.

SPIRIVA HandiHaler is **not** a rescue medicine and should not be used for treating sudden breathing problems. Your doctor may give you other medicine to use for sudden breathing problems.

SPIRIVA HandiHaler has not been studied in children.

Who should not take SPIRIVA HandiHaler?

Do not use SPIRIVA HandiHaler if you:

- are allergic to any of the ingredients in SPIRIVA capsules.
- have had an allergic reaction to atropine or any medicines like it, such as ipratropium (Atrovent®).

What should I tell my doctor before using SPIRIVA HandiHaler?

Before taking SPIRIVA HandiHaler, tell your doctor about all your medical conditions, including if you:

- have kidney problems.
- have glaucoma. SPIRIVA HandiHaler may make your glaucoma worse.
- have an enlarged prostate, problems passing urine, or a blockage in your bladder.

SPIRIVA HandiHaler may make these problems worse.

- are pregnant or plan to become pregnant. It is not known if SPIRIVA HandiHaler could harm your unborn baby.
- are breast-feeding or plan to breast feed. It is not known if SPIRIVA HandiHaler passes into breast milk. You and your doctor will decide if SPIRIVA HandiHaler is right for you while you breast-feed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and eye drops, vitamins, and herbal supplements. Some of your other medicines or supplements may affect the way SPIRIVA HandiHaler works. SPIRIVA HandiHaler is an anticholinergic medicine. You should not take other anticholinergic medicines while using SPIRIVA HandiHaler, including ipratropium. Ask your doctor or pharmacist if you are not sure if one of your medicines is an anticholinergic.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I take SPIRIVA HandiHaler?

- Use SPIRIVA HandiHaler exactly as prescribed. Use SPIRIVA HandiHaler one time every day.
- Read the “Patient’s Instructions for Use” at the end of this leaflet before you use SPIRIVA HandiHaler. Talk with your doctor if you do not understand the instructions.
- **Do not swallow SPIRIVA capsules.**
- **Only use SPIRIVA capsules with the HandiHaler device.**
- **Do not use the HandiHaler device to take any other medicine.**
- SPIRIVA HandiHaler comes as a powder in a SPIRIVA capsule that fits the HandiHaler device. Each SPIRIVA capsule, containing only a small amount of SPIRIVA powder, is one full dose of medicine.
- Separate one blister from the blister card. Then take out one of the SPIRIVA capsules from the blister package right before you use it.
- After the capsule is pierced, take a complete dose of SPIRIVA HandiHaler by breathing in the powder by mouth two times, using the HandiHaler device (take 2 inhalations from one SPIRIVA capsule). See the “Patient’s Instructions for Use” at the end of this leaflet.
- Throw away any SPIRIVA capsule that is not used right away after it is taken out of the blister package. Do not leave the SPIRIVA capsules open to air; they may not work as well.
- If you miss a dose, take it as soon as you remember. Do not use SPIRIVA HandiHaler more than one time every 24 hours.
- If you use more than your prescribed dose of SPIRIVA HandiHaler, call your doctor or a poison control center.

What should I avoid while using SPIRIVA HandiHaler?

Do not let the powder from the SPIRIVA capsule get into your eyes. Your vision may get blurry and the pupil in your eye may get larger (dilate). If this happens, call your doctor.

What are the possible side effects of SPIRIVA HandiHaler?

SPIRIVA HandiHaler can cause serious side effects. If you get any of the following side effects, stop taking SPIRIVA HandiHaler and get medical help right away.

- **Allergic reaction.** Symptoms may include: itching, rash, swelling of the lips, tongue, or throat (trouble swallowing).
- **Sudden narrowing and blockage of the airways into the lungs (bronchospasm).** Your breathing suddenly gets worse.
- **New or worsened increased pressure in the eyes (glaucoma).** Symptoms of acute narrow-angle glaucoma may include: eye pain, blurred vision, seeing halos (visual halos) or colored images along with red eyes.

Common side effects with SPIRIVA HandiHaler include:

- dry mouth
- constipation
- upper respiratory infection
- increased heart rate
- blurry vision
- glaucoma (new onset or worsening)
- trouble passing urine

These are not all the possible side effects with SPIRIVA HandiHaler. Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SPIRIVA HandiHaler?

- **Do not store SPIRIVA capsules in the HandiHaler device.**
- Store SPIRIVA capsules in the sealed blister package at room temperature [68°–77°F (20°–25°C)].
- Keep SPIRIVA capsules away from heat and cold (do not freeze).
- Store SPIRIVA capsules in a dry place. Throw away any unused SPIRIVA capsules that have been open to air.

Ask your doctor or pharmacist if you have any questions about storing your SPIRIVA capsules.

Keep SPIRIVA HandiHaler, SPIRIVA capsules, and all medicines out of the reach of children.

General information about SPIRIVA HandiHaler

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use SPIRIVA HandiHaler for a purpose for which it has not been prescribed. Do not give SPIRIVA HandiHaler to other people even if they have the same symptoms that you have. It may harm them.

For more information about SPIRIVA HandiHaler, talk with your doctor. You can ask your doctor or pharmacist for information about SPIRIVA HandiHaler that is written for health professionals.

For more information about SPIRIVA HandiHaler, you may also call 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in SPIRIVA HandiHaler?

Active ingredient: tiotropium

Inactive ingredient: lactose monohydrate

What is COPD (Chronic Obstructive Pulmonary Disease)?

COPD is a serious lung disease that includes chronic bronchitis, emphysema, or both. Most COPD is caused by smoking. When you have COPD, your airways become narrow. So, air moves out of your lungs more slowly. This makes it hard to breathe.

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SPIRIVA® (tiotropium bromide inhalation powder) is covered by U.S. Patent Nos.
RE38,912, RE39,820, 5,478,578, 6,777,423, 6,908,928, 7,070,800, and 7,309,707 with

other patents pending. The HandiHaler® device is covered by U.S. Design Patent No. D355,029 with other patents pending.

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Revised March 2009

Patient's Instructions for Use

Spiriva®
HandiHaler®
(tiotropium bromide
inhalation powder)



Important Information: Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HandiHaler device. SPIRIVA HandiHaler should only be inhaled by mouth (oral inhalation).

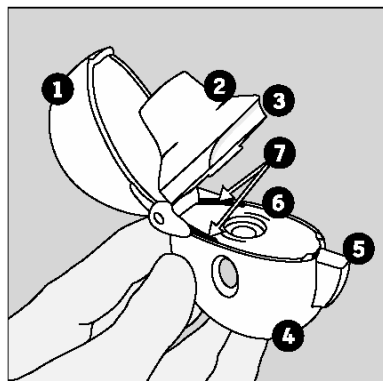
First read the Patient Information that comes with SPIRIVA HandiHaler for important information about using SPIRIVA HandiHaler.

Read these Patient's Instructions for Use before you start to use SPIRIVA HandiHaler and each time you refill your prescription. There may be new information.

For more information, ask your healthcare provider or pharmacist.

SPIRIVA HandiHaler comes with SPIRIVA capsules and a HandiHaler device. The HandiHaler device is an inhalation device that is for use only with SPIRIVA capsules. Do not use the HandiHaler device to take any other medicine.

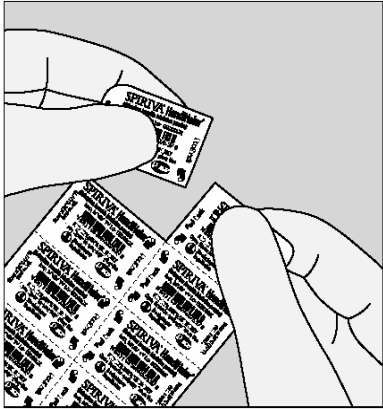
Becoming familiar with SPIRIVA HandiHaler:



Remove the HandiHaler device from the pouch and become familiar with its components. (Figure A)

1. dust cap
2. mouthpiece
3. mouthpiece ridge
4. base
5. green piercing button
6. center chamber
7. air intake vents

Figure A



Each SPIRIVA capsule is packaged in a blister. Each blister can be separated from the blister card by tearing along the perforation. (Figure B)

Figure B

How do I take my SPIRIVA HandiHaler using the HandiHaler device?

Taking your dose of medicine using the HandiHaler device has four main steps:

1. **Open** the HandiHaler device and the blister
2. **Insert** the SPIRIVA capsule
3. **Press** the green piercing button
4. **Breathe in (inhale)** your medicine

(See below for details)

Opening the HandiHaler device:

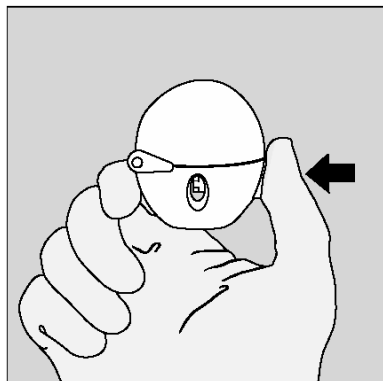


Figure 1

1. Open the dust cap by pressing the green piercing button. (Figure 1)



Figure 2

Pull the dust cap upwards to expose the mouthpiece. (Figure 2)

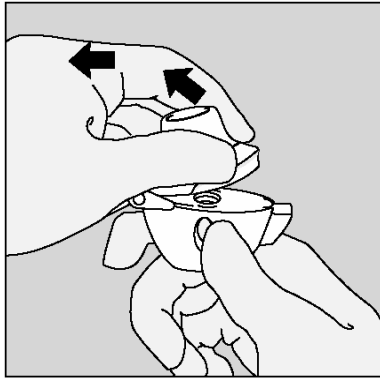


Figure 3

Open the mouthpiece by pulling the mouthpiece ridge upwards away from the base. (Figure 3)

Removing a SPIRIVA capsule:

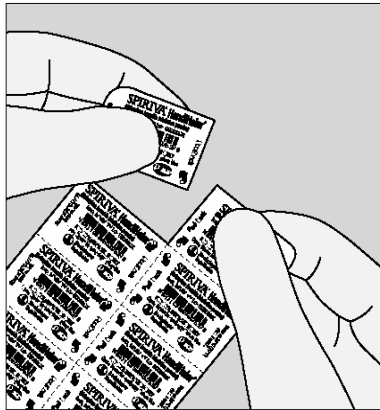


Figure 4

Before removing a SPIRIVA capsule from the blister, separate one of the blisters from the blister card by tearing along the perforation. (Figure 4)

Do not swallow Spiriva capsules.

Always store SPIRIVA capsules in the sealed blisters. Remove only one SPIRIVA capsule from the blister right before use. Do not store SPIRIVA capsules in the HandiHaler device. Inhale the contents of the SPIRIVA capsule using the HandiHaler device right away after the blister packaging of an individual SPIRIVA capsule is opened, or else it may not work as well.

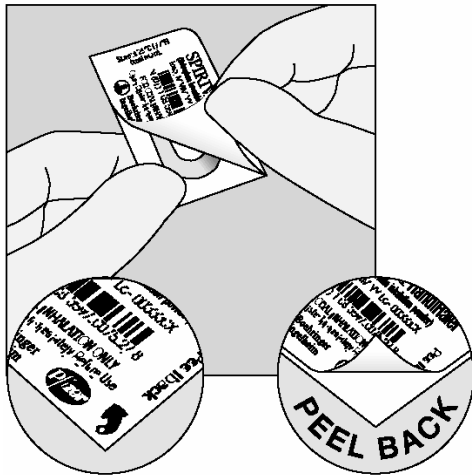


Figure 5

Right before you are ready to use your SPIRIVA HandiHaler:

Bend back and forth one of the corners of the blister that has an arrow and then with your finger separate the aluminum foil layers. Carefully peel back the printed foil until you can see the whole SPIRIVA capsule. (Figure 5)

Turn the blister upside down and tip the SPIRIVA capsule out, tapping the back of the blister, if needed.

Do not cut the foil or use sharp instruments to take out the SPIRIVA capsule from the blister.

If more SPIRIVA capsules are opened to air, they should not be used and should be thrown away.

Inserting the SPIRIVA capsule into the HandiHaler device:

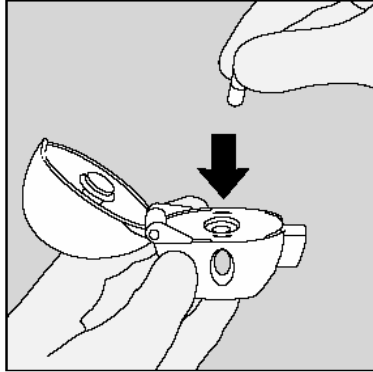


Figure 6

2. Insert (put) the SPIRIVA capsule in the center chamber of the HandiHaler device. It does not matter which end of the SPIRIVA capsule you put in the chamber. (Figure 6)

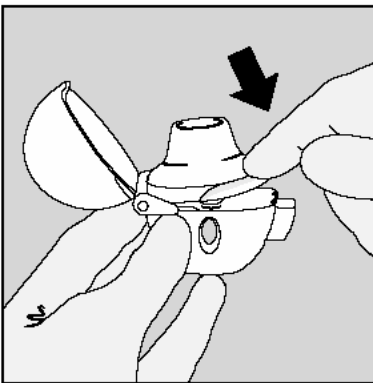


Figure 7

Close the mouthpiece **until you hear a click**, but leave the dust cap open. (Figure 7)

Be sure that you have the mouthpiece sitting firmly against the gray base.

Taking your dose using the HandiHaler device:

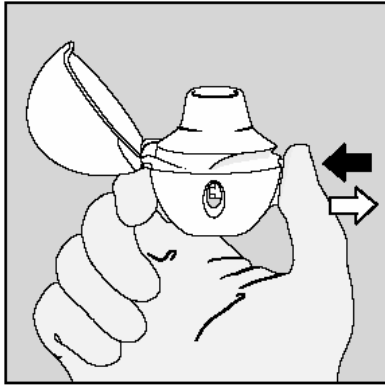


Figure 8

Hold the HandiHaler device with the mouthpiece upright. It is important that you hold the HandiHaler device in an upright position (Figure 8) when pressing the green piercing button.

3. Press the green piercing button until it is flat (flush) against the base, and release. This is how you make holes in the SPIRIVA capsule so that you get the medicine when you breathe in.

Do not press the green button more than one time.

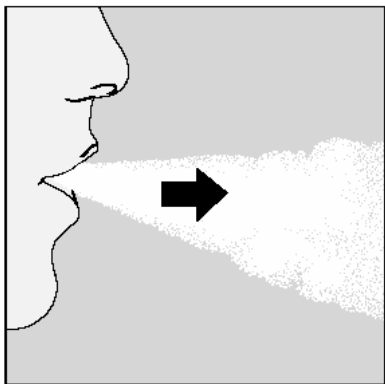


Figure 9

Breathe out completely. (Figure 9)

Important: Do not breathe (exhale) into the mouthpiece of the HandiHaler device at any time.

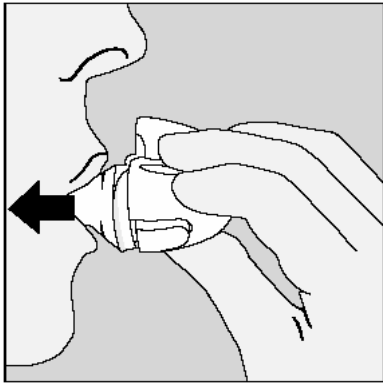


Figure 10

4. Breathe in (inhale)

- Hold the HandiHaler device by the gray base. Do not block the air intake vents.
- Raise the HandiHaler device to your mouth and close your lips tightly around the mouthpiece.
- **Keep your head in an upright position. The HandiHaler device should be in a horizontal position.** (Figure 10)
- Breathe in **slowly and deeply** so that you **hear or feel the SPIRIVA capsule vibrate.**
- Breathe in until your lungs are full.
- Hold your breath as long as is comfortable and at the same time take the HandiHaler device out of your mouth. Breathe normally again.

To make sure you get the full dose, you must breathe out completely, and inhale again as in step 4 above (Figure 10). *Do not press the green piercing button again.*

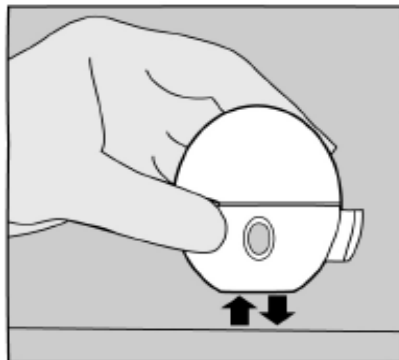


Figure 11

If you do not hear or feel the SPIRIVA capsule vibrate, **do not press the green piercing button again.** Instead, hold the HandiHaler device in an upright position and tap the HandiHaler device gently on a table. (Figure 11)

Check to see that the mouthpiece is completely closed. Then, breathe in again – slowly and deeply.

If you still do not hear or feel the SPIRIVA capsule vibrate after repeating the above steps, throw away the SPIRIVA capsule. Open the base by lifting the green piercing button and check the center chamber for pieces of the SPIRIVA capsule (SPIRIVA capsule fragments). SPIRIVA capsule fragments in the center chamber can cause a SPIRIVA capsule not to vibrate. Turn the HandiHaler device upside down and gently tap to remove the SPIRIVA capsule fragments. Call your doctor for instructions.

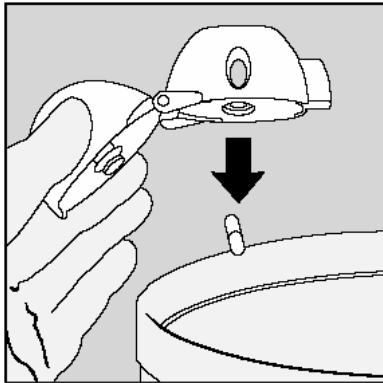


Figure 12

After you finished taking your daily dose of SPIRIVA HandiHaler, open the mouthpiece again. Tip out the used SPIRIVA capsule and throw it away. (Figure 12)

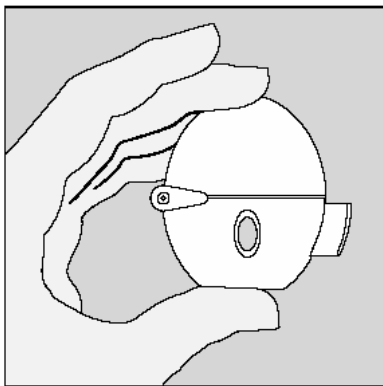


Figure 13

Close the mouthpiece and dust cap for storage of your HandiHaler device. (Figure 13)

Do not store used or unused SPIRIVA capsules in the HandiHaler device.

When and how should I clean my HandiHaler Device?

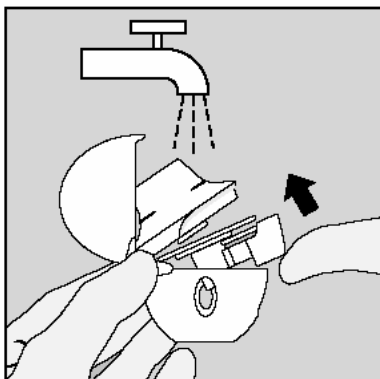


Figure 14

Clean the HandiHaler device one time each month or as needed. (Figure 14)

- Open the dust cap and mouthpiece.
- Open the base by lifting the green piercing button.
- Look at the center chamber for SPIRIVA capsule fragments or powder residue.
- Rinse the HandiHaler device with warm water. Check that any powder buildup or SPIRIVA capsule fragments are removed.
- Do not use cleaning agents or detergents.
- Do not place the HandiHaler device in the dishwasher for cleaning.
- Dry the HandiHaler device well by tipping the

excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open.

- Do not use a hair dryer to dry the HandiHaler device.
- **It takes 24 hours to air dry, so clean the HandiHaler device right after you use it so that it will be ready for your next dose.**
- Do not use the HandiHaler device when it is wet. If needed, you may clean the outside of the mouthpiece with a clean damp cloth.

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SPIRIVA® (tiotropium bromide inhalation powder) is covered by U.S. Patent Nos.
RE38,912, RE39,820, 5,478,578, 6,777,423, 6,908,928, 7,070,800 and 7,309,707 with
other patents pending. The HandiHaler® device is covered by U.S. Design Patent No.
D355,029 with other patents pending.

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